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PERKIN AND KIPPING'S

ORGANIC CHEMISTRY

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ORGANIC CHEMISTRY

Part III

BY

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NEW EDITION

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PERKIN AND KIPPING'S

ORGANIC CHEMISTRY

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PREFACE

THE present volume was first written in 1934 as a continuation of Parts I and II of Perkin and Kipping's *Organic Chemistry*, and was intended mainly for the use of students who are working for an Honours Degree Examination. It was hoped that it might also be helpful to teachers, and to others who are interested in the more recent developments of certain branches of organic chemistry. These aims are unchanged and the main plan remains as before.

The difficulty of selecting the subjects which should be dealt with in such a book, and of deciding the space to be allotted to each, will be appreciated by all those who are confronted with this particular problem in preparing their courses of lectures, and since the first edition this difficulty has grown, as new fields of chemistry, at that time unknown or of little importance, have assumed prominence. There is still the same limit, however, to what a student can remember, and certain deletions have therefore been made of what appeared to be out-of-date material.

Whether the selection of subjects included in this book is the best or otherwise is no doubt a matter of opinion, but it is based on the results of many years of experience in teaching this branch and grade of chemistry.

For the present edition the whole work has been reset, thus allowing complete freedom. In particular almost all the formulae have been redrawn and the opportunity has been taken of introducing a new, and it is hoped, simplified, method of writing many of them.

Two chapters have disappeared: one on the Electronic Formulae of Organic Compounds, as it is considered that the electronic theory of valency is now so well known to students that its inclusion in a text-book of organic chemistry is superfluous; the other, on the Theory of Resonance, has not been deleted but has been transferred piecemeal to appropriate places in Parts II or III. Certain other short sections have been also transferred to Part II where their position seemed more logical, and two short chapters on Alkali Metal Compounds and Free Radicals have been combined.

The two largest additions are the sections on Plastics and on Nucleoproteins: the former has been incorporated in a chapter

with the revised section on Rubber and the latter with an extended section on Vitamins, which have been covered in more detail than before.

The whole of the old text has been entirely rewritten and important additions have been made on the Synthesis of Large Ring Compounds, the Oxidation of Olefines, the Nomenclature of Bridged Ring Compounds, the Interconversion of Sugars, the Oxidation of Sugars with Periodic Acid, Synthetic Sesquiterpenes, Resin Acids, Azulenes, the Synthesis of Polycyclic Compounds, Antibiotics and Adrenal Hormones: to avoid excessive length only the more salient advances in organic chemistry have been included.

By his death in May 1949 I was deprived of the invaluable collaboration of my father, but fortunately the first proof had been received by then and I feel that any merit the present work may have is largely due to him, as he had a critical faculty and a flair for writing which were always my envy.

I am greatly indebted to Dr C. P. Stewart, who read the whole of Part III in proof and made many valuable suggestions: also to Professor C. W. Shoppee for reading Chapter 64, and Professor A. R. Todd, who read Chapters 62 and 63.

NOTE ON 1958 EDITION

In the 1958 edition a new Chapter on the Applications of the Electronic Theory to Organic Chemistry has been added at the beginning. In many places modern electronic interpretations of organic reactions have been given, as, for example, in discussions of racemisation, the Walden inversion, aromatic substitution, etc. The Chapter on Physical Properties of Organic Compounds has been rewritten to give more prominence to those properties most used nowadays for determining constitution. Modern views of strainless ring structures are given and a short account of tropolones and ferrocene. Various other small alterations have been made in an endeavour to bring the matter thoroughly up to date in so far as possible without too extensive alterations.

My very best thanks are due to Professor D. H. Peacock for valuable advice and many discussions throughout, to Professor G. W. Kenner for reading Chapter 43 and parts of Chapter 59 and to Dr. N. Sheppard for comments on parts of Chapter 44. F. B. K.

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PUBLISHER'S NOTE

Chapter 43 bears page numbers 695*a* to 695*t*: the device, admittedly awkward, is for technical reasons unavoidable.

ORGANIC CHEMISTRY

Part III

CHAPTER 43

APPLICATIONS OF THE ELECTRONIC THEORY TO ORGANIC CHEMISTRY

THE introduction of Kekulé's structural theory of organic chemistry nearly a century ago provided a valuable framework for the systematic study of the subject and led to rapid and major developments; the ideas of stereochemistry of van't Hoff and Le Bel extended the theory to account for the existence of isomerides for which, up to that time (1874), there was no explanation. In spite of these great advances the theory was handicapped in providing an interpretation of the behaviour of organic compounds by an incomplete knowledge of atomic structure and of the nature of valency: such phenomena as the Walden inversion and *trans*-addition were completely inexplicable. The introduction of the Rutherford-Bohr atom (1913), subsequently modified by de Broglie, Dirac, Heisenberg and Schrödinger, led to the ideas of valency of Lewis and Langmuir which were later extended by others. Gradually a theory to explain the nature of the reactions of organic compounds and of linking these reactions with the Kekulé structures has been developed largely by Lowry, Lapworth, Robinson, Ingold, Pauling and others.

The fundamental postulates of this theory are based on assumptions of movements of electrons within the molecules leading to the development of positive and negative charges at certain atoms, which thereby become reactive. It is assumed in the first place that the electrons taking part in a co-valent bond may be shared unequally. In the C—Cl bond, for example, the condition may be represented by C⟶—Cl, and the result will be a permanent polarisation of this complex; but such a change is not restricted to the heteropolar bond in question, and may be transmitted along a

saturated chain until damped out, C⟶C⟶C⟶Cl. This is known as the *inductive effect:*[1] it is to be noted that it does not produce an actual transfer of electrons from one atom to another and that the usual valencies of the elements concerned are maintained.

In compounds containing multiple links there is more scope for the movement of electrons and *mesomeric effects* are present; the basic principles of mesomerism or resonance have already been pointed out in a consideration of the structure of benzene, and it has been mentioned that compounds in which mesomerism is present are more stable than they would otherwise be.

As a simple example of a group with a multiple link the carbonyl radical may be considered; this is usually represented by >C=O, but it could change into (I) by a transfer of two of the electrons of the double bond entirely to the oxygen atom. The theory assumes that there is a tendency for this change to occur and that these

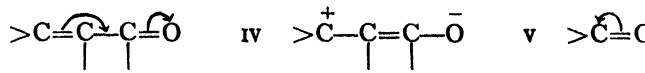
I $>\overset{+}{C}-\overset{-}{O}$ II $>C=\overset{\curvearrowright}{O}$

two forms contribute to the final mesomeric state of the radical; this may be indicated by (II). At the instant of reaction with any reagent the group undergoes *electromeric* change into (I) in which the carbon and oxygen atoms have positive and negative charges respectively. Although the oxygen atom maintains its octet of electrons, it acquires a negative charge and the carbon atom is left with a sextet of electrons until reaction has taken place. In mesomeric molecules such as this the contribution to the mesomerism or resonance of the form in which the octets are not maintained is small until electromeric change occurs, on the demand of a reagent. It will be seen in the sequel that the electromeric change which precedes reaction is controlled by the inductive and mesomeric effects in the molecules concerned.

As shown above and as previously indicated (p. 517) the mesomeric effect is usually shown by the use of curved arrows and in the case of a chain of alternate single and double bonds (conjugated chain, p. 815) such mesomerism extends along the whole length of the

[1] The inductive effect is often denoted by the letter I and its direction by a positive or negative sign: unfortunately there is no general agreement as to whether electron attraction is to be called +I or −I. A similar ambiguity is found in the sign of the mesomeric effect (above), denoted by M. These symbols are, however, unnecessary and are not further employed in this book.

chain, (III), so that the atoms at the ends become charged when electromeric change takes place, (IV).



The above may be summarised thus :

The *inductive effect* gives rise to unequal sharing, but no transfer, of the electrons of co-valent bonds between atoms ; it is a permanent state of the molecule.

The *mesomeric effect* is present only in molecules containing multiple links and means that the actual state of the molecule is somewhere between those of the end forms; it also is a permanent state. Both the inductive and mesomeric effects cause permanent dipole moments (p. 702) and the latter alterations in bond lengths.

The *electromeric effect* is only brought about at the instant of reaction, when the molecule goes over into one of the contributors to the mesomeric state.

In order to apply these ideas to an explanation of the mechanism of organic reactions it is obviously necessary to find out in which direction inductive and mesomeric effects act : it might be thought, for example, at first sight equally plausible to write the carbonyl group (V) ; this seems unlikely, however, as the oxygen atom has a higher nuclear charge than carbon and will probably therefore demand a larger share of the bonding electrons. More definite information on the subject may be obtained from quite simple considerations, among which may be mentioned the ease with which a hydrogen atom leaves a molecule as a proton.

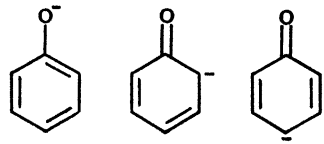
When an acid ionises its acidic hydrogen atom separates from the rest of the molecule as a proton which carries a positive charge,

$$HA \rightleftharpoons H^+ + A^-,$$

or more correctly, in aqueous solution, as a hydrated proton ; it is largely the tendency of water to form hydrated ions which provides the energy for ionisation, but the argument is the same whether the ions are hydrated or not and this factor need not be further considered. The ease with which ionisation occurs will therefore depend primarily on the demand made by the group A on a share of the pair of electrons forming the co-valent link between H and A ; the greater the attraction of A for electrons the stronger will be the acid, HA. In a molecule of hydrogen the two electrons of the co-

valent link must clearly be shared equally between the two atoms ; similarly in ethane it is reasonable to assume equal sharing of the two electrons forming the bond between the two carbon atoms (but not necessarily equal sharing in the carbon-hydrogen bonds). In the case of hydrogen chloride the sharing is very unequal and the chlorine atom demands a far greater share ; the electrons are withdrawn from the hydrogen atom which can therefore separate as a proton when the gas is dissolved in water. The inductive effect of chlorine is thus shown to be, H—→—Cl or H :Cl. Water ionises to a much smaller extent so that it may be assumed that the oxygen atom is demanding a smaller share of the electrons than does chlorine, but there is still some inductive effect. Methanol, in which one of the hydrogen atoms in water is replaced by a methyl group, ionises much less still ; it is surely reasonable to assume therefore that the methyl radical repels electrons and thereby satisfies the demands of the oxygen atom, which in its turn does not demand a large share from the hydrogen atom of the hydroxyl group, CH_3—→—OH.

Phenol is a much stronger acid than water and at first sight it would seem that the phenyl radical has a strong electron attracting inductive effect ; this is so, but it does not cover all the facts. In considering the mechanism of any reaction the stability of the final product or products and of any transition state (p. 695*i*) there may be, must be considered. Now when the phenolate ion is produced by the separation of a proton, the ionic charge can be distributed over several atoms instead of being localised and increased stability results ; the ion is a mesomeric form of possible structures as indicated :



Similar mesomerism exists in phenol itself (p. 1012), but the mesomerism of phenol is less complete than that of the phenolate ion ; that is to say the contribution of forms such as the second two above to the mesomerism of the ion is greater than that of similar forms in phenol itself, so that stabilisation of the ion displaces the equilibrium in the direction of ionisation.

The acidity of a carboxylic acid can be explained as due to the electron attraction of the carbonyl group and mesomerism of the resulting ion (p. 517); this implies that the carbonyl group has a mesomeric effect (II, p. 695*b*) and not (V, p. 695*c*). The relative strengths of various acids under similar conditions are as shown

Dissociation Constants of Acids ($\times 10^5$)

Formic acid	17		
Acetic acid	1·7	Benzoic acid	6·3
Propionic acid	1·3	Phenylacetic acid	4·9
n-Butyric acid	1·5	β-Phenylpropionic acid	2·2
Monochloroacetic acid	138	α-Chloropropionic acid	158
Dichloroacetic acid	5130	β-Chloropropionic acid	8·3
Trichloroacetic acid	224000		

and the relationships between some of these figures may be explained qualitatively as follows:

(1) The electron-repelling inductive effect of the alkyl groups is shown by the fall as the series of fatty acids is ascended; the large initial fall from formic acid to acetic acid, however, is perhaps unexpected and may not be due entirely to the inductive effect (p. 1013). The slightly larger value for butyric acid as compared with propionic acid is anomalous, but insignificant.

(2) The electron-attracting effect of the phenyl group is shown by the greater strength of benzoic acid as compared with acetic acid and the damping of the inductive effect in a saturated chain by the fall in strength in passing to phenylacetic acid and β-phenylpropionic acid.

(3) The strong electron attracting inductive effect of chlorine is well shown by the figures for the chloroacetic acids and chloropropionic acids and the damping effect of the saturated chain is illustrated by the much lower figure for β- than for α-chloropropionic acid.

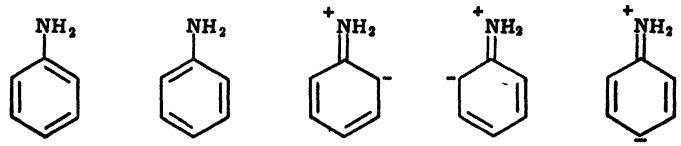
The most important organic bases are the amines and amino-compounds, and their basic character is due to the unshared pair of electrons on the nitrogen atom, which can be used to attach a proton to give an ammonium salt:

$$R_3N: + H^+ + Cl^- \longrightarrow [R_3NH]^+ + Cl^-.$$

The strength of the base will depend on the availability of the unshared pair of electrons of the nitrogen atom. When one of the

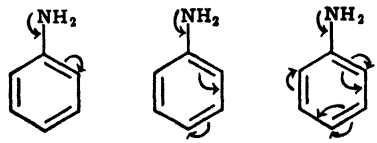
hydrogen atoms of ammonia is replaced by an alkyl group the inductive effect of the latter should act to make the unshared pair more available, $CH_3 \longrightarrow NH_2$, and in accordance with this premise, methylamine is in fact a stronger base than ammonia. In dimethylamine the effect is increased with a consequent increase in basic strength, but trimethylamine, although a stronger base than ammonia, is weaker than methylamine, whereas it might be expected that the inductive effect of three methyl groups would cause it to be the strongest base of the four compounds considered. There is no very clear explanation of this anomaly, but it has been suggested that the presence of the three relatively large methyl groups round the nitrogen atom may prevent the approach of the proton by a steric effect. This seems most unlikely.

The very weakly basic character of the aromatic amino-compounds is accounted for by the tendency of the unshared pair of electrons of the nitrogen atom to participate in the mesomerism of the aromatic nucleus : aniline may be represented by the mesomeric form of (I) and (II), but in addition forms (III), (IV) and (V) contribute to the mesomerism :



I II III IV V

Forms (III) (and (IV), which are in fact identical) and (V) may be indicated by (VI) and (VII) respectively and (VIII) shows the final mesomeric form combining all the contributors,



VI VII VIII

This example illustrates how it is permissible and useful to use the Kekulé formula for benzene in dealing with such problems. It

is to be noted that in (III), (IV) and (V) all the octets are maintained. In consequence of the contributions of forms (III)-(V) the unshared pair of electrons is not available for the attachment of a proton: in the anilinium ion, $Ph \cdot NH_3^+$, such participation in the mesomerism of the ring is impossible so that energy would be required for its formation and there is little tendency for it to form.

In diphenylamine the demands of the two aromatic nuclei on the unshared pair of the nitrogen are so great that it will not give salts in aqueous solution and indeed such is the mesomeric effect that the hydrogen atom of the amino-group is incipiently ionisable and diphenylamine gives salts with alkali metals; in the anion of these salts the negative charge is distributed over the two phenyl groups and thereby stabilised by mesomerism. Triphenylamine is not basic.

The very weakly basic nature of amides in contrast to that of amines is another example of the electron attraction of the carbonyl group and the forms contributing to the mesomerism have already been mentioned (p. 517). The presence of two carbonyl radicals in an imide, such as succinimide or phthalimide, has the effect of producing an acidic hydrogen atom and a mesomeric anion, and in the sulphonamides one $—SO_2—$ group is sufficient to give solubility in alkali.

In all the above cases of acidity or incipient acidity the mobile proton was attached to oxygen or nitrogen, but if the ion formed can be sufficiently stabilised by resonance it is possible for a proton to be liberated from a $>C—H$ link. A simple example of this is, of course, hydrogen cyanide (p. 366), but such ionisation is also shown in the aliphatic nitro-compounds, the anion of which (in the case of nitromethane) may be represented by the mesomeric form with contributors, $^-CH_2—NO_2$ and $CH_2=NO—O^-$: in this case there is also the usual mesomerism of the nitro-group (p. 438). The β-diketones and β-ketonic esters (p. 831) are similar in that the mesomeric ion is formed from the keto-form by direct ionisation of a hydrogen atom attached to carbon, due to the electron attraction of the two carbonyl groups, $—OC \leftarrow CH_2 \rightarrow CO—$, and then stabilisation of the ion by resonance. Almost all reactions of ionisation are, to all intents and purposes, instantaneous, but this is not so in the case of ionisation of hydrogen attached to carbon, a fact which accounts for the relatively slow solution of aliphatic nitro-compounds, ethyl acetoacetate, etc., in alkali.

The formation of metallic derivatives of *cyclo*pentadiene (p. 789) is another excellent example of stabilisation of an ion by resonance ; when the proton is lost from the $>CH_2$ group the anion is left with six electrons which are not required for any definite links and are free to form the same system as in benzene (aromatic sextet), with its very great stability.

Substitution Reactions

Substitution of one of the groups attached to a carbon atom by another as for example,

$$A+RB = RA+B,$$

where R is a hydrocarbon radical and the group A displaces the group B, may occur in various ways depending on how the bond between R and B is broken ; thus

(1) one electron may remain with each, giving free radicals $R^{\cdot}$ and $B^{\cdot}$ (p. 1044),

(2) both electrons may remain with B, giving R^+ and B^-,

(3) both electrons may remain with R, giving R^- and B^+.

The first of these modes of fission is known as *homolytic* and the last two as *heterolytic* and the type of reaction occurring in any particular case depends on the nature of A and of RB and on the experimental conditions, etc. Homolytic and heterolytic reactions are governed by different principles and laws. Homolytic reactions are favoured by light, high temperatures and such catalysts as organic peroxides which themselves tend to produce free radicals. Heterolytic reactions are unaffected by light, free radicals and peroxides, but are often catalysed by acids and bases which tend to promote ionisation. Homolytic reactions are inhibited by substances such as quinol which combine with free radicals thereby stopping the chain mechanism ; such substances have no effect on heterolytic reactions. Homolytic reactions usually occur in the vapour phase or in non-polar solvents, whereas ionising solvents are usually best for heterolytic reactions.

As examples of homolytic or free radical reactions the halogenation of paraffins and of toluene in the side chain in sunlight may be mentioned : in each case a photochemical decomposition of

the halogen molecule into atoms is assumed, which initiates a chain reaction as follows :

$$Cl^{\cdot} + CH_4 \longrightarrow HCl + CH_3^{\cdot},$$
$$CH_3^{\cdot} + Cl_2 \longrightarrow CH_3Cl + Cl^{\cdot},$$
$$Cl^{\cdot} + CH_3Cl \longrightarrow HCl + CH_2Cl^{\cdot}, \text{ etc.}$$

The high temperature halogenation of olefines, previously ascribed to addition followed by dehydrohalogenation (p. 246), is probably a direct homolytic substitution of the same type, as is the high temperature nitration of paraffins. Other examples of free radicals are given later (pp. 1040 *seq.*).

Most aliphatic substitutions are heterolytic, and of a type in which the entering group A supplies both electrons for its union with R, type 2, (p. 695*h*) ; this is shown in the following examples :

$$R{\cdot}Br + OH^- = R{\cdot}OH + Br^-,$$
$$R{\cdot}Br + CN^- = R{\cdot}CN + Br^-,$$
$$R{\cdot}NH_2 + NO^+ + Br^- = RBr + H_2O + N_2,$$
$$R{\cdot}Br + {}^-CH(COOEt)_2 = R{\cdot}CH(COOEt)_2 + Br^-.$$

In all cases the entering group A (OH^-, CN^-, Br^-, $^-CH(COOEt)_2$), has a negative charge and brings with it a pair of unshared electrons ; a slightly different type of reaction is shown by the addition of a halide to ammonia or amines,

$$R{\cdot}Br + R'_3N = R'_3RN^+ + Br^- ;$$

here the entering group is neutral but it has unshared electrons which are used to create the new bond. In both the above cases the entering group is known as *nucleophilic*, because it is seeking a nucleus with which to combine, and a substitution of this sort is *nucleophilic substitution.*

Investigation of nucleophilic substitution (Hughes, Ingold and others) by various physico-chemical processes has shown that the reactions may proceed in two different ways.

Firstly RB may be attacked by A and a transition state reaction complex A . . . R . . . B formed from which B is then eliminated : this reaction goes in one step, the union of A with R being synchronous with the elimination of B. Two entities, A and RB are concerned, the reaction is bimolecular and is called S_N2 (*substitution nucleophilic bimolecular*).

Secondly RB may ionise, $RB \rightleftharpoons R^+ + B^-$, and then A^- combines

with R^+ : in this case there are two steps and of these the former, the splitting of RB, is much slower than the latter. The slow stage controls the speed of the overall reaction and as only one molecule is concerned in this the reaction is known as S_N1 (*substitution nucleophilic unimolecular*). It is clear therefore that the rate of an S_N2 reaction will be given by k[A][RB], and of an S_N1 reaction by k[RB] and a careful study of the reaction kinetics enables a decision to be reached as to the mechanism of a given reaction ; it is of course obvious that as usual, if one component of a bimolecular reaction is in such an excess that its concentration remains virtually constant during reaction, then that reaction will appear to be of the first order (pseudounimolecular).

There are various factors which affect the mechanism of reactions and some of these may be illustrated by considering the hydrolysis of alkyl halides. When such compounds are hydrolysed in aqueous ethanol with dilute alkali the reaction may be S_N2 or S_N1 ; in the case of methyl and ethyl bromides it is entirely S_N2, but tertiary butyl bromide is hydrolysed by the S_N1 mechanism and *iso*propyl bromide may be hydrolysed by either mechanism. It is clear that for an S_N1 reaction there must be a tendency for a bromide ion to be split off from the alkyl halide and this is assisted by the electron repulsion of the methyl groups in tertiary butyl (and to a less extent in *iso*propyl) bromide. Another factor is a steric one : in an S_N2 reaction the attacking group, ^-OH in this case, approaches the molecule at the face of the carbon tetrahedron opposite to the released group, thus giving a linear arrangement of the transition state, A . . . R . . . B. It has been shown theoretically that such an approach requires less energy than any other. This approach is clearly hindered in tertiary butyl bromide by the screening effect of the three methyl radicals. In the series CH_3Br, $MeCH_2Br$, Me_2CHBr, Me_3CBr the reaction mechanism therefore gradually changes from S_N2 to S_N1 owing to two factors, that is to say, the electron repulsion of the alkyl groups and the steric effect. The screening effect is also shown by the fact that *neo*pentyl halides, $Me_3C \cdot CH_2X$, react only very slowly by an S_N2 mechanism (X= halogen).

When the ionisation of hydrogen was considered it was shown how great an effect was produced by the stabilising of the anion by resonance and the same factor must be considered with regard to R^+ in an S_N1 reaction ; in an alkyl halide no stabilisation of this cation by mesomerism is possible (except possibly by hyper-

conjugation, p. 1013), but in an allyl halide, $CH_2{:}CH \cdot CH_2X$, it is so stabilised by dispersal of the charge over the whole molecule, which is a mesomeric form of $CH_2{:}CH \cdot CH_2^+$ and $^+CH_2 \cdot CH{:}CH_2$ (in this case the contributors to the mesomeric form are identical, as in the case of benzene). Allyl halides therefore often react rapidly by an S_N1 reaction and in the case of a substituted allyl compound the product of hydrolysis may be a mixture (pp. 695*m*, 840) as the entering group, A, can combine with the mesomeric ion in either of two different positions. The benzyl radical is similarly stabilised by resonance and the benzyl halides are very reactive.

Consideration of the vinyl and acyl halides shows how the facts must first be known before the theory can be applied. In a vinyl halide it is assumed that there is mesomerism between $CH_2{=}CH{-}X$ and $^-CH_2{-}CH{=}X^+$ and this is shown to be so by the fact that the carbon-halogen bond length is shorter than in an alkyl halide; this mesomerism prevents ionisation and hence an S_N1 reaction. In the case of an S_N2 reaction the ease of such change will depend on the positive charge on the carbon atom to which the halogen is attached and that charge is partially neutralised by the mesomerism so that this type of mechanism is also difficult.

Acyl halides, $O{=}CR{-}X$, might appear at first sight to be similar to the vinyl halides, and in order to account for the easy hydrolysis of the halogen atom in such compounds the stability of the transition state in the S_N2 reaction must be considered: this will be $^-O{-}CR(OH){-}X$ from an acyl halide and $^-CH_2{-}CH(OH){-}X$ from a vinyl halide, and it may be assumed that as oxygen is more electron attracting than carbon, the transition state with the charge on oxygen (from the acyl halide) is more stable than that with it on carbon (from the vinyl halide). An acyl halide is thus hydrolysed readily. Similarly the ready hydrolysis of esters and amides as compared with ethers and amines respectively is explained by the electron attraction of the carbonyl group and the fact that the charge of the transition state can be on an oxygen atom in esters and amides but not in ethers and amines. The steric consequences of the two types of nucleophilic substitutions are considered later (p. 753).

Hydrolysis and Esterification

It has been described above how the hydrolysis of esters of halogen acids can proceed by either an S_N1 or S_N2 mechanism: in the case

of esters of carboxylic acids the reaction is more complex, and similarly with the reverse process of esterification.

Firstly there are two ways in which the ester or carboxyl group may be split, as indicated by the dotted lines (M and R=hydrocarbon radicals),

$$\mathrm{M{\cdot}CO\,|\,OR{+}HO\,|\,H} \rightleftharpoons \mathrm{M{\cdot}CO\,|\,OH{+}H\,|\,OR} \quad (1)\ \mathrm{Ac}$$

$$\mathrm{M{\cdot}COO\,|\,R{+}H\,|\,OH} \rightleftharpoons \mathrm{M{\cdot}COO\,|\,H{+}HO\,|\,R} \quad (2)\ \mathrm{Al}$$

The former of these is known as *acyl-oxygen* (Ac) fission as union of the acyl group to oxygen is broken both in hydrolysis and esterification; the latter is *alkyl-oxygen* (Al) fission as the union of the alkyl group to oxygen is broken.

It has been found that alkaline hydrolysis of esters usually, but not invariably, involves Ac fission, (1), whilst acid hydrolysis or esterification (alkaline esterification, of course, does not occur) may proceed by either route according to the nature of M and R and the experimental conditions. In addition either reaction may be unimolecular or bimolecular and of the eight possibilities for hydrolysis, acid or alkaline, Ac or Al, unimolecular or bimolecular, six different mechanisms have been observed.

It is unnecessary to discuss all these, but some interesting points may be illustrated by a comparison of two modes of hydrolysis by alkali involving the bimolecular Ac and the unimolecular Al fission respectively; the mechanisms suggested for these processes are as follows:

Bimolecular Acyl-oxygen Fission

$$\mathrm{M{\cdot}COOR} \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}} \mathrm{M{\cdot}C(O^-){\cdot}OR} \underset{\text{slow}}{\overset{\text{fast}}{\rightleftharpoons}} \mathrm{M{\cdot}CO{\cdot}OH} \xrightarrow{\text{fast}} \mathrm{M{\cdot}CO{\cdot}O^-} \quad (1)$$

$$\mathrm{{}^-OH} \qquad\qquad \mathrm{OH} \qquad\qquad \mathrm{{}^-OR} \qquad\qquad \mathrm{H{\cdot}OR}$$

Unimolecular Alkyl-oxygen Fission

$$\mathrm{M{\cdot}COOR} \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}} \mathrm{M{\cdot}COO^- + R^+} \underset{\text{slow}\ (-H_2O)}{\overset{\text{fast}\ (+H_2O)}{\rightleftharpoons}} \mathrm{M{\cdot}COO^- + R{\cdot}OH_2^+} \xrightarrow{\text{fast}} \mathrm{M{\cdot}COOH + R{\cdot}OH} \quad (2)$$

In the former case the reaction is driven from left to right by the neutralisation of the acid by the alkali and in the latter by the final rapid transfer of a proton from $R \cdot OH_2^+$ to $M \cdot COO^-$: the order of the reactions is found in the usual way from kinetic experiments and is, of course, as usual controlled by the slowest stage.

The mode of fission is proved by using water containing isotopic oxygen (indicated by an asterisk) in the hydrolysis: if it is acyl-oxygen, (1), none of the isotopic oxygen appears in the alcohol produced, but in alkyl-oxygen fission, (2), the alcohol contains such oxygen:

$$M \cdot CO \,|\, OR + H\overset{*}{O}H = M \cdot C\overset{*}{O}OH + R \cdot OH \qquad (1)$$

$$M \cdot COO \,|\, R + H\overset{*}{O}H = M \cdot COOH + R \cdot \overset{*}{O}H \qquad (2)$$

Another difference between the two types of fission is that in (1) the group R is never parted from the oxygen to which it is attached, whereas in (2) the R—O bond is broken and during the reaction a free ion R^+ is produced. Two consequences follow. Firstly, if the alcohol is optically active and its hydroxyl group is one of the four radicals of an asymmetric carbon group, the alcohol formed by hydrolysis of an optically active ester by mechanism (1) retains its optical activity; in mechanism (2), however, the positive ion R^+ *i.e.* $(CXYZ)^+$, cannot retain its configuration and combines with the hydroxyl ion in the two possible ways to give the *d*- and *l*-alcohols in equal quantities, and racemisation results. Secondly, if R^+ has a structure which is mesomeric, as for example $CH_3 \cdot CH{:}CH \cdot CH_2^+$ (cf. p. 695*k*), the product of mechanism (2) may be

$$CH_3 \cdot CH{:}CH \cdot CH_2 \cdot OH \text{ or } CH_3 \cdot CH(OH) \cdot CH{:}CH_2$$

or a mixture of the two, whereas in mechanism (1) no such isomeric change is possible (cf. p. 840). These differences have been observed experimentally and one of the factors which determines whether mechanism (1) or (2) occurs is the concentration of the alkali; the rate of the slow stage of reaction (1) is controlled by the rate of attack of the carbon atom of the carboxyl group by the hydroxyl ion, but the rate of the slow stage of (2) is independent of the reagent. If then the concentration of hydroxyl ions is gradually diminished the rate of (1) will decrease and may finally fall below the rate of (2); the mechanism will then change from (1) to (2).

It thus often happens that racemisation of an optically active alcohol occurs when dilute alkali is used in the hydrolysis, (2), but not with concentrated alkali, (1), a result which was very difficult to understand before the mechanisms of the reactions had been elucidated.

Addition Reactions to the Carbonyl Group

Lapworth, from a kinetic investigation of the interaction of acetone and hydrogen cyanide, in which it was found that the rate of reaction was greatly increased by the addition of alkali, concluded that the first stage in the addition process was

$$Me_2\overset{+}{C}-\overset{-}{O}+CN^- \longrightarrow Me_2C(CN)O^-;$$

the intermediate ion then combines with a proton to give the cyanohydrin. Such an addition is therefore nucleophilic as the attacking negative ion is nucleus seeking. In the same way the addition of sodium hydrogen sulphite to aldehydes or ketones is initiated by $^-SO_3H$ which attaches itself to the positive carbon atom of the carbonyl group. With ammonia the unshared electron pair acts in a similar manner and the common condensations of the carbonyl radical with hydroxylamine, hydrazines, etc., are of the same type, only in these cases the final change is an elimination of water;

$$CH_3\cdot CHO \longrightarrow CH_3\cdot CH(\overset{-}{O})\cdot \overset{+}{N}H_2OH \longrightarrow CH_3\cdot CH{:}NOH+H_2O.$$

Reactivity of α-Hydrogen Atoms

One of the most useful groups of reactions in organic chemistry is that due to the reactivity of the hydrogen atoms on a carbon atom α- to a carbonyl, carbethoxy, cyano-, or other group of a similar kind or those hydrogen atoms attached to the same carbon atom as a nitro-group: these groups are often spoken of as negative groups and they are, in fact, all strongly electron attracting. Some of the reactions coming under this heading are the aldol reaction, the Claisen condensation and the Perkin reaction; the occurrence of them all, usually in the presence of a basic catalyst, is due to incipient ionisation of an α-hydrogen atom. In the aldol reaction, for example, the strong electron attraction of the carbonyl group allows a basic catalyst (^-OH) to remove a proton from the α-position to form a mesomeric anion,

$CH_3—CH\overset{\curvearrowright}{=}O + HO^- \longrightarrow {}^-CH_2—CH=O/CH_2=CH—O^- + H_2O$,[1]

which then undergoes nucleophilic addition to another molecule of the aldehyde. Addition of a proton completes the reaction,

$$CH_3—\overset{+}{C}H—\overset{-}{O} + {}^-CH_2—CHO \longrightarrow CH_3—CH(\overset{-}{O})—CH_2—CHO \longrightarrow CH_3—CH(OH)—CH_2—CHO.$$

The Claisen reaction is very similar and is discussed later (p. 826).

Addition to the Ethylenic Linkage

Addition to an ethylenic linkage is similar to that to a carbonyl group in that polarisation or electromeric change precedes addition. That this is in fact the mechanism of addition was indicated by the experiments of Lowry and Norrish on the interaction of bromine and ethylene: it was found that combination only occurs very slowly in a vessel coated internally with paraffin wax, faster when stearic acid was the coating agent and still more rapidly in an uncoated glass vessel. The explanation is that the surface of the containing vessel acts catalytically in bringing about the polarisation of the ethylenic linkage and the more polar the surface the greater the effect. The mechanism of the addition of bromine to ethylene is now assumed to be

$$\overset{+}{C}H_2—\overset{-}{C}H_2 + Br^+ \longrightarrow \overset{+}{C}H_2—CH_2Br \xrightarrow{Br^-} CH_2Br—CH_2Br$$

and there is further evidence for this view. That it is indeed the positive bromide ion which adds first is indicated by the fact that bromine in the presence of aqueous sodium chloride gives a chlorobromide, in the presence of water gives a bromohydrin, and of a nitrate gives a bromo-nitrate,

$$\begin{aligned} {}^+CH_2—CH_2Br + Cl^- &\longrightarrow CH_2Cl—CH_2Br, \\ {}^+CH_2—CH_2Br + OH^- &\longrightarrow CH_2(OH)—CH_2Br, \\ {}^+CH_2—CH_2Br + NO_3^- &\longrightarrow CH_2(NO_3)—CH_2Br. \end{aligned}$$

The formation of the bromohydrin is suppressed by the addition of potassium bromide which, of course, increases the concentration of negative bromide ions required for the second stage of the addition of bromine. It is to be noted that this type of addition is

[1] The contributors to the mesomeric ion (molecule) are separated by the sloping line /.

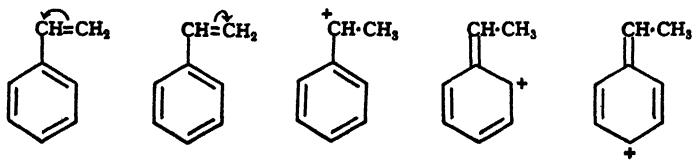
initiated by an electrophilic reagent, Br^+, and is quite different from the nucleophilic addition to the carbonyl group, but there is no clear explanation of this; in ethylene an electromeric change giving a negative charge to one carbon atom must obviously give an identical positive charge to the other, which should then be reactive towards nucleophilic reagents. When the double bond is conjugated with a carbonyl group (p. 825), it is so reactive, but not otherwise.

It is assumed by analogy from the addition of bromine (and other halogens) that when a halogen acid adds to ethylene the reaction is also electrophilic and that a proton adds first, followed by a negative halide ion. In substituted ethylenes the direction of the electromeric change is controlled by the substituents: in propylene, for example, the electron repelling inductive effect of the methyl group gives (I) and the positive hydrogen adds to the

I $CH_3 \longrightarrow CH{=}CH_2$ II $CH_2{=}CH{-}C{=}O(OH)$

CH_2 group (Markownikoff rule, pp. 95, 804). In acrylic acid the carbonyl group controls the electromeric change (II) and the product is β-bromopropionic acid. If the carboxyl group is further away from the double bond the inductive effect is lost and undecylenic acid, $CH_2{:}CH\cdot[CH_2]_9\cdot COOH$, for example, gives $CH_3\cdot CHBr\cdot[CH_2]_9\cdot COOH$ with hydrogen bromide.

When the case of styrene is considered difficulties arise. Electromeric change could give either (III) or (IV), and might be expected to give the former; when substitution in the nucleus is considered (p. 1012), in fact, (III) is assumed to occur. If this were the direction of change when hydrogen bromide is added the intermediate state would be $Ph\cdot CH_2\cdot CH_2^+$, and the final product $Ph\cdot CH_2\cdot CH_2Br$ whereas it is in fact $Ph\cdot CHBr\cdot CH_3$; it is assumed that the intermediate ion, (V), from (IV) is stabilised by mesomerism (V, VI and VII) which cannot be so with $Ph\cdot CH_2\cdot CH_2^+$:



III IV V VI VII

at first sight it seems very unsatisfactory to have to bring in new assumptions to account for the facts, but it can be shown that in the cases considered earlier the intermediate states in the explanations given are also the most stable. In the vinyl halides electromeric change to $^{-}CH_2—CH=X^{+}$ has already been assumed and the product of addition would therefore be $CH_3—CHX_2$ in accordance with experiment. The stereochemistry of additions to ethylenic linkages is considered later (p. 712), as are the peroxide effect (p. 805) and additions to a conjugated chain (p. 813).

Ferrocene

*Cyclo*pentadiene reacts with Grignard reagents in a similar manner to acetylene and with methyl magnesium iodide, for example, yields *cyclo*pentadienyl magnesium iodide; when this Grignard reagent reacts with ferric chloride, some of the latter is reduced and the ferrous chloride so formed is further changed by excess of the Grignard reagent,

$$2C_5H_5MgBr+FeCl_2=(C_5H_5)_2Fe+MgBr_2+MgCl_2;$$

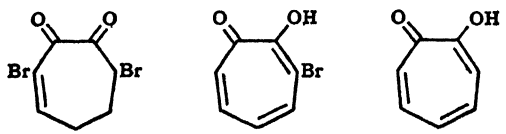
a very interesting compound, di*cyclo*pentadienyl iron, which has been given the name *ferrocene*, is produced.

Ferrocene is a typical co-valent compound; it melts at 173°, is soluble in organic solvents, is readily volatile, and may be distilled in steam. Its chemical reactions are those of an aromatic compound; it shows no additive reactions, but it can be sulphonated, undergoes acetylation by the Friedel-Crafts method and can be mercurated. Other typical aromatic substitutions such as nitration and chlorination are complicated by the fact that ferrocene is readily oxidised. The structure of ferrocene cannot be written in a classical manner, but the iron atom is bound symmetrically to all five carbon atoms of each ring by a single co-valent bond resonating equally between the five carbon atoms of each ring: each ring therefore has the aromatic sextet with consequent aromatic properties. It is interesting to note that it has been shown that in solution (or in the molten state) the two rings are free to rotate about an axis vertical to the planes of the rings. Compounds similar to ferrocene have been obtained in which the metal atom is cobalt, nickel, chromium, vanadium, magnesium and other metals, and in some such compounds the metal carries a charge, e.g. $(C_5H_5)_2Ti^{+}$.

Tropolones

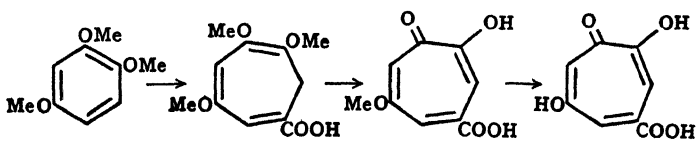
Tropolone, α-hydroxy*cyclo*heptatrienone, (III), and its derivatives are a very interesting group of compounds the chemistry of which has been studied mainly in the last ten years after their fundamental structure had been suggested by M. J. S. Dewar. Various methods of preparation are known, but on the whole they are not very readily accessible as either the starting products for syntheses are themselves difficult to make or the yields in the syntheses are poor.

Tropolone itself has been prepared as follows: *cyclo*heptanone is oxidised with selenium dioxide to *cyclo*hepta-1:2-dione and the latter is brominated; the product, (I), which is probably formed by the elimination of hydrogen bromide from a tribromide, is treated with alkali to give (II) which on reduction with hydrogen in the presence of palladium-charcoal gives tropolone, (III):



I II III

Another general method for the preparation of tropolone derivatives involves enlarging an aromatic ring by the use of diazomethane or ethyl diazoacetate: using this method Johnson and his co-workers synthesised stipitatic acid, an important naturally occurring tropolone derivative, by the series of reactions shown:

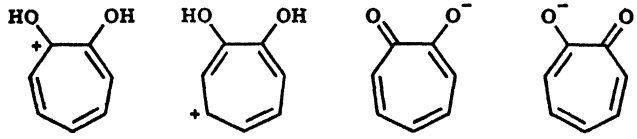


IV V VI

1:2:4-Trimethoxybenzene with ethyl diazoacetate gives first a substance with a *cyclo*propane ring fused to the six membered ring (p. 781) which then spontaneously gives the seven membered ring compound, (IV); the addition of bromine causes demethylation and oxidation to give (V), which is demethylated with hydrobromic acid

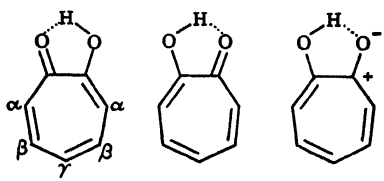
to stipitatic acid, (VI). It is to be noted that this synthesis does not prove conclusively the structure of the acid, but there is other evidence for this.

The properties of tropolone are very interesting; it gives salts with acids such as the hydrochloride and benzoate and is also acidic: the ion present in its salts with acids is a mesomeric form of (I), (II), etc., in which the seven ring carbon atoms have six unlocalised electrons between them forming an aromatic sextet. The positive charge is distributed over the whole system. The anion of the sodium salt is also mesomeric, (III) and (IV):



I II III IV

Tropolone shows the high volatility of an internally hydrogen bonded compound (compare *o*-nitrophenol and enol ethyl acetoacetate) and is also tautomeric, (V) and (VI); it is also probable that forms such as (VII) contribute to the final mesomeric structure giving the ring once again an aromatic sextet:



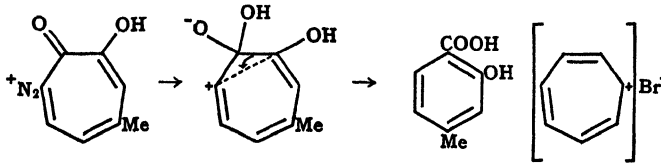
V VI VII

In agreement with these views X-ray analysis of the copper salt of tropolone shows the ring to be an almost regular heptagon with a carbon-carbon bond length of 1.4 A.U. and calorimetric measurements give a resonance energy of 33,000-36,000 cal. compared with that of 36,000 cal. for benzene.

Tropolone shows no ketonic properties and when the hydroxyl group is methylated with diazomethane, dimethyl sulphate and alkali or methyl alcoholic hydrogen chloride the product is easily hydro-

lysed and reacts with ammonia like an ester rather than like an ether: similarly the acyl derivatives are not easily prepared by direct acylation and behave as acid anhydrides rather than as esters. If the structure of tropolone is studied it will be seen that the $>CO$ and $\geqslant C \cdot OH$ groups are joined round the ring by a conjugated chain and might then be expected to behave like a simple carboxyl radical.

Tropolone shows no ethylenic properties: with bromine in acetic acid it gives a mono-substitution derivative. It also shows aromatic properties in that it can be nitrated and sulphonated in the α- and γ-positions and couples with diazonium salts in the γ-position; γ-aminotropolones can be diazotised in the usual way. β-Aminotropolones, however, give the corresponding hydroxy compounds with nitrous acid even at $-20°$ and the α-amino-compounds usually undergo isomeric change and give derivatives of salicylic acid:



VIII

Similar rearrangements to benzene derivatives are shown by many tropolone derivatives with alkaline reagents. Many tropolone derivatives are products of mould metabolism.

Another very interesting compound related to tropolone has been prepared by heating the dibromide of *cyclo*heptatriene: a molecule of hydrogen bromide is lost and *tropylium bromide* is formed. In this substance so great is the tendency to form the aromatic system that it is salt like, soluble in water, insoluble in organic solvents and gives an instantaneous precipitate with silver nitrate; it should therefore be represented as a mesomeric cation combined with the bromide ion (VIII).

CHAPTER 44

THE PHYSICAL PROPERTIES OF ORGANIC COMPOUNDS

FROM the earliest days of structural organic chemistry relationships between physical properties and structure have been examined, and attention has already been drawn in Part I to regular variations in the melting-point, boiling-point and solubility in water of members of a homologous series. Such relationships are for the most part more or less limited and empirical and afford little evidence of structure in the case of compounds whose constitutions are unknown. A study of the behaviour of molecules towards electro-magnetic waves has, however, given much more valuable results, and in many cases, theoretical considerations support the experimental findings. Among such effects are molecular refraction, molecular rotation, absorption spectra, X-ray analysis, dipole moments, nuclear magnetic resonance and magnetic susceptibility. One outstanding advantage of physical methods for the determination of structure, particularly in the case of natural products whose isolation and purification except in very small quantities may be a very difficult task, is that all the material used in the examination is recovered unchanged; another is that the compound examined is not submitted to the action of reagents which might produce structural changes.

A brief account of the more important of these methods follows and also a mention of heats of combustion; this is strictly speaking a chemical method, but it gives the most direct evidence of the relative stabilities of molecules.

Melting-point. The melting-points of corresponding members of a homologous series either rise continuously, or rise and fall alternately as the series is ascended; in both cases they finally attain a nearly constant value. The paraffins afford an example of a continuous rise, the fatty acids of an alternating one (p. 183), since those normal acids containing an odd number of carbon atoms melt at a lower temperature than the preceding normal member containing an even number of carbon atoms; the melting-points gradually

approach constancy at 60–70°. A similar alternation holds for the normal dibasic acids, as is shown in the following table :

Melting-points of Normal Dibasic Acids

No. of carbon atoms	M.p.	No. of carbon atoms	M.p.
3	136°	4	185°
5	97°	6	151°
7	105°	8	144°
9	106°	10	133°
11	110°	12	129°
13	114°	14	126·5°
15	114°	16	123°
17	118°	18	124°

X-ray investigation has shown that this alternation of melting-points depends on the way in which the long zig-zag chain molecules are arranged in the crystals and that those of the even-numbered are more closely packed than those of the odd-numbered acids ; this is confirmed by the values for the heats of crystallisation of the acids (Piper, *J.* 1929, 234).[1]

Of any three isomeric di-substitution products of benzene, the *p*-derivative usually melts at the highest temperature. When the two substituents are both *op*- or both *m*-directing then the melting-point of the *o*-derivative is often higher than that of the *m*-, but if the two substituents are of different directing power then the *m*-isomeride has the higher melting-point :

	M.p. *o*-	M.p. *m*-	M.p. *p*-
Nitrophenols	45°	96°	112°
Dibromobenzenes	7·8°	−6·5°	89°
Dinitrobenzenes	118°	90°	173°
Dihydroxybenzenes	104°	119°	169°
Nitroanilines	71°	114°	147°
Phenylenediamines	102°	63°	147°

The melting-points of geometrical isomerides are considered on p. 710.

[1] A list of the abbreviations used in references to the literature is given on p. 1130.

The determination of a melting-point is not only of great practical importance for ascertaining the purity or the identity of a compound, but may also be used for finding the proportions of two compounds in a mixture (thermal analysis). Thus, in the investigation of aromatic substitution the proportions of, say, *o*- and *p*-derivatives may be ascertained without separating the two substances, provided that the complete melting-point curve of the mixture has been ascertained with the aid of the two pure compounds ; the observed melting-point of the unknown mixture lies somewhere on that curve, and its position, determined experimentally, may show the proportions of the two components.

Many organic substances, particularly azo- and azoxy-compounds, melt first to a doubly refracting ' crystalline liquid ' or ' liquid crystal,' which when further heated becomes clear. When the liquid is cooled the reverse changes are observed.

Boiling-point. In a homologous series, the boiling-point usually rises in a regular manner as the series is ascended, with an approximately constant difference between the boiling-points of successive members except the first two (pp. 63, 121, 181).

In the case of isomerides, the normal compound has the highest, and that in which the largest number of carbon atoms is attached to a single atom has usually the lowest, boiling-point :

n-Pentane	b.p. 36°	*n*-Valeric acid	b.p. 186°
*Iso*pentane	b.p. 28°	*Iso*valeric acid	b.p. 176°
Tetramethylmethane	b.p. 9·5°	Methylethylacetic acid	b.p. 175°
		Trimethylacetic acid	b.p. 163°

Similarly, with isomeric alcohols (and isomeric halides), the primary compounds have the highest, and the tertiary the lowest, boiling-point :

n-Butyl alcohol	b.p. 117°	Methylethyl carbinol	b.p. 99°
*Iso*butyl alcohol	b.p. 108°	Trimethyl carbinol	b.p. 83°

The substitution of a hydroxyl group for a hydrogen atom of a hydrocarbon usually raises the boiling-point by about 80–120° :

n-Butane	b.p. −0·5°	*Cyclo*hexane	b.p. 81°
n-Butyl alcohol	b.p. 117°	*Cyclo*hexanol	b.p. 161°
		Benzene	b.p. 80°
		Phenol	b.p. 183°

In this case the attraction between the molecules is increased by hydrogen bonding and by large dipole moments and often causes association ; in the ethers where hydrogen bonding is absent, the boiling-point is usually below that of the isomeric alcohols. Compounds in which internal hydrogen bonding is possible often have lower boiling-points than isomeric compounds in which such bonding is impossible ; thus *o*-nitrophenol is more volatile than the *p*-compound, and the enol-form of ethyl acetoacetate boils at a lower temperature than the keto-form (p. 833).

Solubility. Organic compounds are usually good examples of the rule that similar compounds dissolve one another. Hydrocarbons and their halogen derivatives are usually sparingly soluble in water but soluble in one another. The introduction of oxygen, especially in the form of hydroxyl groups, increases the solubility in water owing to the combined effects of hydrogen bonding (between solute and solvent) and dipole attractions. Polyhydroxy compounds (glycerol, sugars, polyphenols) show this effect very markedly. The long chain alcohols such as dodecyl alcohol exhibit surface solubility, the effect of one hydroxyl group is not sufficient to make the whole molecule soluble in water, but the water surface becomes covered with an orientated film of molecules with the hydroxyl groups immersed in the water. In macromolecules like starch the attraction between water and the large molecule leads to the formation of a jelly. Molecules containing two or more hydroxyl groups in not too large a hydrocarbon skeleton usually have a sweet taste (glycol, glycerol, sugars).

Other groups which notably enhance the solubility in water are $-NH_2$, $-COOH$, and particularly $-SO_3H$, and here, as in the case of hydroxy-compounds, the solubility depends on the molecular weight (and structure) of the hydrocarbon radical as well as on the number and nature of the substituent groups. The sulphates and sulphonates of the higher hydrocarbons show surface solubility (detergents). Ethers are generally very sparingly soluble, and esters also, except those very rich in oxygen, such as dimethyl oxalate.

Compounds which are soluble in water may also be soluble in the lower alcohols and ketones ; those which are sparingly soluble or insoluble in water, salts excepted, usually dissolve in benzene, chloroform, carbon tetrachloride, and other compounds free from oxygen.

As a general rule compounds containing atoms united by electro-

valencies (electrolytes) are insoluble in hydrocarbons and allied solvents, comparatively non-volatile and have a high melting-point, whereas those containing only atoms united by co-valencies are usually soluble in hydrocarbon solvents, volatile, and have a low melting-point.

Molecular Volume and Parachor. The molecular volume is the volume in cubic centimetres occupied by one gram molecule of a compound, and more than a century ago Kopp worked on this property. Sugden (1942) introduced the term parachor to denote a constant which compares molecular volumes under conditions of equal surface tension. Both these properties were at one time used for the determination of structure, because both depend on constitution, but few useful results were obtained from their use. They are dealt with more fully in previous editions of this book.

Molecular Refraction. The molecular refraction (R) of a compound is calculated from the formula $R=(n^2-1)M/(n^2+2)D$, where n = refractive index, M = molecular weight, and D = density (Lorentz and Lorenz). It is necessary to use monochromatic light in determining n, since its value depends on the wave-length. From the results of determinations made with suitably chosen compounds of known structure it has been found that the molecular refraction is dependent on constitution and, for example, an open chain olefine has a higher value than an isomeric 5- or 6-membered ring compound : it is possible to ascertain, therefore, from the molecular refraction of a substance of unknown structure whether the compound is cyclic or an open chain olefine, a point of very considerable importance in the study of the sesquiterpenes. It is also possible to distinguish between ketonic and enolic forms, since the values of R for —CO—CH_2— and —C(OH)=CH— show a sufficient difference.

More delicate constitutive effects are often shown ; open chain conjugated systems (p. 815), for example, may show optical *exaltation*, and give a value of R, greater than that calculated for two isolated double bonds :

		R obs.	R calc.
Diallyl	$CH_2=CH\cdot CH_2\cdot CH_2\cdot CH=CH_2$	28·77	28·74
Hexa-2:4-diene	$CH_3\cdot CH=CH\cdot CH=CH\cdot CH_3$	30·46	

This exaltation is greatly reduced by the substitution of alkyl groups for the central hydrogen atoms of the system, but is increased when the substituents are —OH or —OMe. A similar exaltation

is shown by conjugation of the double bond with the carbonyl group as in carvone and pulegone (p. 922).

*Cyclo*pentadiene (p. 789), instead of exaltation, shows optical *depression*, and gives a molecular refraction less than that calculated for two isolated double bindings, as do furan, pyrrole and thiophene. Δ-1:4-*Cyclo*hexadiene (p. 799) shows the normal behaviour of a non-conjugated diolefine, but benzene shows a slight optical depression.

Molecular Rotation. The method for the determination of the specific and the molecular rotations of compounds has already been given (p. 308), and the relations between molecular rotation and structure are briefly referred to later (p. 744); the phenomenon of *rotatory dispersion* is also mentioned (p. 743).

Absorption Spectra. The internal energy of the molecules of an organic compound is increased by light absorption and the molecules thereby become excited; the absorbed energy may increase either the electronic or the vibrational or the rotational energy of the molecules and with a given molecule only radiation of particular wave-lengths is effective for increasing each sort of energy, and from continuous radiation absorption spectra are therefore produced. In studying absorption spectra it is usual to divide the spectrum more or less arbitrarily thus:

Micro-wave	10–0·1 cm.
Infra-red	1–100 μ ($1\ \mu = 10^{-4}$ cm.)
Visible	4,000-8,000 A.U. (1 A.U. $= 10^{-8}$ cm.)
Ultra-violet	1,000-4,000 A.U.

The energy required to increase the electronic energy of a molecule is greatest, and to increase the rotational energy the least; and in general, absorption in the visible and ultra-violet indicates changes in the electronic energy, whereas infra-red absorption causes only changes in vibrational and rotational energy. Electronic changes require more energy the more firmly bound are the electrons, and hence the alkanes with their very firmly bound electrons absorb in the far ultra-violet whereas the alkenes show fairly strong absorption at 1,800-2,000 A.U. due to the less firmly bound electrons of the double bond. In the conjugated dienes such as butadiene a very strongly absorbing band at 2,170 A.U. appears which is characteristic and has been used for confirming the structure of terpenes, steroids and other compounds, as it lies in the more readily accessible ultra-

violet region (>2,000 A.U.). Conjugation of a double bond with an aromatic nucleus as in styrene also produces a strongly absorbing band in the same region. Carbonyl unsaturation gives rise to a fairly strong absorption band at about 1,850 A.U., characteristic of aldehydes and ketones, and strongly affected by conjugation either with aromatic systems as in benzaldehyde or with ethylenic systems as in mesityl oxide and crotonaldehyde. These bands have been used in the determination of structure, thus it was found that the absorption spectra of mesityl oxide and of carvone showed similar bands, confirming the similarity of structure.

The relation between colour and structure in organic compounds has already been considered in Chapter 42 and since absorption in the visible region is broadly speaking due to transitions similar to those giving rise to ultra-violet absorption a close relation between absorption in these two regions is indicated. This has been confirmed by studies on the polyenes (p. 982).

Absorption in the infra-red region depends upon the inter-atomic vibrational and the rotational frequencies of the molecule. From observations of such spectra the inter-atomic forces, distances and angles may be calculated. Although molecules vibrate as a whole, yet in some cases the vibration of part of the molecule may be little affected by changes in the rest of the molecule. Thus in the alcohols there is a characteristic band at 2·73–2·83 μ whose presence can be used to detect the hydroxyl group and whose removal to about 3μ provides evidence of hydrogen bonding. In *o*-nitrophenol the band is at even longer wave-length and difficult to observe, indicating chelation.

Closely connected with infra-red absorption is the Raman effect. When light of a given frequency is incident upon a dust-free liquid a portion of the scattered light is observed to have its frequency altered by an amount depending on the nature of the compound. These changes in frequency of Raman lines relative to that of the incident light correspond to vibrational and rotational frequencies. They are often complementary to the infra-red absorption effects and in a similar way show characteristic values for particular groups. The Raman and infra-red spectra of ferrocene are important as indicating that it has a highly symmetrical molecular structure.

Colorimetric methods have long been used in organic chemistry, pure and applied, and with the improvements in ultra-violet and infra-red spectroscopy similar methods are now used in these

spectral regions. Infra-red spectroscopy has proved especially valuable in the examination of hydrocarbon mixtures in the petroleum industry, the intensities of the bands giving quantitative data of the occurrence of individual compounds. It may be added that absorption spectra may be mapped not only for pure liquids but also for solutions of solids or liquids in solvents which have little (known) absorption and even for crystalline powders by suspending them in liquids of known absorption.

X-ray Crystal Analysis. The diffraction of X-rays by the molecules of a crystal, suitably examined in an apparatus more or less analogous to a spectrometer, and recorded on a photographic plate, give a pattern from which a picture of the structure of the molecules may be deduced; X-ray analysis, as shown by W. H. and W. L. Bragg, is, in fact, a very valuable method for determining the disposition of the atoms in a molecule, but the interpretation of X-ray data is by no means easy. A unique answer to the problem of the structure of the compound examined is rarely given, but a decision between two or more suggested formulae is usually possible and the method was of very great value in the examination of the sterols, penicillin and vitamin B_{12}. In the case of the phthalocyanines, examined by J. M. Robertson, a complete answer was provided.

X-ray analysis has also shown that many substances which were hitherto classed as amorphous, as, for example, cellulose, rubber and some of the fibrous proteins, have a structure approaching that of crystals, which can be seen when the molecules are suitably aligned. The now generally accepted helical structure of certain proteins is based mainly on the work of Astbury and Pauling.

The values of inter-atomic distances may often be found from X-ray data and those of carbon to carbon are important. Carbon atoms united by single, double and treble bonds are said to have bond orders of one, two and three respectively and each type of bond has a characteristic length, C—C, 1·54; C=C, 1·33, C≡C, 1·21 A.U.; the bond order may therefore be found by measuring the bond length. In compounds where the nature of the bond is intermediate between single and double owing to mesomerism, the bond order is between one and two and the bond length also intermediate, as in benzene (p. 1002).

Dipole Moments. When, in a molecule, the electrical centre (analogous to the centre of gravity) of all the protons does not coin-

cide with that of all the electrons, the molecule has a permanent electrical moment, which is known as its *dipole moment*, μ. If the electrical charges be represented by $+e$ and $-e$ respectively, and the distance between them by d, it follows that $\mu=ed$. This conception is due to Debye, who has published many papers on the subject.

The theoretical considerations involved in the experimental determination of μ are not given here, but it may be noted that measurements of the dielectric constant and refractive index of a compound afford the necessary data.

Determinations of the dipole moments of a large number of substances have now been made, by several different methods, and among other results, important conclusions with regard to the spatial arrangements of some of the atoms of certain molecules have been drawn. In the case of water, for example, if the oxygen and the two hydrogen atoms lie in a straight line, then it would appear that the electrical centres of the protons and electrons must coincide and the dipole moment would be zero; actually, however, water has an appreciable moment. This result can be explained if the atoms, instead of being in a line, are situated at the corners of a triangle, and on the assumption that the four pairs of electrons of the oxygen octet occupy the corners of a tetrahedron, the molecule of water may be represented by Fig. 24, and the angle between the two H—O bonds (valency angle of oxygen) would be 109° for a regular tetrahedron.

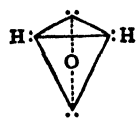


Fig. 24

Such a spatial arrangement does not in fact agree very well with the actual value for the dipole moment, but the results show that the molecule is not linear. Wave-mechanical calculations and infra-red spectra lead to the conclusion that the H—O—H angle is in fact about 105°.

From a measurement of the dipole moment of ammonia, it is concluded that the three hydrogen atoms are arranged at three corners of a tetrahedron of which the nitrogen atom occupies the fourth, a conclusion which is confirmed by spectroscopic evidence.

Methane and carbon tetrachloride have zero moments, in accordance with their accepted configurations, and a further study of other physical properties of the hydrocarbon confirms the regular tetrahedral configuration of the molecule. All saturated aliphatic hydrocarbons derived from methane have a zero moment, and this is also true in the case of benzene, diphenyl, and some symmetrically substituted benzene derivatives such as *p*-dichlorobenzene and 1:3:5-trichlorobenzene. Certain symmetrical benzene derivatives, such as *p*-diethoxybenzene, have, however, a dipole moment; this fact may be accounted for in a manner similar to that given in the case of water, that is to say, by assuming that the bonds joining the oxygen atom to the ethyl group and to the benzene nucleus are not in a line. Dipole moments are also shown by *p*-dialkylamino-derivatives of benzene, and may be accounted for in a similar manner.

Dipole moments have been of great value in the detection of restricted rotation. The *cis-* and *trans-* isomerides of substituted ethylenes, where free rotation is prevented show marked differences (p. 711). 1:2-Dichloroethane has a dipole moment which varies with the temperature and as the latter is raised approaches that calculated for uninhibited rotation of the two $-CH_2Cl$ groups; an energy barrier to free rotation is thus indicated (p. 796).

Evidence of resonance is also afforded by dipole moments. Thus in the nitro-group the dipole moment of (I) would be directed along the line of the co-ordinate bond, and not along that of the union of the nitro group to the rest of the molecule. If that structure were correct, therefore, *p*-dinitrobenzene would be analogous to *p*-diethoxybenzene, and would show a dipole moment; actually it appears to have a zero moment. Now in the mesomeric state represented here by (II) the moment of the nitro-group will lie along the line of the bond joining the group to the rest of the molecule; in *p*-dinitrobenzene, therefore, the two moments will exactly oppose one another and the result will be in accordance with experiment.

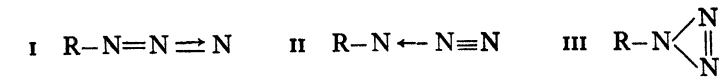


I II

Measurements of the electron diffraction[1] of methyl azide vapour

[1] A beam of electrons is diffracted by the atoms in much the same way as a beam of light by a diffraction grating.

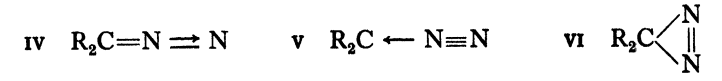
have shown that the three nitrogen atoms are linear, and a similar structure may, therefore, be inferred for all azides. It is possible, however, to write two linear formulae for an organic azide, namely, (I) and (II), and both structures will represent molecules having



large dipole moments, in opposite directions in the two cases. Now it can be calculated that if R is C_6H_5, each would have a moment of at least 4×10^{-18} e.s.u.; but the actual value is $1{\cdot}5\times10^{-18}$ e.s.u., with the negative end remote from the nucleus. These facts indicate that resonance occurs and that the actual state of the group probably approaches more nearly to (I) than to (II). A tautomeric mixture of (I) and (II) would give a moment between those of the two forms, as a mixture of highly polar substances will also be highly polar.

A study of their heats of combustion confirms the view that the azides exist in the mesomeric form of (I) and (II), and cannot be represented by the conceivable ring structure (III).

Dipole moment measurements have also shown that the aliphatic diazo-compounds cannot have either of the structures (IV) or (V), but might exist in their mesomeric state or else have the ring structure, (VI). Electron diffraction measurements, however, prove conclusively that (VI) is untenable, so that the resonance form of (IV) and (V) is inferred.



Measurements of the dipole moments of *iso*nitriles point to the formula R–N≡C. Further examples of the application of dipole moments to questions of structure or configuration are given later (see index).

Nuclear Magnetic Resonance. When an atom is placed in a magnetic field its nucleus may absorb electromagnetic radiation of a definite frequency, depending on the environment of the atom; this causes absorption lines in the field spectrum and is known as nuclear magnetic resonance. Particularly important from the point of view of organic chemistry is proton magnetic resonance shown by the hydrogen nucleus, whilst carbon and oxygen nuclei

show no resonance and hence cause no magnetic resonance spectra. The spectrum of hydrogen varies according to the neighbouring groups : in ethyl alcohol, for example, different resonance peaks of intensities in the ratio 3:2:1 correspond to the protons in the methyl, methylene and hydroxyl groups respectively. It is possible therefore to detect these groups and to determine their number even in quite complex molecules, such as sugars. It would appear that this method of investigating structure may prove of very great value in the future as it is one of the most direct ways in which hydrogen atoms show up, as it were.

Magnetic Susceptibility. Electrons in an atom or molecule give rise to two magnetic effects. The so-called spin of the electron produces a magnetic field so that each electron behaves like a small magnet. Secondly, the electrons in the various orbitals produce by their motion another magnetic field. This is much smaller than the spin field. In an ordinary two-electron single bond the two electrons must be of opposite spin and so their electrical moments cancel. When an odd electron is present as in a free radical, the molecule behaves like a magnet and the compound shows paramagnetic susceptibility, that is to say, it is attracted by a magnet. The measurement of paramagnetism has been of great use in the detection of free radicals and the determination of the extent of dissociation of molecules into such radicals.

In a normal organic molecule in which no unpaired electrons exist the molecule as a whole is repelled weakly by a magnet, i.e. it shows diamagnetic susceptibility. Pascal has shown that this property is additive and constitutive and it has been used in resolving questions of constitution. In measuring paramagnetic susceptibility correction has to be made for the (usually much) smaller diamagnetic effect.

Heat of Combustion. An important regularity observed in a study of the heats of combustion or organic compounds is that, in a homologous series, the addition of a methylene group, ($>CH_2$), to the molecule produces a nearly constant increase (154 Cal. per gm. mol.) in the heat of combustion. That the property is not entirely additive, however, is seen from the difference between the heats of combustion of isomeric substances. Further, a molecule in any condition of strain, such as is due to a double or treble bond, or to a small ring structure, gives a greater heat of combustion than that calculated from the values obtained for corresponding saturated

open-chain compounds (p. 790), and indeed the heat of combustion is a direct measure of the stability of a molecule. Consequently a molecule showing resonance has a smaller heat of combustion than that calculated for any one of its contributors, and the difference is the resonance energy, as in the case of benzene (p. 391).

Another example is that a molecule containing a conjugated system of double bonds (p. 815) has generally a smaller heat of combustion than that of an isomeric compound with the same number of isolated double bonds ; the conjugated system is thus more stable and this is also due to resonance.

The determination of resonance energies from heats of combustion involves the subtraction of two large quantities and leads to considerable errors in these differences. Kistiakowsky (1935) measured the heats of hydrogenation of unsaturated compounds ; these are much smaller than heats of combustion; as apart from other causes only the unsaturated bonds are affected, and allow of more accurate calculations of resonance energy.

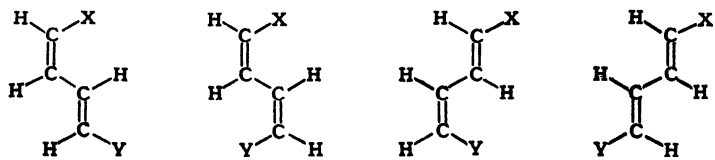
Heats of formation may be calculated from heats of combustion and from them bond energies and bond strengths.

CHAPTER 45

GEOMETRICAL ISOMERISM

A SHORT description has already been given (pp. 347, 528) of the phenomenon of geometrical isomerism in the case of compounds, CRX=CR'X', where R and R' or X and X' are either identical or different atoms or groups of *any kind*. Even a simple substance, such as symmetrical dichloroethylene, CHCl:CHCl, may exist in *cis*- and *trans*-forms, and corresponding isomerides are known in the case of stilbene (diphenylethylene), CHPh:CHPh (p. 565), and many other ethylenic derivatives.

The presence of a second ethylenic linkage in a substituted carbon chain increases considerably the number of possible isomerides. Thus the most familiar diolefinic derivatives, namely those such as the compound, CHX=CH—CH=CHY, which contain conjugated systems (p. 813), may exist in the four stereoisomeric forms shown below : [1]



I II III IV

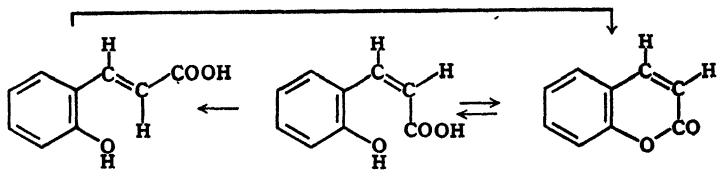
In general the number of geometrical isomerides of this type of olefinic compound is 2^n, where n = the number of double bonds. If, however, the two ends of the chain are identical (X = Y), the number of possible forms is reduced; in the above case, for instance, (I) would be identical with (III). More complex examples of this sort of isomerism are mentioned later (p. 982).

Now it is possible in many cases to determine the *configurations* of such *cis*- and *trans*-isomerides, and one example of this has already been given, namely that of maleic and fumaric acids (p. 349).

Another of a similar type is that of the two stereoisomeric o-*hydroxycinnamic acids*, known as *coumarinic acid* and *coumaric*

[1] This and many other matters concerning geometrical isomerism should be studied with the aid of the models already mentioned (p. 297).

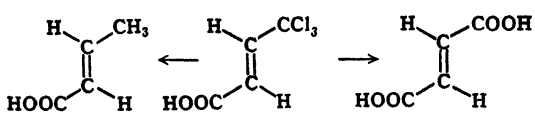
acid respectively. The former loses a molecule of water spontaneously, yielding coumarin (p. 986), which is reconverted into a salt of coumarinic acid by alkali; coumaric acid also yields coumarin, but only when it is heated with hydrobromic acid. Concentrated boiling alkalis convert coumarinic acid into coumaric acid. These facts seem to prove that coumaric acid is the *trans*-isomeride, as shown below, because it is only in the *cis*-acid that the carboxyl and hydroxyl groups are suitably situated in space for the formation of a closed chain.



Coumaric acid Coumarinic acid Coumarin

The stereoisomeric o-*aminocinnamic acids* behave in a similar manner; one (the *cis*-form) loses a molecule of water, yielding a closed chain lactam, α-hydroxyquinoline (carbostyril), whilst the other (the *trans*-form) does not.

These examples show that if one of the stereoisomerides is readily converted into a closed chain and the other is not, their configurations may be determined with a high degree of probability. In many cases, however, the two forms cannot be distinguished in this way, and other methods must be used. Thus, of the two stereoisomeric crotonic acids (p. 350), one (crotonic acid, m.p. 72°) may be obtained by the reduction of one of the stereoisomeric trichlorocrotonic acids;[1] this trichlorocrotonic acid, on hydrolysis, gives fumaric acid, the configuration of which is known. It follows, therefore, that this crotonic acid (m.p. 72°) and the trichlorocrotonic acid from which it is formed are the *trans*-isomerides,



The other crotonic acid (*cis*- or *iso*crotonic acid) melts at 15°. Similarly the *o*-aminocinnamic acid which gives carbostyril yields

[1] Chloral is condensed with diethyl malonate giving diethyl trichloroethylidenemalonate, which, boiled with hydrochloric acid, gives trichlorocrotonic acid.

*allo*cinnamic acid by the elimination of the amino-group ; the latter is therefore the *cis*-compound. Other chemical methods for determining configurations are given later (p. 730).

In their chemical properties *cis*- and *trans*-isomerides are usually very similar, as most of their reactions depend, of course, on their constituent groups, and are therefore determined by their structures rather than by their configurations (compare pp. 848, 922). In their physical properties, however, such isomerides differ very considerably, so that if they are solids they can usually be separated from one another by fractional crystallisation ; liquid stereoisomerides, such as many dihydroxy-derivatives, may first be converted into some crystalline ester, with the aid of, say, phthalic, dinitrobenzoic, or toluene-*p*-sulphonic acid, or they may be transformed into crystalline urethanes, and then separated by fractional crystallisation.

When the physical properties of *cis*- and *trans*-isomerides of *known* configurations are compared, the following regularities are observed : The *cis*-isomerides, as a rule, are less stable, have a lower melting-point, a greater heat of combustion and, if they are acids, a greater dissociation constant than the *trans*-forms, as shown below:

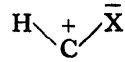
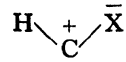
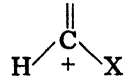
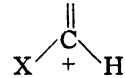
	M.p.	Heat of combustion	Dissociation constant ($\times 10^5$)
Maleic acid (*cis*-)	130°	327 Cal.	1170
Fumaric acid (*trans*-)	287°	320 Cal.	93
*Iso*crotonic acid (*cis*-)	15°	486 Cal.	3·6
Crotonic acid (*trans*-)	72°	478 Cal.	2·0
Oleic acid (*cis*-)	14°	2682 Cal.	
Elaidic acid (*trans*-)	51°	2664 Cal.	
*Allo*cinnamic acid (*cis*-)	68°	1048 Cal.	13·8
Cinnamic acid (*trans*-)	133°	1041 Cal.	3·5

The *cis*-forms are also more readily reduced by hydrogen and a catalyst than the *trans*-isomerides.

On the assumption that these rules hold good in all cases, the configurations of *cis-trans*-isomerides, including those of cyclic compounds, may be ascertained from a study of such physical properties.

The measurement of the dipole moments of *cis-trans*-isomerides may afford more conclusive evidence of configuration, since a symmetrical *trans*-isomeride should clearly have a zero (or very small) moment, whilst that of the *cis*-form should be considerable.

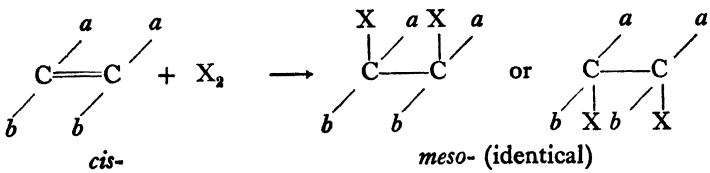
Actual measurements with the halogen substitution products of ethylene gave the following results ($\mu \times 10^{18}$), from which it is concluded that the configurations of the compounds are as shown :

	cis-	*trans-*	*cis-*	*trans-*
Dichloroethylene	1·9	0		
Dibromoethylene	1·4	0		
Di-iodoethylene	0·8	0		

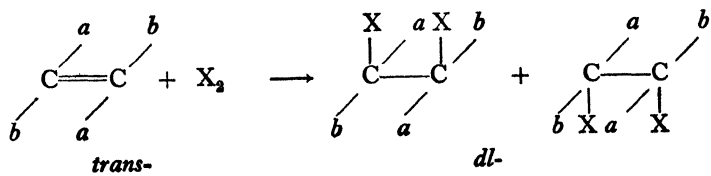
This conclusion has been confirmed by Debye, in the case of the dichlorides, by X-ray methods, since it is found that the distance between the chlorine atoms in the *cis*-compound is 3·6, and in the *trans*-isomeride 4·7 A.U.

Cis- *and* trans-*Additive Reactions*

It was at one time believed that the configurations of the *cis*- and *trans*-forms could be determined by an investigation of the additive products of the two compounds. Thus, if the *cis*- and *trans*-forms of C*ab*=C*ab*, are separately converted into C*ab*X—C*ab*X by the addition of X_2, it would seem that different results should be obtained with the two isomerides, provided that addition brings about only a partial fission of the ethylenic bond. From the *cis*-form, no matter which half of the double bond undergoes fission, identical *meso*-configurations would be produced, but from the *trans*-isomeride equal quantities of two enantiomorphously related compounds should be obtained :



cis- *meso-* (identical)



trans- *dl-*

These changes may also be represented (and examined) with the aid of the tetrahedral models (Fig. 25):

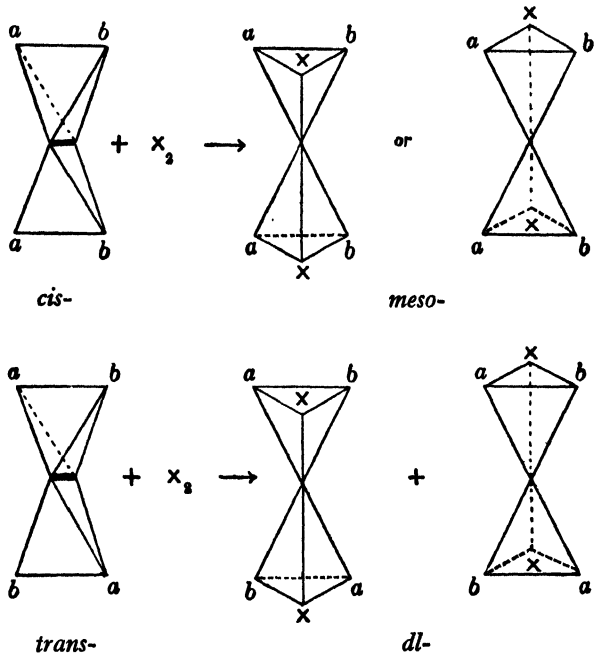


Fig. 25

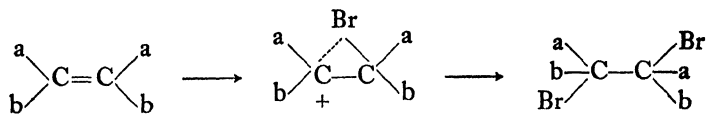
Now it has been found that, on oxidation with permanganate (X = OH), maleic acid yields *meso*tartaric acid, whereas fumaric acid gives racemic acid: in both cases, therefore, the addition of the two HO-groups takes place in the expected manner (*cis*-addition) as shown above. A similar 'normal' or *cis*-addition occurs in many, probably in all, other cases in which an olefinic compound is converted into its dihydroxy-derivative by oxidation with permanganate; this reaction, therefore, may be used with some assurance to determine the configurations of the isomerides.

When, however, maleic acid is treated with bromine it gives mainly *dl*-dibromosuccinic acid, and fumaric acid gives mainly the *meso*-compound, an 'abnormal' or *trans*-addition taking place; halogens (and halogen acids) usually give a *trans*-addition, but in most of such additive reactions mixtures of the *meso*- and *dl*-

isomerides are formed. Thus, *dimethylmaleic acid* is reduced by hydrogen in the presence of a catalyst giving mainly *meso*-dimethylsuccinic acid (*cis*-addition); *dimethylfumaric acid* yields a mixture containing both the *meso*- and *dl*-reduction products, but *trans*-addition predominates.

Unexpected, or 'abnormal,' reactions also occur when the elements of water, or of a halogen acid, are *eliminated* from a saturated compound with the production of an olefinic derivative; thus in the case of some cyclic *cis*- and *trans*-hydroxy-compounds, *trans*- takes place more readily than *cis*-elimination (p. 848). It has also been shown that *cis*-dichloroethylene (p. 711) loses the elements of hydrogen chloride very much more readily than does the *trans*-isomeride, the opposite of what might have been expected.

Such *trans*-additions and eliminations cannot be accounted for with the aid of the ordinary formulae and their models, but can be explained by the applications of the electronic theory. The addition of bromine to an ethylenic linkage has been shown (p. 695*o*) to involve the initial formation of a positive ion; if there is an attraction between the bromine atom and the positive carbon atom, as would appear not unlikely, the configuration of the molecule will be rigidly held. Now when the Br^- attacks this group it must approach from the far side to the bromine atom already present, as in an S_N2 reaction. Addition therefore occurs in the *trans*-position to the first bromine atom:



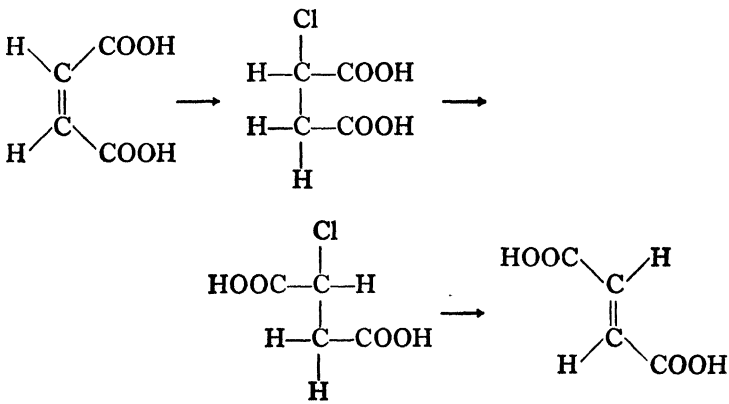
no matter which end of the double bond is attacked first the final result will be *trans*-addition. If the configuration of the intermediate ion is not very firmly held, mixtures of *cis*- and *trans*-additive products may be formed.

Interconversion of Geometrical Isomerides

The change of a *cis*- into a *trans*-isomeride often takes place very readily in the presence of a suitable reagent, while the reverse change, involving an increase of energy (p. 710), is often brought about by the action of light, heat, etc. Traces of halogen or halogen

acid convert diethyl maleate into diethyl fumarate, as does also potassium; nitrous acid at ordinary temperatures converts oleic into elaidic acid, although the former can be distilled unchanged in superheated steam at 250°. Cold mineral acids convert maleic into fumaric acid, and copper maleate, with hydrogen sulphide, gives fumaric acid; conversely fumaric acid yields maleic anhydride when it is heated. On exposure to ultra-violet light, both maleic and fumaric acids are converted into an equilibrium mixture of the two forms.

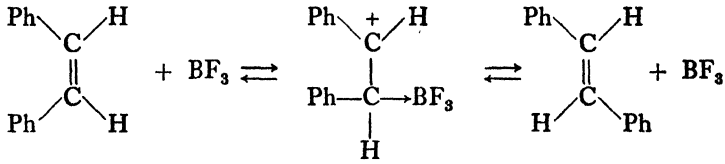
Wislicenus suggested that first an addition and then an elimination of the reagent takes place during such changes; after addition has occurred the carbon atoms are singly bound and consequently free to rotate around their common axis. Assuming that a certain rotation has taken place, the subsequent elimination of the reagent would give a stereoisomeride of the original substance. The conversion of maleic into fumaric acid by hydrochloric acid might therefore be represented as follows:



It is known, however, that chlorosuccinic acid is stable towards hydrochloric acid at the temperature at which the conversion of maleic into fumaric acid occurs. Further it has been shown that when deuterium chloride is used instead of hydrogen chloride, the resulting fumaric acid is free from deuterium. The above simple explanation of the transformation, therefore, cannot be adopted.

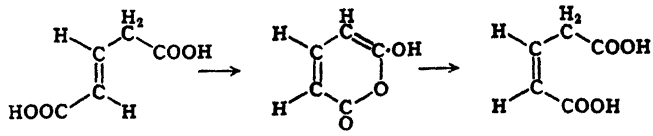
It is possible nevertheless that in some cases addition of the reagent does in fact occur, and it has been suggested that the con-

version of *cis*- into *trans*- stilbene by boron trifluoride, takes place in the following manner :



The occurrence of electromeric change would also account for the facts, as the more stable *trans*-isomeride would then be produced.

An interesting example of the readiness with which a *cis*- may be converted into a *trans*-isomeride is met with in the case of *glutaconic acid*.[1] The *trans*-compound, (I), m.p. 138°, has long been known, but its configuration was not established, and during many years all attempts to prepare its geometrical isomeride were fruitless. When the *trans*-acid is heated with acetyl chloride containing some phosphorus trichloride, it does not give a normal anhydride but is converted into hydroxy-α-pyrone, (II), as shown by Bland and Thorpe (*J.* 1912, 856). This compound, with cold sodium carbonate, gives a salt of the original acid (which was therefore supposed to be the *cis*-isomeride), but when it is very cautiously treated with cold water and the solution is then evaporated as quickly as possible under low pressure, the *cis*-acid, (III), m.p. 136°, is obtained (Malachowski, *Ber.* 1929, 1323) :



I II III

The latter, however, is extraordinarily unstable in aqueous solution, being quickly converted into the *trans*-acid, apparently as the result of tautomeric change (p. 839). This example shows clearly that

[1] Acetonedicarboxylic acid is first reduced to β-hydroxyglutaric acid, and the latter is then converted into glutaconic acid by the elimination of a molecule of water.

unexpected phenomena may occur in what seem to be very simple reactions, in consequence of which entirely erroneous conclusions may be drawn.

Stereochemistry of Cyclic Compounds

When a saturated homocyclic ring system, C_nH_{2n}, where $n = 3$, 4, or 5, is constructed with the usual models, it will be seen that all the carbon atoms lie in one plane and the hydrogen atoms are distributed symmetrically on both sides of this plane, as shown below:



*Cyclo*propane *Cyclo*butane

Fig. 26

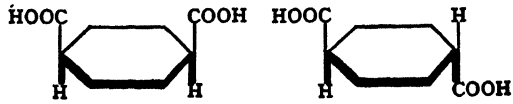
In the case of rings containing 6 (or more) carbon atoms, the mean positions of the carbon atoms of the ring may also be planar (p. 792), and similar configurational formulae may be used to represent these structures; for clarity, however, the symbols of the carbon atoms are usually omitted. In all such compounds the displacement of two atoms of hydrogen of *different* $>CH_2$ groups, by two atoms or radicals, with the formation of a complex CH*a*-----CH*b* (where *a* and *b* may be identical or different) gives rise to the possibility of stereoisomerism, just as in the case of corresponding derivatives of ethylene (the simplest *cyclo*paraffin, p. 789).

The first example of such isomerism was observed by Baeyer, who found that *hexahydroterephthalic acid* (cyclo*hexane*-1:4-*dicarboxylic acid*[1]) existed in two forms, one of which melted at 162°, whereas the other melted at about 300° and was much more sparingly soluble than its isomeride. These acids were distinguished as the *cis*- and *trans*-forms respectively, and from analogy with other substances whose configurations had already been proved (p. 710), the isomeride of higher melting-point was assumed to be the *trans*-form. This view was confirmed by Malachowski (*Ber.* 1934, 1783),

For the system of numbering see p. 777.

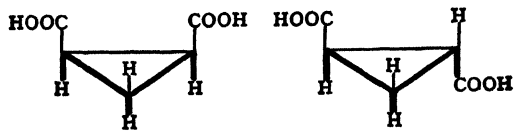
who showed that the acid, m.p. 162°, gives a monomolecular anhydride, which yields the same acid on hydrolysis.

The molecules of both these acids possess at least one plane of symmetry, and are therefore optically inactive :



cis *trans-*

Corresponding forms of cyclo*propane*-1:2-*dicarboxylic acid* have also been obtained :



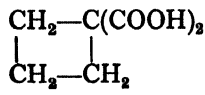
cis- *trans-*

In this case also one of the acids yields an anhydride, which with water regenerates the original compound ; this, therefore, is the *cis*-acid, in which the carboxyl groups are suitably disposed for anhydride formation. The molecule of the *cis*-acid has a plane of symmetry, whereas that of the *trans*-form has neither a plane nor a centre of symmetry, and should therefore be a *dl*-substance (p. 299) ; this is, in fact, the case, as the *trans*-acid has been resolved into its *d*- and *l*-forms with the aid of brucine. It might be thought at first sight that the *cis*-acid should also be optically active, as its molecule contains two asymmetric carbon-groups : it is, however, a *meso*-compound, and, like *meso*tartaric acid, its molecule contains two identical asymmetric groups of opposite sign.

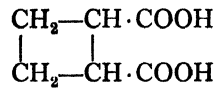
In dealing with the optical isomerism of cyclic compounds, however, instead of considering asymmetric groups, it is better to study the configuration of the molecule as a whole ; one having neither a plane nor a centre of symmetry is non-superposable on its mirror image and exists in *antimeric* forms, as in the case of open chain compounds.

A simple method of showing the number of forms of such cyclic compounds is to represent the ring in the plane of the paper, and

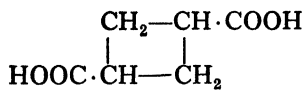
substituents by a positive sign, if above, and a negative sign, if below, this plane. Thus, cyclo*butanedicarboxylic acid*, $C_4H_6(COOH)_2$, exists in three *structurally* isomeric forms, namely, the 1:1-, (I), 1:2-, (II), and 1:3-, (III):



I

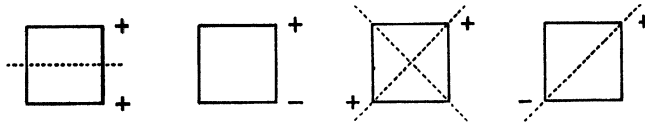


II



III

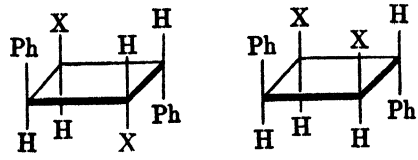
In the case of (I) no geometrical or optical isomerism is possible, but both (II) and (III) give *cis-* and *trans*-isomerides, as can be easily seen from the following four figures:



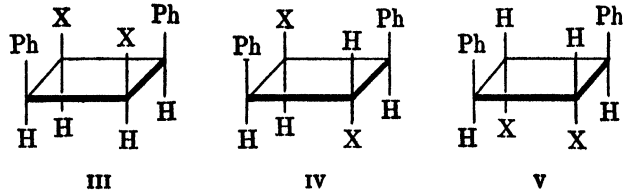
II, *cis-* II, *trans-* III, *cis-* III, *trans-*

of these only the *trans*-modification of (II) lacks a plane (indicated by the dotted lines) or centre of symmetry and exists, therefore, in *d-* and *l*-forms.

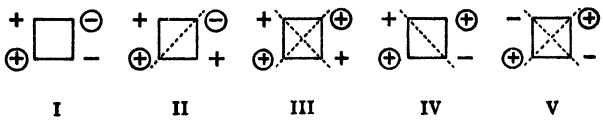
A rather more complex case is presented by *truxillic acid*, which occurs in nature in coca-leaves (p. 604) and which can also be formed by the polymerisation of cinnamic acid. Truxillic acid is a 1:3-*diphenyl*cyclo*butane*-2:4-*dicarboxylic acid*, and it exists in the following five stereoisomeric forms, in which X represents —COOH:



I II

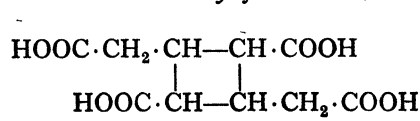


These stereoisomerides are also shown below in the simpler form, in which the carboxyl group is indicated by + or − and the phenyl radical by ⊕ or ⊖ :



It will then be seen that each of the acids, (II) to (V) inclusive, has at least one plane, and (I) has a centre of symmetry : none of these acids, therefore, is resolvable. When, however, one of the carboxyl groups is converted into the anilido-group, —CO·NHPh, those acids, (I) and (II), in which the phenyl groups are in *trans*-positions become dissymmetric, whilst the others retain a plane of symmetry. The two *dl*-anilido-acids so formed have been resolved and possess therefore the configurations (I) and (II); from a study of the stability and ease of anhydride formation of each acid, configurations have been definitely assigned to all the five isomerides.

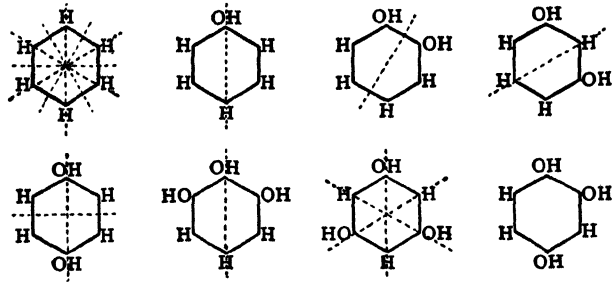
Five stereoisomeric 2:4-*dicarboxy*cyclo*butane*-1:3-*diacetic acids*,



corresponding with the truxillic acids, have been isolated by Ingold, Perren, and Thorpe (*J.* 1922, 1765).

Inositol (*hexahydroxy*cyclo*hexane*), $C_6H_6(OH)_6$ (p. 798), exists theoretically in eight geometrical forms, the configurations of which may be indicated as on p. 720, only the atoms and groups *above* the

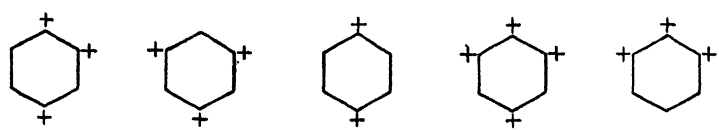
plane of the ring being shown; the four atoms of any >CH·OH group lie in a plane at right angles to that of the ring.



Planes of symmetry are indicated by the dotted lines, which show, therefore, that all the isomerides are optically inactive, except the last, which has no plane or centre of symmetry. The active inositols and two of the inactive compounds occur in nature (p. 798).

The fact that the *cyclohexane* ring is really puckered (p. 792) makes no difference to the number of isomerides theoretically obtainable, provided that, as with *cyclohexane* itself, there is equilibrium between the boat and chair forms. When, however, many large atoms or groups are attached to the ring the change from boat to chair or *vice versa* may thereby be rendered impossible, or certain isomerides, otherwise capable of existence, may be inhibited owing to the space requirements of the large groups.

In the case of benzene hexachloride (hexachloro*cyclo*hexane) seven of the eight theoretically possible forms have been isolated; the configurations of the first five to be prepared are shown below and the letters indicate the disposition (axial or equatorial, p. 792) of the chlorine atoms starting in each case at the top of the hexagon and working clockwise, assuming that the rings are in the chair form.

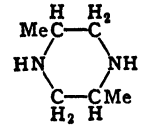


(α) aeeeea (β) eeeeee (γ) aaeeea (δ) aeeeee (ε) aeeaee

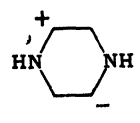
The γ-compound, *gammexane*, is by far the most active insecticide of the various isomerides; it is remarkable that in any chair form

of this two *cis*-chlorine atoms in the 1:3-position must both be axial on the same side of the ring, and if a model is made there is no room for such atoms, without some distortion of the ring. The configurations of the isomerides were determined by X-ray methods.

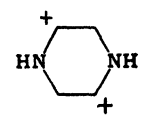
The considerations which have just been applied to saturated homocyclic ring systems may be extended to saturated heterocyclic rings containing, for example, nitrogen or oxygen. The configuration of the piperazine molecule (p. 1060), for example, assuming the planar arrangement, or at any rate a *mean* planar position, of the three nitrogen bonds, may be represented by a plane ring; 2:5-*dimethylpiperazine*, (I), would therefore exist in two forms, namely, *trans*-, (II), and *cis*-, (III), of which the *trans*- has a centre of symmetry, which is lacking in the *cis*-isomeride; the latter, consequently, is resolvable into its antimeric forms (Kipping, F. B., and Pope, *J.* 1926, 1076), whereas the former affords another example of a compound which has a centre, but no plane, of symmetry:



I

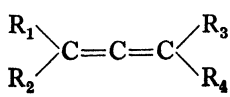


II



III

A model of an *allene* derivative of the structure, (IV), shows that the four groups, R_1, R_2, R_3, R_4, are situated in two planes at right angles to one another and occupy the corners of an irregular tetrahedron (Fig. 27):



IV

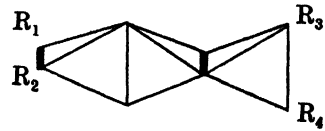
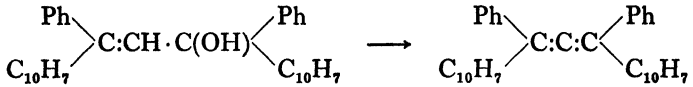


Fig. 27

The stereochemical problem involved here is different from that concerned with one carbon atom, inasmuch as the tetrahedron is irregular, and therefore the four groups need not all be different to cause dissymmetry. A compound, $R_1R_2C{:}C{:}CR_2R_1$, in fact, should exhibit enantiomorphism.

The unsaturated alcohol, (I, p. 722), can be prepared by treating

the diketone, $Ph \cdot CO \cdot CH_2 \cdot CO \cdot Ph$, with α-naphthyl magnesium bromide (1 mol.) and then with dilute acid, which brings about hydrolysis, followed by the elimination of the elements of water: the product, with α-naphthyl magnesium bromide (1 mol.) and dilute acid successively then gives (I), which boiled with a solution of *d*-camphorsulphonic acid is converted into a strongly dextrorotatory *diphenyldi-α-naphthylallene*, (II). This last change is an extremely interesting example of an asymmetric dehydration (Mills and Maitland, *J.* 1936, 987).



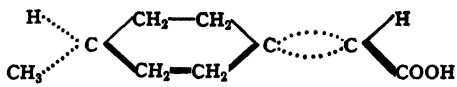
I II

The acid, $C_{10}H_7(Ph)C{:}C{:}C(Ph) \cdot COO \cdot CH_2 \cdot COOH$, has also been resolved by the fractional crystallisation of its brucine salt (Kohler, Walker and Tishler, *J. Am. Chem. Soc.*, 1935, **57**, 1743).

In such allene compounds there is no asymmetric group; it is the molecule as a whole which exhibits dissymmetry.

Certain compounds containing a carbon atom which forms a link in a saturated ring, and which also has a group $=CR_1R_2$ directly attached to it, exhibit similar optical isomerism.

The first compound of this kind, 4-*methyl*cyclo*hexylideneacetic acid*,[1]

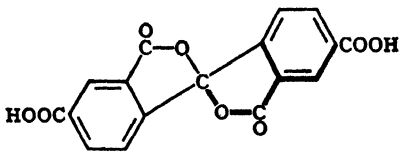


was prepared by Perkin, Pope, and Wallach (*J.* 1909, 1789), who resolved it into its *d*- and *l*-components by the crystallisation of its brucine salt. In the molecule of this compound the hydrogen atom and the methyl group on the left-hand side of the formula lie in a plane which is at right angles to that in which are situated the hydrogen atom and the carboxyl group on the right-hand side, as indicated. As this was the first case of a compound which could be resolved and which did not contain an asymmetric group, its resolution was a milestone in the history of stereochemistry.

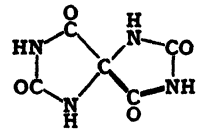
A substance in the molecule of which one atom forms a part of

[1] The bonds represented by dotted lines lie in a plane which is at right angles to the plane of the *cyclo*hexane ring.

two closed chains is known as a *spirocyclic* compound or *spirane*. The stereochemistry of such compounds is very similar to that of allene derivatives and suitable structures may exist in antimeric forms. The first compound of this type to be resolved was the keto-dilactone of a *benzophenonetetracarboxylic acid*,[1] (I, Mills and Nodder), and a very simple spirane, spiro*dihydantoin*, (II), has been resolved, in its acidic lactim form, by Pope and Whitworth,



I



II

Such compounds lack a plane or a centre of symmetry ; further examples of optically active spiranes are given later (pp. 763, 775).

[1] Obtained by heating the acid with hydrochloric acid.

CHAPTER 46

GEOMETRICAL ISOMERISM OF THE OXIMES AND OTHER COMPOUNDS OF TERVALENT NITROGEN

THE question of the arrangement in space of the atoms or groups which are directly united to a tervalent nitrogen atom in a compound, NR_3, is discussed later (p. 765); in the case of many compounds, in which a nitrogen atom is doubly bound to another atom, there is abundant evidence that the spatial distribution of the nitrogen valencies determines the existence of *optically inactive* isomerides.

The first example of this phenomenon was observed in 1883 by Goldschmidt, who found that the dioxime of benzil, heated with alcohol at 170°, was converted into an isomeride. Shortly afterwards Beckmann discovered a second benzaldoxime, and later a great many *aromatic* aldoximes and ketoximes were obtained in isomeric forms, generally distinguished by the letters α and β.

In those days it was thought that the three valencies of the nitrogen atom were symmetrically distributed in one plane and on this basis, in spite of the relative simplicity of their molecules, an explanation of the existence of such isomerides was impossible; many years elapsed before the problem was solved satisfactorily.

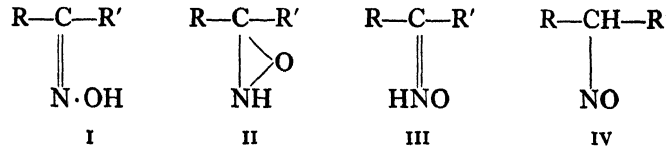
Both isomerides seemed to be produced by a simple interaction,

$$>CO+NH_2\cdot OH = >C{=}N\cdot OH+H_2O,$$

and both were often formed simultaneously. Nevertheless they were *not* merely tautomeric, since they retained their individuality in solution, could be recovered unchanged from solvents, and could be separated by fractional crystallisation. Both seemed to be hydroxy-compounds; they gave isomeric acyl derivatives with acid chlorides and isomeric alkyl derivatives with sodium ethoxide and an alkyl halide. Further, one of the two oximes could sometimes be transformed into the isomeride under conditions which seemed to exclude or render improbable a structural change.

Notwithstanding this difficulty it was suggested that the two forms

might be represented respectively by two of the following *structurally* different formulae :



The first compound, (I), might be produced by a direct condensation, as indicated above, whereas (II) might be obtained if an additive compound, RR′C(OH)·NH·OH, were first formed and then lost the elements of water (compare p. 727) ; the structure, (II), might then pass into (III or IV) by isomeric change.

It was then suggested by Hantzsch and Werner (1890) that the isomerism of the oximes was due, not to a difference in structure, but to a difference in *configuration.* It was pointed out that in a closed chain compound, such as pyridine, the nitrogen atom, N≪, takes the place of a HC≪ group of benzene, with very little alteration in the stability of the ring ; it was therefore probable that the three nitrogen valencies concerned in ring formation have the same spatial directions as those of a carbon atom, and if so, they would be directed towards three corners of a tetrahedron.

Aldoximes and certain ketoximes might then exist in geometrically isomeric forms, as indicated by the configurations, (V) and (VI) :

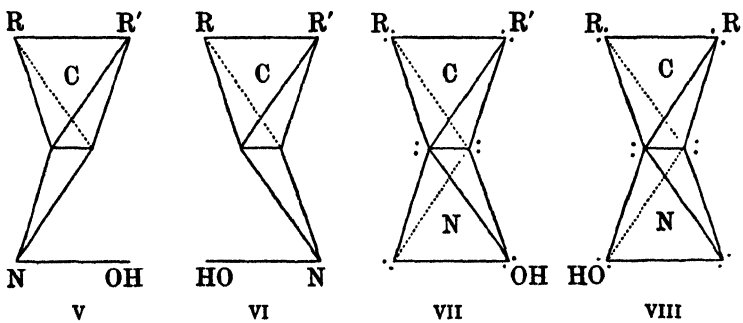
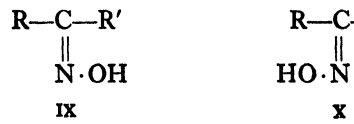


Fig. 28

This hypothesis, after a great deal of discussion and investigation, is now generally accepted, but in a slightly modified form. Since

in compounds, NR_4X, the four atoms or radicals linked by covalencies are believed to be tetrahedrally arranged around a central nitrogen atom (p. 763), the molecules of the geometrically isomeric oximes are represented in a corresponding manner, as shown in (VII) and (VIII). For convenience, the configurations of the two isomerides are usually indicated by the projection formulae, (IX) and (X),



IX X

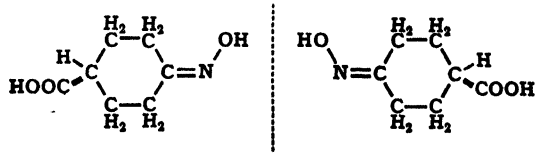
which correspond with those of the *cis*- and *trans*-forms of certain olefinic compounds; as shown by models, the three radicals R, R′, and OH, all lie in one plane, as do the four atoms or radicals in *cis*- and *trans*-isomerides.

The stereoisomeric oximes, however, are distinguished by the prefixes *syn*- and *anti*-. Thus, if in a ketoxime, R represents phenyl, and R′ tolyl, the compound (IX) is called *anti*-phenyltolyl or *syn*-tolylphenyl ketoxime, whereas (X) would be *anti*-tolylphenyl or *syn*-phenyltolyl ketoxime. In the case of aldoximes, if R represents hydrogen, (IX) is called the *anti*- and (X) the *syn*-aldoxime, according to the juxtaposition or otherwise of the hydrogen atom and the hydroxyl group; the letters α and β, however, are also used, in which case the isomeride directly produced by the action of hydroxylamine on the aromatic aldehyde is generally distinguished as the α-compound; this is the more stable form, which according to present views (p. 733) is the *syn*-modification.

The evidence that the oximes are geometrically and not structurally isomeric seems to be conclusive, as will be seen from the following facts. The isomerism cannot be due to structural differences of the nature shown on p. 725; if this were so there should be the same number of isomerides whether R and R′ are the same or different, whereas, in fact, two oximes have never been obtained from a symmetrical ketone. Compounds of the formulae, (II) and (IV) (p. 725), should both give rise to optically active oximes if the two hydrocarbon radicals are different, as in each case the molecule contains an ordinary asymmetric carbon-group; no such optically active oximes have, however, been obtained.

On the other hand, Mills and Bain (*J.* 1910, 1866) have provided very strong evidence in favour of the Hantzsch-Werner hypothesis

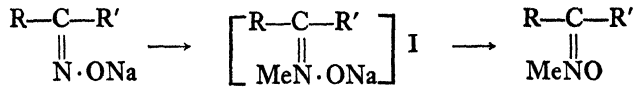
by resolving the oxime of cyclo*hexanone*-4-*carboxylic acid* into optically active components :



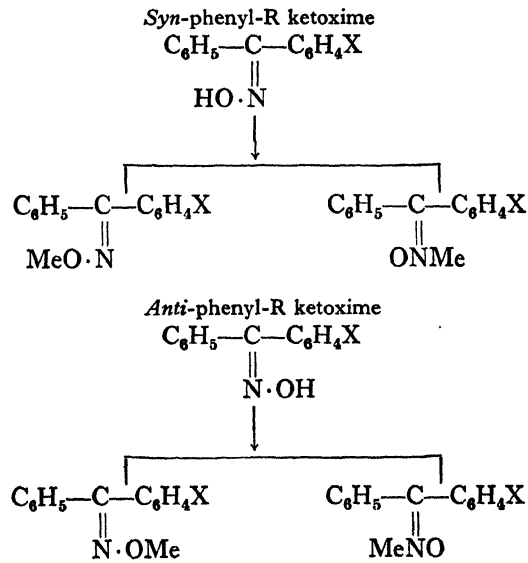
This compound can show dissymmetry only if the hydroxyl radical is *not* in the same plane as the hydrogen atom and carboxyl group which are attached to the carbon atom in the 4-position. It will be seen, therefore, that the spatial relationship of these substituents is similar to that of any three of the four terminal groups in 4-methyl*cyclo*hexylideneacetic acid (p. 722).

Although there is no evidence of any structural differences between isomeric oximes, it has been proved that a given pair of isomerides may afford *structurally* isomeric derivatives. The two benzaldoximes, for example, give two such *benzyl* derivatives, in one of which the benzyl group is directly united with oxygen, whereas in the other it is combined with nitrogen. These facts, if taken alone, would afford strong evidence that the *syn-* and *anti-*benzaldoximes are themselves structurally different, but further investigation has shown that another explanation is necessary ; either or both of a pair of stereoisomerides may give *two* structurally isomeric alkyl or benzyl derivatives. Benzophenoneoxime, of which only one form is actually known, gives two isomeric methyl derivatives, and both the *syn-* and *anti-*forms of *p*-nitrobenzophenoneoxime give two analogous structural isomerides (below). That such isomeric alkyl derivatives are *structurally* different is proved by the fact that, when they are decomposed with mineral acids, the one gives an *O*-alkylhydroxylamine, $NH_2 \cdot OR$, and the other an *N*-alkyl derivative, $NHR \cdot OH$; it must be concluded, therefore, that in one case the alkyl group has displaced hydrogen of a hydroxyl radical, in the other hydrogen of an HN-group. The existence of *N*-methyl derivatives of oximes is confirmed by the fact that they may sometimes be obtained by treating an aldehyde or ketone with N-*methylhydroxylamine*, $NHMe \cdot OH$; in such cases it would seem that an additive compound is first produced and then loses the elements of water (p. 725).

The formation of structurally isomeric alkyl derivatives from a given oxime may also be accounted for by assuming that, in the case of one, namely the *N*-compound, the reaction involves the initial formation of an additive product :



It is now known, therefore, that a given aromatic aldehyde or unsymmetrical ketone may form two stereoisomeric oximes, each of which may yield *O*-alkyl and *N*-alkyl derivatives. Complete series of such compounds have been obtained by Semper and Lichtenstadt (*Ber.* 1918, 928) from *phenyl*-p-*tolyl ketone*, and by Brady and Mehta (*J.* 1924, 2297) from p-*nitrobenzophenone* (*phenyl*-p-*nitrophenyl ketone*) ; the configurations of the isomerides on the basis of the Hantzsch-Werner hypothesis are shown below (X = CH_3 or NO_2 and R = C_6H_4X) :



It will be seen that the *N*-alkyl derivatives which contain the group, R·NO=, may be compared with the amine oxides (p. 764), the doubly bound carbon atom, combined with this group, having taken

the place of two of the hydrocarbon radicals in the oxide ; but as C_6H_5, C_6H_4X, Me, and O (above) are all in one plane, the molecule does not exist in enantiomorphously related forms. In the production of these *N*-alkyl derivatives, it is assumed that the oxygen atom retains its position in the tetrahedral arrangement around the nitrogen atom, while the alkyl group takes the unoccupied corner (VII and VIII, Fig. 28, p. 725).

The Beckmann Transformation

When the only known form of acetophenoneoxime is treated with phosphorus pentachloride in ethereal solution, or merely dissolved in concentrated sulphuric acid, it is almost completely transformed into acetanilide. Under similar conditions many other ketoximes undergo an *isomeric* change of this type giving substituted amides, and the change is known as the *Beckmann transformation*. A simple way of regarding the conversion of acetophenoneoxime into acetanilide is to *assume* that the ketoxime is a *syn*-phenyl derivative, (I), and that by some means the phenyl and hydroxyl groups are transposed, giving (II), which then by another isomeric change is converted into (III) :

$C_6H_5\cdot C\cdot CH_3$	$HO\cdot C\cdot CH_3$	$OC\cdot CH_3$	$C_6H_5\cdot C\cdot CH_3$
$\parallel$	$\parallel$	$\vert$	$\parallel$
$HO\cdot N$	$C_6H_5\cdot N$	$C_6H_5\cdot NH$	$N\cdot OH$
I	II	III	IV

It seemed possible, therefore, that the Beckmann transformation might be used to determine the configurations of any two stereoisomeric ketoximes on the assumption that the *syn*-radical changed places with the hydroxyl group. If, for example, acetophenoneoxime has not the *syn*-phenyl but the *syn*-methyl (or *anti*-phenyl) configuration, (IV), it might be expected to give methylbenzamide, $C_6H_5\cdot CO\cdot NH\cdot CH_3$, by the transposition of the methyl and hydroxyl groups as assumed above.

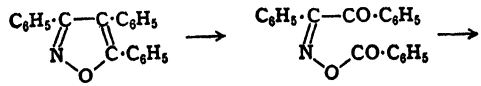
When, for this purpose, the two stereoisomerides of a ketoxime are separately submitted to the Beckmann transformation, it is found that, as expected, two different substituted amides are obtained ; in some cases, however, a given *syn*- or *anti*-form affords both the isomeric amides (of which one is produced only in relatively small proportions), possibly as the result of the prior conversion of the one oxime into the other. *Anti*-phenyl-*p*-nitro-

phenyl ketoxime (p. 728), for example, gives *p*-nitrobenzanilide (hydrolysed to *p*-nitrobenzoic acid and aniline), but the *syn*-phenyl oxime gives a mixture of this anilide with a larger quantity of benzoyl-*p*-nitroaniline (hydrolysed to benzoic acid and *p*-nitroaniline).[1]

Determination of the Configurations of Ketoximes

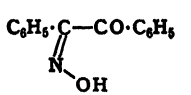
It will be obvious that the formation of two substituted amides from a given ketoxime, even if one is produced in small proportions only, lessens the value of the Beckmann transformation as a means of determining configuration, but there is an even greater difficulty to be considered. It was first assumed (p. 729) that it was the adjacent *syn*-radical which changed places with the hydroxyl group, and the question arose, has this assumption any justification? Fortunately it is possible to obtain experimental evidence on this point, as has been done by Meisenheimer and his co-workers (*Ber.* 1921, 3206; *Ann.* **446**, 205; **495**, 249), and others.

Of the two benzilmonoximes, the one of lower melting-point can be obtained in the form of its benzoyl derivative, (II), by treating *triphenylisoxazole*, (I, cf. p. 1057), with ozone and then decomposing the ozonide:

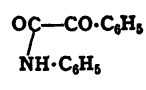


I

II



III



IV

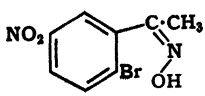
As it seems very probable that the fission of the ethylenic binding by ozone takes place in the usual way (p. 810) and does not involve any change in configuration, it must be inferred that the benzoyl derivative, (II), corresponds with the *anti*-phenyl-oxime, (III).

But when this same oxime undergoes the Beckmann transformation with phosphorus pentachloride it gives (a chloro-derivative of)

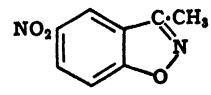
[1] It is assumed here that the *anti*-radical and the hydroxyl groups are transposed (p. 732), and that the oximes are respectively represented by the configurations shown on p. 728.

(IV), the *anti*- (—C_6H_5) and not the *syn*-radical (—CO·C_6H_5) having changed places with the hydroxyl group.

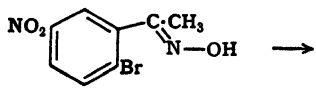
A second method for studying the Beckmann transformation is based on the possibility or otherwise of ring formation. Of the two oximes of 2-*bromo*-5-*nitroacetophenone*, one, (I), is immediately decomposed by caustic alkalis giving a closed chain compound, (II), with the elimination of hydrogen bromide, whereas the other, (III), is only very slowly attacked.[1]



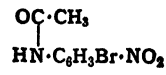
I



II



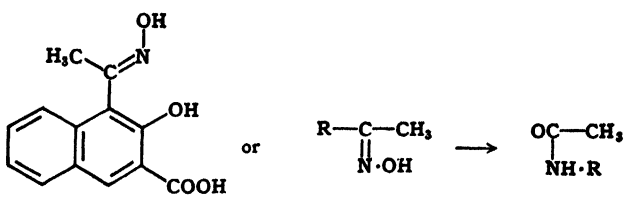
III



IV

Clearly the more stable ketoxime must be regarded as the *syn*-methyl isomeride, (III), as already assumed; when, however, this compound undergoes the Beckmann transformation it gives (IV), that is to say the *anti*-radical and the hydroxyl group have changed places as in the preceding case.

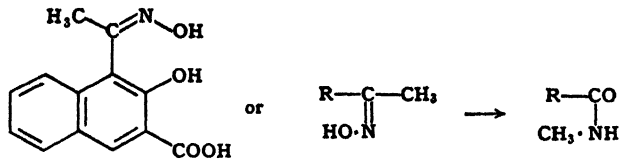
A third method, illustrating various interesting points, is based on a consideration of steric interference or restricted rotation.[2] Two oximes are derived from 1-*acetyl*-2-*hydroxynaphthalene*-3-*carboxylic acid* (p. 845), and their configurations may be represented as follows:



I

[1] A halogen atom in the *p*-position to a nitro-group is often particularly reactive (p. 425).

[2] This phenomenon is described later (p. 758).



II

Of these, one can be resolved into *d*A*l*B and *l*A*l*B forms by the crystallisation of its salts with active bases, but the other cannot. It is obvious, therefore, that the *dl*-compound must be represented by (II), because it is only in this oxime that the free rotation of the group —C(CH$_3$)=N·OH is rendered impossible owing to steric interference (just as in the case of certain other naphthalene derivatives, p. 760).[1] The occurrence of optically active forms of this compound affords, therefore, further evidence in favour of the Hantzsch-Werner hypothesis; if the =N—OH group were linear no clashing could occur. Now the oxime, (II), in the form of its methyl ester, undergoes the Beckmann transformation, giving R·CO·NH·CH$_3$, whereas the isomeride, (I), gives R·NH·CO·CH$_3$, the *anti*-radical and the hydroxyl group changing places in each case.

From all these results it seems justifiable to conclude that the Beckmann transformation always takes place by an *anti*- or *trans*-interchange, and may therefore be safely used for determining the configuration of a ketoxime. This conclusion is strongly supported by Mills (*British Association Reports*, 1932) from a consideration of the changes involved from a mechanical point of view.

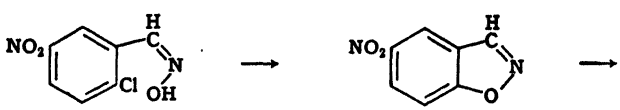
The Configurations of the Aldoximes

Aldoximes do not undergo the usual Beckmann transformation, although certain of their additive compounds with metallic salts can be converted into substituted amides; benzaldoxime, for example, may be transformed into benzamide with the aid of cuprous chloride (Comstock, *Amer. Chem. J.* 1897, 485). As a rule, however,

[1] This interference is not apparent in the ordinary graphic formulae; the hydroxyl group attached to the nitrogen atom in (II) collides both with the *o*-hydroxyl group and with the hydrogen atom (not shown) in the 8-position.

when isomeric aldoximes are treated with various reagents, one of them loses the elements of water, giving a cyanide, whereas the other does not; the acetyl derivative of the less stable aldoxime also loses the elements of acetic acid, when it is treated with alkalis, whereas the isomeric acetyl derivative is unchanged or merely hydrolysed.

It was at first assumed that the unstable oxime (which gives the unstable acetate) is the *syn*-compound, with the hydrogen atom and the hydroxyl group in juxtaposition. This view, however, is contrary to the results obtained by Brady and Bishop (*J.* 1925, 1357) with the isomeric *2-chloro-5-nitrobenzaldoximes*; of these two compounds one is completely converted into *5-nitrosalicylonitrile* when it is boiled with sodium hydroxide solution during thirty minutes, whilst the stereoisomeride is only slightly changed. The oxime which is thus decomposed should, apparently, be the *anti*-form, (I), on the assumption that the halogen reacts with the sodium derivative of the oxime to give (II), which then undergoes isomeric change to (III); but this same oxime is given the *syn*-formula, (IV), when its configuration is based on the fact that it readily loses the elements of water. It seems, therefore, that those stereoisomerides which show this behaviour have in fact the *anti*-configuration and that the elimination of water occurs *trans*- or crossways.



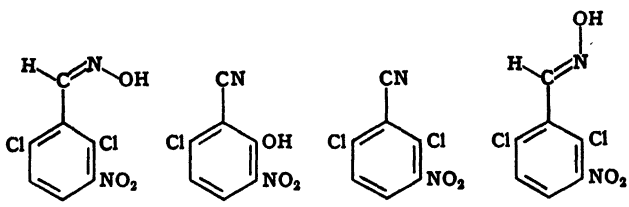
I II



III IV

In a similar manner Meisenheimer (*loc. cit.*) has shown that of the two oximes of *3-nitro-2:6-dichlorobenzaldehyde*, (I and IV, p. 734), one is decomposed by ice-cold 0·25 normal sodium hydroxide solution with the elimination of hydrogen chloride, giving first a ring

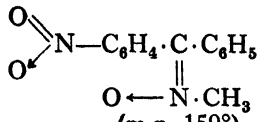
compound and then 2-*hydroxy*-3-*nitro*-6-*chlorobenzonitrile*, (II); the other isomeride is not attacked under these conditions. The former therefore must be represented by (I); but the same oxime, (I), is readily converted into 3-*nitro*-2:6-*dichlorobenzonitrile*, (III), by acetic anhydride and sodium carbonate, whereas (IV) yields an acetyl derivative. Here again it is the *anti*-form which loses the elements of water; consequently such reactions are *trans*- and not *cis*-eliminations as previously believed.



I II III IV

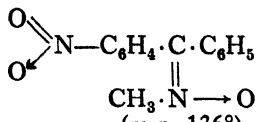
Mills (*loc. cit.*) has also discussed this problem, and concludes that the elimination of water must be crossways.

When the configurations of various pairs of stereoisomerides have been determined, by methods such as those given above, the physical properties of the *syn*- and *anti*-compounds may be compared or contrasted; if, then, there are any constant differences of any kind, a study of these properties may be employed to determine unknown configurations. Very little use can be made of such methods at the present time; the unstable aldoximes generally melt at a lower temperature than their stereoisomerides, but regularities in other physical properties such as viscosity, dissociation constant, and absorption spectra, have not been observed. It has been suggested, however (Sutton and Taylor, *J.* 1931, 2190), that measurements of the dipole moments of certain derivatives of stereoisomeric ketoximes might afford evidence of the configurations of the latter; thus in the case of the *N*-methyl derivatives of the *p*-nitrobenzophenoneoximes, (V) and (VI), since the dipole moments of the two N⟶O groups are comparable, (V) should have a larger dipole moment than (VI). As actual measurements gave (V), $\mu \times 10^{18}$, 6·60, and (VI), 1·09, the results confirmed the configurations, which had been previously assigned to the compounds on chemical evidence.



(m.p. 159°)

V



(m.p. 136°)

VI

It has also been shown by Taylor and Sutton (*J.* 1933, 63) that a comparison of the electric moments of the isomeric *O*-ethers of a given aldoxime, with those of the corresponding derivatives of a ketoxime, may afford information as to the configurations of the aldoximes, provided that those of the *O*-ethers of the ketoximes are known, and that the conversion of the aldoxime into its ether is not accompanied by a change in configuration. Thus in the case of the compounds shown below, the following results have been obtained :

	$\mu\times10^{18}$		$\mu\times10^{18}$
$NO_2\cdot C_6H_4\cdot C(=N\cdot OMe)\cdot C_6H_5$	3·75	$NO_2\cdot C_6H_4\cdot CH=N\cdot OMe$	3·39
$NO_2\cdot C_6H_4\cdot C(=N\cdot OMe)\cdot C_6H_5$	4·26	$NO_2\cdot C_6H_4\cdot CH=N\cdot OMe$	3·88
diff.	0·51	diff.	0·49

It may therefore be concluded that the ketoxime and aldoxime derivatives having the larger moments correspond in configuration, as shown above ; this conclusion accords with other evidence.

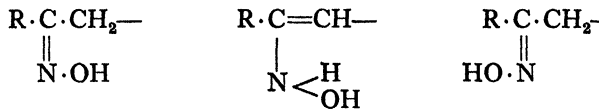
The conditions which determine the production and interconversion of stereoisomeric oximes are very varied. Sometimes only one isomeride (then called the α-compound) is produced when the aldehyde or ketone is treated with hydroxylamine, but very often both are formed and their separation may be very troublesome. The transformation of one into the other may sometimes be brought about by merely heating the compound with a solvent, such as alcohol or benzene, or by exposure to ultra-violet light, but as a rule treatment with mineral acids, or occasionally with alkalis, is required.

The non-existence of stereoisomerides of *symmetrical* aromatic ketones is of course in accordance with the Hantzsch-Werner hypothesis ; crystalline aliphatic aldoximes and the oximes of most

aliphatic unsymmetrical ketones are also known in one form only, contrary to what might have been expected.

It has been shown, however, by Hückel and Sachs that certain cyclic ketoximes (from *methyl*cyclo*pentanone* and trans-*β-decalone*) exist in stereoisomeric forms, and Furukawa has prepared stable stereoisomeric oximes of ethylpalmityl, propylpalmityl, and ethylstearyl ketones.

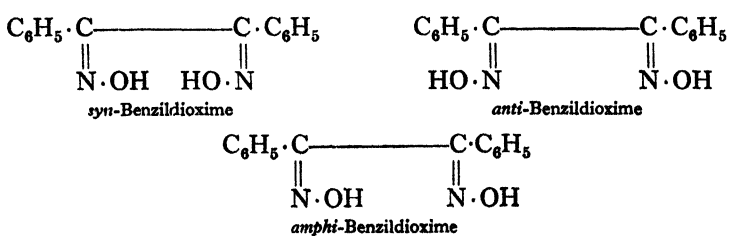
To account for the customary non-existence of aliphatic isomerides, Raikowa has pointed out that such oximes may undergo a simple tautomeric change, whereby one isomeride might be transformed into the other so readily as to render impossible the isolation of the unstable form. If, for example, the compound, (I), actually existed in a stereoisomeric form, (III), either might change into the other by passing through the form, (II), where R represents H or a hydrocarbon group :



I II III

So far as is known, all aliphatic aldoximes readily lose the elements of water ; nevertheless the liquid compounds might be mixtures of stereoisomerides and the decomposition of the *syn*-form might be due to its previous transformation into the isomeride in the manner just suggested. When oximes of unsymmetrical aliphatic ketones undergo the Beckmann transformation, the one form gives both the theoretically possible substituted amides ; this fact might also be accounted for by adopting Raikowa's views.

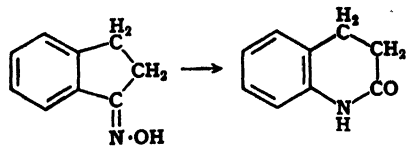
Diketones, such as benzil, in accordance with the Hantzsch-Werner hypothesis, give three stereoisomeric dioximes, which are distinguished by the prefixes shown below :



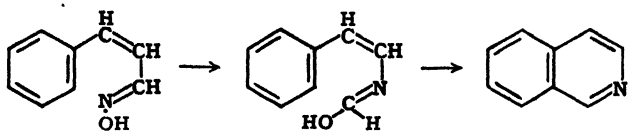
syn-Benzildioxime *anti*-Benzildioxime

amphi-Benzildioxime

The Beckmann transformation has been applied to bring about an isomeric change of certain cyclic oximes; the monoxime of phenanthraquinone (p. 567), for example, heated with hydrochloric and acetic acids is converted into *diphenimide*, which on hydrolysis gives diphenic acid. Similarly *α-indanoneoxime* with phosphorus pentachloride gives *dihydrocarbostyril*, which is the lactam of *o-aminophenylpropionic acid*:

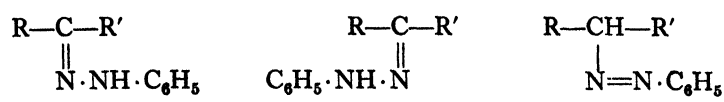


The elimination of water from an aldoxime has also been utilised for ring formation. Thus when *cinnamaldoxime* is treated with phosphorus pentoxide it seems to undergo an isomeric change, giving a product which loses water and passes into *iso*quinoline:



Stereoisomerism of Hydrazones and Semicarbazones

Since the group, $>C{=}N\cdot OH$, in oximes gives rise to stereoisomerides, it is clear that the group, $>C{=}N\cdot NH\cdot C_6H_5$, of the phenylhydrazones of aldehydes and unsymmetrical ketones might determine the existence of corresponding *syn-* and *anti*-forms, (I) and (II):



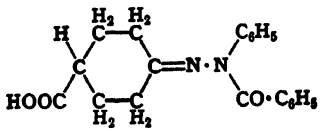
I II III

Such isomerides have, in fact, been obtained; that they are not structurally different as would be the case if one had the constitution, (III), is shown by the existence of isomeric diphenylhydrazones,



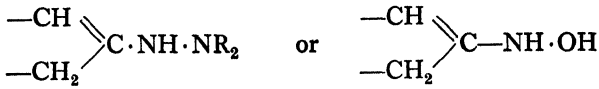
IV

(IV), in the molecules of which there is no possibility of isomeric change due to the migration of a hydrogen atom in this way. It has also been proved by Mills and Bain (*J.* 1914, 64) that the benzoyl derivative of the *phenylhydrazone* of cyclo*hexanone*-4-*carboxylic acid*, (V), can be resolved into optically active components; this fact shows that the double and single bonds of the nitrogen atom are inclined to one another, and therefore, that stereoisomeric hydrazones are capable of existence.



V

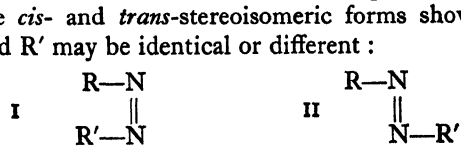
This hydrazone and the corresponding oxime (p. 727) might conceivably undergo isomeric change, giving the group,



respectively, and the compounds so formed would be dissymmetric whatever the disposition of the nitrogen valencies; to meet this possible objection Mills and his co-workers also resolved a hydrazone and an oxime in which such a transformation is impossible (*J.* 1923, 312; 1931, 537).

Isomeric semicarbazones, $>C{:}N\cdot NH\cdot CO\cdot NH_2$, presumably *syn*- and *anti*-compounds, have also been obtained.

Molecules in which there occurs the complex —N=N— also exist in the *cis*- and *trans*-stereoisomeric forms shown below, in which R and R′ may be identical or different:



Azobenzene, the simplest azo-compound, has been known since 832. From its zero dipole moment, and the X-ray examination

of its crystal structure, it was assigned the *trans*-configuration, (II). It was not until 1938, however, that the corresponding *cis*-isomeride was isolated by G. S. Hartley.

trans-Azobenzene is partially converted into the orange-red *cis*-isomeride when its solutions are exposed to light and the two forms can be separated by chromatographic analysis (p. 980); the unstable *cis*- is readily converted into the *trans*-modification in solution.

Azoxy-compounds are also known in two physically different forms (Müller, *Ann.* **493**, 167; **495**, 132), and from an examination of their absorption spectra it is inferred that they are geometrical isomerides,

$$\begin{array}{l} R\cdot N \\ \quad \| \\ R\cdot NO \end{array} \qquad \text{and} \qquad \begin{array}{l} R\cdot N \\ \quad \| \\ ON\cdot R \end{array}$$

and not dimorphous forms of one substance.

Metallic Diazotates and Iso*diazotates*

When phenyldiazonium chloride is treated with an equivalent of silver oxide, or phenyldiazonium sulphate with an equivalent of barium hydroxide, in aqueous solution, strongly alkaline solutions of the diazonium hydroxide are produced; these solutions couple immediately (p. 463), but the hydroxides rapidly decompose, even at ordinary temperatures, giving resinous products.

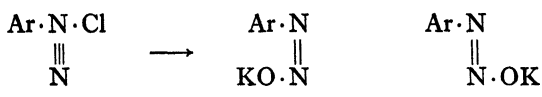
On adding a solution of a phenyldiazonium salt to concentrated potassium hydroxide solution at 0°, a crystalline (normal) *potassium diazotate*, $C_6H_5\cdot N_2\cdot OK$, is precipitated, but if this salt is then heated with the alkali at 130–140°, it undergoes a quantitative isomeric change and gives *potassium* iso*diazotate* (Schraube and Schmidt, *Ber.* 1894, 514).

Corresponding metallic diazotates and *iso*diazotates can be prepared from other diazonium salts, but in the case of *p*-nitrophenyldiazonium chloride the conversion of the former into the latter may occur even at −10°, so that the *iso*diazotate only can be isolated. The normal diazotates couple immediately with phenols, etc., but the *iso*diazotates do so only very slowly. On treatment with mineral acids, the normal diazotates give diazonium salts; the *iso*diazotates, on the other hand, afford solutions which at first couple only very slowly, but which do so immediately when they have been kept

during some time. Hydroxides, corresponding with the normal diazotates, cannot be isolated ; the alkali salts, with one equivalent of acid under certain conditions, give explosive oils which seem to be anhydrides and which, with alkali, regenerate the diazotates, and with acids, the diazonium salts. The metallic *iso*diazotates, with acetic acid, give oils which have acidic properties and which slowly change into neutral nitrosoamines. The normal alkali diazotates yield *O*-ethers, $R \cdot N_2 \cdot OCH_3$, whilst the *iso*diazotates give *N*-ethers, $R \cdot N(CH_3) \cdot NO$; the former are yellow oils which couple readily, and regenerate the diazotates with alkali, whereas the latter are identical with the nitroso-derivatives of secondary amines and do not couple, or do so only very slowly. The silver salts, prepared either from the normal or from the *iso*diazotates by precipitation with silver nitrate, yield *O*-ethers with methyl iodide. When the *N*-ethers are fused with alkali they afford *iso*diazotates.

Various explanations of the above facts have been put forward by Bamberger, Angeli, and others, but the following, due to Hantzsch, is now generally accepted :

Diazonium salts, (I), give both normal diazotates, (II), and *iso*-diazotates, (III), which are *syn*- and *anti*-stereoisomeric forms respectively corresponding with those of the oximes,



I II III

but, since all the substances concerned are ionised, they may also be represented by (IV), (V), and (VI) respectively :



IV V VI VII

It may be inferred, moreover, that the *anti*-diazotate can also react in the form (VII) because, as already mentioned above, it gives *N*-ethers.

The existence of three isomeric cyanides, $R \cdot N_2 \cdot CN$, has been proved ; one of these is colourless, readily soluble in water and behaves like a salt, whereas the other two are sparingly soluble,

coloured compounds, which are not electrolytes. It would seem, therefore, that the soluble cyanide is of the type (I), the other two being the *syn*- and *anti*-isomerides corresponding with (II) and (III) respectively; it has been shown by dipole moment measurements that the *syn*-form is the less stable (Le Fèvre, *J.* 1938, 431). It does not follow, however, that the metallic diazotates and *iso*-diazotates are also *syn*- and *anti*-compounds, because in this case structural isomerism, unlikely in the cyanides, is conceivable.

CHAPTER 47

OPTICAL ISOMERISM

Racemic Substances and Conglomerates

WHEN a solution of equal quantities of the two crystalline antimeric forms of any compound is evaporated, the *dl*-deposit may be either a racemic substance or a *dl*-conglomerate, and in some cases there is a transition temperature which determines the nature of such a deposit (p. 299). Now the *dl*-crystals thus obtained may be so small or ill-defined as to be unsuitable for goniometrical examination, and other methods must be used to ascertain which of the two *dl*-types has been formed. For this purpose, if one of the active isomerides is available, the following methods, mainly due to Roozeboom, may be used.

(1) The densities of the active and inactive modifications are determined under the same conditions; if these are different the *dl*-substance is racemic.

(2) The melting-point of the *dl*-substance alone, and mixed with different proportions of one of the active modifications, is observed; if the melting-points of all mixtures are higher than that of the *dl*-substance alone, the latter is a conglomerate, but if the melting-point of any mixture is lower, then the *dl*-substance is racemic. This method is based on a study of the melting-point curves of mixtures of the two enantiomorphs in variable proportions. The curve thus obtained with a conglomerate is of the type shown in (I), Fig. 29, with a minimum when equal quantities of the *d*- and

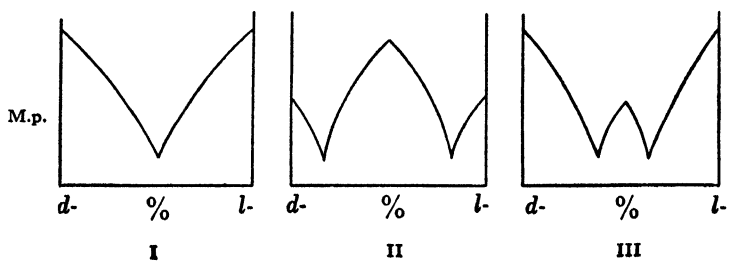


Fig. 29

l-forms are present, so that the addition of either isomeride raises the melting-point. The curves for a racemic substance are shown in (II) and (III), according as its melting-point is higher or lower than (or the same as) that of the *d*- or *l*-form ; in either case, with certain proportions of either of the isomerides, the melting-point is depressed.

The conclusions drawn from such observations refer only to the nature of the *dl*-substance at the observed melting-point, since a conglomerate at the ordinary temperature might become a racemic substance when it is heated, and *vice versa*.

(3) A saturated solution of the *dl*-substance is shaken with a small proportion of one of the active isomerides, and after filtration, if necessary, is then examined in a polarimeter ; if the solution shows optical activity the *dl*-substance is racemic, whereas it is a conglomerate if no rotation is observed. A determination of the weight of substance in a given volume of the saturated solution before and after it has been shaken with the active form, also distinguishes between the two possibilities. If the substance is a conglomerate the two quantities are identical, but if it is racemic this will not be so. Both these methods depend on the fact that a mixture of equal quantities is more soluble than any other mixture of the *d*- and *l*-forms, and a saturated solution of such a mixture cannot dissolve either isomeride ; a solution saturated with a racemic substance, however, is still unsaturated with regard to either the *d*- or the *l*-form.

Variation in the Specific Rotation with Experimental Conditions

The specific rotation of a substance varies with the temperature, in some cases increasing, in others diminishing, as the temperature rises. It also varies with the wave-length of the light with which it is observed (footnote, p. 309), a phenomenon which is known as *rotatory dispersion* ; when, therefore, a specific rotation is given, the wave-length of the light and the temperature must be indicated as in $[\alpha]_{D}^{15^\circ}$, where D refers to the sodium line, or $[\alpha]_{5461}^{20^\circ}$, where the lower figures refer to the green line of the mercury-vapour spectrum. The specific rotation may vary very considerably with the nature of the solvent ; also with the concentration of the solution, but except in the case of optically active electrolytes dissolved in ionising liquids, the variation is quite irregular.

In aqueous solution, however, in the case of electrolytes important

regularities have been established. It was observed by Landolt that the molecular rotations, [M] (p. 309), of all normal salts of *d*-tartaric acid were practically the same in sufficiently dilute aqueous solution, and Oudemans showed that this was also true of the salts of *quinic acid* (1:3:4:5-tetrahydroxy*cyclo*hexanecarboxylic acid); further, it was found that the molecular rotations of various salts of a given active alkaloid with mineral or with organic acids were also practically identical in sufficiently dilute solution, but varied with the concentration. These observations were explained by Hädrich, who concluded that in a completely ionised state the specific rotation is independent of the inactive ion; in concentrated solutions the observed rotation may be greater or less than the value in dilute solution, because it is due both to the active ion and to the non-ionised molecule, but as dilution and ionisation increase, it becomes practically constant. This explanation cannot be accepted nowadays as all salts are completely ionised under all conditions, but as the rotation of solutions of optically active non-electrolytes in non-ionising solvents frequently varies with the concentration it is not surprising that similar variations occur with electrolytes in aqueous solution.

All salts of the very strong acid, d-*α-bromocamphor-π-sulphonic acid* (p. 931), which were examined by Walden, gave a constant value $[M_D]+270°$ for the *d*-α-bromocamphor-π-sulphonate ion[1] in aqueous solution. It is thus possible to determine the unknown molecular rotation of one of the ions of such a salt when that of the other is known. If, for example, the *d*-bromocamphorsulphonate of a base gives $[M]_D+180°$, the ion of the base would have $[M]_D-90°$ (compare p. 762).

Relation between Structure and Specific Rotation

The pronounced influence of temperature, solvent, and concentration of the solution, and also the facts observed in the case of electrolytes, show clearly that the observed specific rotation depends on the state of the optically active molecules under the experimental conditions, as well as on their structure. It is not

[1] This value is probably too low and should be about $[M]_D$ 280°, because, as usually prepared, the acid contains a small proportion of an optical isomeride having a much lower $[M]_D$ than 270° (F. S. Kipping, *J.* 1905, 628).

surprising, therefore, that in consequence of the disturbing influences of association and other factors, attempts to determine the relation between the specific rotation of a substance and its constitution have so far met with little success. Even in the case of homologous compounds, such as the alcohols, $CH_3 \cdot CH(OH) \cdot R$ and $C_2H_5 \cdot CH(OH) \cdot R$, where R is a normal alkyl radical, there does not appear to be any simple numerical relation between the molecular rotations, whether determined in the liquid state or in solution (Pickard and Kenyon, *J.* 1913, 1923). This is also true as regards other closely related compounds such as derivatives of *o*-, *m*-, and *p*-nitrobenzoic acids containing structurally identical optically active groups (Frankland and Harger, *J.* 1904, 1571).

The addition of borax, boric acid, certain metallic hydroxides, acids, or salts such as molybdates, tungstates, uranates, etc., to a solution of an optically active substance, often causes a great change in the specific rotation, owing to the interaction of the active and inactive compounds ; the specific rotation of malic acid, for example, is increased to about 500 times its original value by the addition of a uranate. In the case of some optically active compounds, such as the sugars, the effect of the addition of boric acid on the specific rotation may be utilised to distinguish between *cis*- and *trans*-configurations of a group —CH(OH)·CH(OH)—, since the former only may react with the acid, giving a cyclic complex of very different rotatory power.

Optical Superposition

When one of the atoms or radicals in an asymmetric group is displaced by an atom or radical of a very different nature, as, for example, when lactic acid is converted into α-chloro-, bromo-, or amino-propionic acid, it may be presumed that there will be a considerable change in the molecular rotation. If, however, in an asymmetric group one of the radicals were displaced by another, which is different in *configuration* only, it would seem that little change in molecular rotation should occur, unless the entering group is itself optically active ; in the latter case the molecular rotation should be increased or diminished according as the rotation of the entering group is *d*- or *l*-, and the observed value should be the algebraic sum of those of the two dissymmetric radicals. This is the principle of *optical superposition*, formulated by van't Hoff ; it has been found to hold good approximately in many cases.

The ester of *l*-lactic acid with *dl*-amyl alcohol, for example, has $[M]_D = -10{\cdot}2°$, a value which may be assigned to the *l*-lactyl complex; the *l*-amyl ester of *dl*-lactic acid has $[M]_D = +4{\cdot}2°$, and this value may be attributed to the *l*-amyl group. The molecular rotation of the *l*-amyl ester of *l*-lactic acid should therefore be the algebraic sum of the above values for the two radicals, and is, in fact, $[M]_D = -6{\cdot}3°$. The principle of optical superposition is of considerable importance in the study of the sugars (p. 868), but many exceptions to the rule have been observed.

Asymmetric Synthesis

When lactic acid is synthesised from acetaldehyde or by the reduction of pyruvic acid, the *dl*-acid is obtained; similarly when tartaric acid is synthesised from glyoxal or from succinic acid, an optically inactive dihydroxy-acid is produced, because in all these reactions the *d*- and *l*-groups in the molecule are generated in almost exactly equal quantities.[1] When, however, an optically active aldehyde, such as *l*-arabinose (p. 335), is combined with hydrogen cyanide, the two cyanohydrins, and the two acids (gluconic and mannonic) obtained from them by hydrolysis, are not produced in equal quantities; the original molecule is dissymmetric and directs the course of the additive reaction. If, therefore, a symmetrical molecule is temporarily transformed into a dissymmetrical molecule by the introduction of some optically active radical and is then treated in such a way that a new asymmetric group is formed, ***unequal*** quantities of this group may result and, after the removal of the optically active radical, a product which shows some activity may be obtained; in extreme cases only the *d*- or the *l*-form of the new group might be generated (p. 747).

Now *methylethylmalonic acid* is decomposed when it is heated, giving dl-*methylethylacetic acid* and the product is inactive. When, however, the methylethylmalonic acid is converted into its brucine hydrogen salt and the mixture of the two *diastereoisomerides*[2] is then heated, unequal quantities of the salts of *d*- and *l*-methylethylacetic

[1] According to the laws of probability, the quantities of the *d*- and *l*-forms will not be exactly equal, but the excess of either will be so small that it cannot be detected (Mills, *J. Soc. Chem. Ind.* 1932).

[2] Structurally identical compounds which are optically active but not enantiomorphously related are said to be diastereoisomeric, as, for example, the + + and + − forms of chlorohydroxysuccinic acid and salts *d*A*l*B and *d*A*d*B, or *d*A*l*B and *l*A*l*B in general.

acids are formed, and, after the removal of the brucine, the product is distinctly laevorotatory (Marckwald).

When *benzoylformic acid*, $C_6H_5 \cdot CO \cdot COOH$, is reduced it gives equal quantities of *d*- and *l*-mandelic acids; when, however, the acid is converted into its *l*-menthyl ester and the latter is reduced with aluminium amalgam and water, unequal quantities of the *d*- and *l*-forms of the $>CH(OH)$ group are generated and the product contains an excess of the ester of the *l*-acid: on hydrolysis, however, after the removal of the menthol, an optically inactive mandelic acid is obtained owing to racemisation (p. 748). In a similar manner, when l-*menthyl benzoylformate* is treated with methyl magnesium iodide, the product is a mixture of unequal quantities of the esters of *methylphenylglycollic acid*, but in this case, after hydrolysing the ester and removing the *l*-menthol, there remains an acid, which consists of about 60% of the *l*-, to 40% of the *d*-isomeride (McKenzie). It has also been shown that when l-*bornyl fumarate* is oxidised with permanganate it yields a *bornyl* ester from which unequal quantities of *d*- and *l*-tartaric acids are obtained (McKenzie).

Syntheses of this kind which, starting from a symmetrical molecule, convert it into unequal quantities of *d*- and *l*-isomerides, are termed *asymmetric syntheses*.

These results show that the dissymmetry of a molecule may determine the course of reactions brought about by symmetrical substances only, a fact which seems to have an important bearing on the syntheses which occur in animals and plants; in the synthesis of aldohexoses in plants, for example, only very few of the sixteen optically active isomerides seem to be produced or else the other isomerides, if formed, are selectively decomposed. Even in laboratory syntheses such dissymmetric influences may be very pronounced; when, for example, mannoheptose is prepared from *d*-mannose (p. 320) only one of the two theoretically possible aldoheptoses is obtained because, in the addition of the elements of hydrogen cyanide to the aldehyde group, the course of the reaction is directed by the dissymmetry of the molecule.

Since a dissymmetric group may direct symmetrical reagents, it would seem that dissymmetric reagents should show a very different behaviour towards a given optically active molecule; this, in fact, is so, and enantiomorphously related compounds often show differences in smell, in taste, and in physiological activity in general, properties which no doubt depend on their reactions towards other

optically active compounds contained in animal matter. Of great importance also is the difference in the behaviour of *d*- and *l*-enantiomorphs, and of optical isomerides in general, towards enzymes (pp. 863, 890, 902), but perhaps the most interesting fact is that these dissymmetric agents may convert a *symmetrical* molecule into *one* only of two enantiomorphously related derivatives (p. 905).

It was found by Cotton in 1896 that *d*- and *l*- circularly polarised beams of light are unequally absorbed by solutions of certain coloured, optically active compounds, a phenomenon which he called *circular dichroism*. It seemed, therefore, that if the optically active compound is decomposed by the light, the *d*- and *l*-forms might be changed at different rates by a given beam, in which case a solution of a *dl*-substance would become optically active. This was found to be so; when dl-*α-azidodimethylpropionamide*, $CH_3 \cdot CH(N_3) \cdot CO \cdot NMe_2$, is treated in this way in hexane solution, one of the forms is decomposed more rapidly than the other, and in consequence the unchanged material shows optical activity; an asymmetric photochemical resolution has thus been accomplished (Kuhn, W. and Knopf). In a similar manner, as was shown by Mitchell (*J.* 1930, 1829), the *dl*-nitrosite of a sesquiterpene, *caryophyllene* (from hop-oil), undergoes photochemical decomposition, with the evolution of nitrogen, and the original solution of the *dl*-substance becomes optically active. More recently Mitchell and Dawson (*J.* 1944, 452) have shown that when β-chloro-β-nitroso-αδ-diphenylbutane, $Ph \cdot CH_2 \cdot CCl(NO) \cdot CH_2 \cdot CH_2 \cdot Ph$, dissolved in methyl alcohol is irradiated with circularly polarised light until about 90% of it is decomposed, the unattacked portion is optically active; the decomposition products, of which the chief is αδ-diphenyl-β-butanoneoxime, contain no asymmetric group.

Racemisation and Epimeric Change

The *d*- and *l*-forms of many compounds are convertible one into the other, with the aid of heat or of a suitable reagent. When the change is carried to completion the product is a mixture of equal quantities of the two forms and is optically inactive; the optically active compound is then said to have *racemised* or to have undergone racemisation. The first case of racemisation was observed by Pasteur, who found that, when the cinchonine salt of *d*- or of *l*-tartaric acid is heated at 170° during some hours, it gives a mixture

of salts from which *dl*-tartaric acid can be isolated ; *d*-tartaric acid, heated during many hours with water at 175°, is also converted into *dl*- (and *meso*) tartaric acids, and *l*-tartaric acid, of course, behaves like the *d*-acid. Mandelic acid, and other acids, the optical activity of which, as in the case of tartaric acid, is due to the presence of an asymmetric group, —CH(OH)·COOH, undergo racemisation when they are heated, and certain esters such as *methyl α-chloropropionate* and *dimethyl bromosuccinate* undergo spontaneous racemisation (*autoracemisation*) at ordinary temperatures in the presence of traces of mineral acids. *Methylbenzylacetyl chloride* also racemises when it is heated at 120°. Optically active β-methyl-α-indanone is stable in alcoholic solution, but is immediately racemised on the addition of a little alkali ; many other optically active ketones behave similarly.

In all these cases a hydrogen atom is one of the four different groups associated with optical activity and racemisation is probably due either to the formation of a planar mesomeric anion (p. 831), $>C^-—CR=O/>C=CR—O^-$ whose formation is catalysed by bases, or to the formation of a planar enolic form >C=CR—OH. If there is no hydrogen atom associated with the asymmetric centre, as, for example, in atrolactic acid, Ph·C(OH)Me·COOH, then racemisation does not usually occur and in general when a mesomeric ion or an enolic form cannot be produced, an asymmetric carbon-group retains its configuration, and an optically active compound does not racemise unless it is submitted to very vigorous treatment.

The racemisation of *l*-limonene at high temperatures is probably due to the lability of the hydrogen atom in position 6 (p. 912), which is sufficiently easily ionised to give a mesomeric anion $—^-CH—CMe=CH—/—CH=CMe—CH^-—$ to which a proton may be added in position 2 or 6.

The sodium derivative of optically active amyl alcohol is racemised, but only at a high temperature (about 200°). In this case it is possible that a trace of the aldehyde is formed by oxidation and that then a reversible change occurs, as in the Ponndorf-Meerwein reaction, whereby each molecule of the alcohol is oxidised to one of the aldehyde at some stage in the process and then reduced again ; the aldehyde is racemised by the formation of a mesomeric ion. Other cases of racemisation of compounds which owe their optical activity to restricted rotation are mentioned later (p. 759, 760).

The phenomenon of racemisation is closely related to that of epimeric change. When *d*-gluconic acid is heated with quinoline

(to prevent the formation of lactone) at 140° it gives *d*-mannonic acid; the >CH(OH) group, directly combined to the carboxyl radical, undergoes a change, giving >C(OH)H, up to a condition of equilibrium, but the three other >CH(OH) groups in the molecule retain their original configurations (*d*- or *l*-). The product, therefore, although a mixture of optical isomerides, is not a *dl*-compound and is not enantiomorphously related to the original substance. An *optical inversion* of this kind is a reversible reaction and is known as an *epimeric* change; the two substances concerned are *epimerides*. At the condition of equilibrium the product is not necessarily, or usually, a mixture of equal quantities of the two epimerides because the two forms differ in stability.

Many other examples of epimeric change are met with in studying the acids derived from the sugars and also the sugars themselves, and many of the latter show *mutarotation* (p. 866) in aqueous solution owing to transformations of this nature. Some camphor derivatives also undergo epimeric changes and, in consequence, show mutarotation (p. 836).

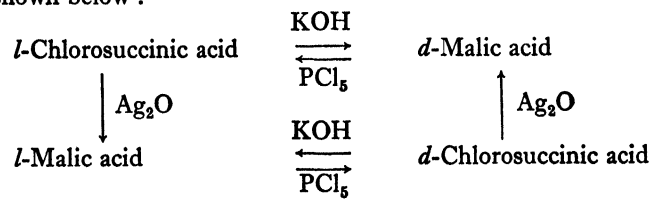
Interesting cases of optical change of an exceptional character have been observed during the resolution of certain *dl*-substances. dl-*Chloroiodomethanesulphonic aicd*, $CHICl \cdot SO_3H$, has been resolved into its *d*- and *l*-components by Pope and Read (*J.* 1914, 811), who found that the active acids were stable at the ordinary temperature and thus proved that optical activity may occur in a compound containing one carbon atom only. The corresponding *dl*-chlorobromo-acid, $CHBrCl \cdot SO_3H$, was investigated by Read and McMath (*J.* 1925, 1572), who prepared its l-*hydroxyindylamine*[1] salt and found that in undried acetone solution the *d*-acid was partly converted into the *l*-isomeride, giving an equilibrium mixture of about 81% of the *l*B*l*A and 19% of the *l*B*d*A salt. Under similar conditions, but with *d*-hydroxyindylamine, the *l*-acid was converted into the *d*-acid until a corresponding condition of equilibrium was reached; the pure *l*B*l*A and *d*B*d*A salts, therefore, showed mutarotation in aqueous alcoholic solution owing to the transformation of each into the equilibrium mixture. A similar phenomenon had been previously studied by Pope and Peachey (*Proc. Chem. Soc.* 1900, 42, 116) during the resolution of dl-*methylethylpropylstannic*

[1] *dl*-α-Hydroxy-β-indylamine is prepared by shaking indene with bromine water and treating the bromohydroxyindane thus formed with ammonia; it is resolved with the aid of *d*-α-bromocamphor-π-sulphonic acid.

d-α-*bromocamphor-π-sulphonate* (p. 767) from solutions of which only the *d*-base *d*-acid crystallised. In this case the interconversion of the *d*- and *l*-forms is probably due to the existence of the ion $MeEtPrSn^+$ and the lesser solubility of the salt of the *d*-base causes it to crystallise from the solution. Another interesting case is described on p. 760.

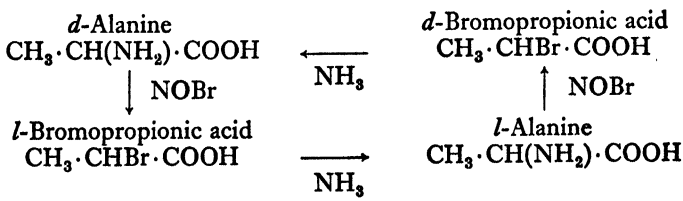
The Walden Inversion

It was observed by Walden in 1896 that *l*-chlorosuccinic acid, treated with moist silver oxide gave *l*-malic acid, but with potassium hydroxide solution it afforded *d*-malic acid ; further, it was found that *l*-malic acid was converted into *d*-chlorosuccinic acid by the action of phosphorus pentachloride. The two malic acids, and the two chlorosuccinic acids, could thus be converted one into the other as shown below :

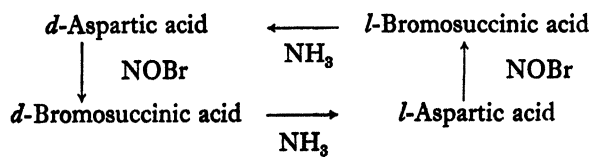


Such a transformation of a *d*- into an *l*-isomeride, or *vice versa*, was known as a *Walden inversion.*

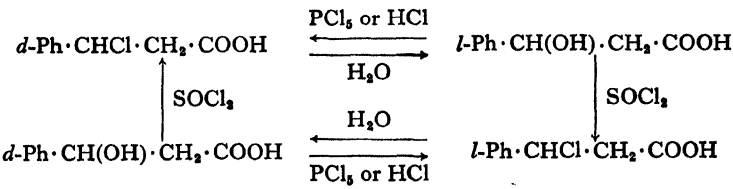
Corresponding inversions were observed by Fischer in the case of *d*-alanine, which can be converted into the *l*-isomeride and *vice versa* :



Aspartic acid shows similar behaviour :



In all the above examples the Walden inversion occurs with compounds in which the asymmetric group is directly combined with the carboxyl radical, but this is not a necessary condition as is shown for example in the following transformations of *β-phenyl-β-hydroxypropionic acid* studied by McKenzie :



It should be carefully noted that in all the above examples the letters *d-* and *l-* show *only* whether the substance is dextro- or laevorotatory, and it cannot be assumed that because dextrorotatory malic acid is converted into laevorotatory chlorosuccinic acid, an inversion of configuration has in fact occurred ; the chlorine atom may occupy the same position in the molecule as the hydroxyl group which has been displaced, and yet the sign of the rotation may be changed. A change of configuration is not established until the *l*-chloro-acid has been converted into *l*-malic acid. It is also clear that *either* the reaction of malic acid with phosphorus pentachloride *or* that of the resulting chloro-acid with silver oxide must involve an inversion of configuration, but that both reactions cannot do so.

As stated above, the term Walden inversion was originally applied to the change of a *d-* into an *l*-isomeride (or *vice versa*), but it is now more commonly applied to any single reaction in which an inversion of configuration occurs : for example, as will be shown later, such an inversion of configuration occurs in the conversion of *l*-chlorosuccinic acid into *d*-malic acid and hence a Walden inversion is said to have taken place in this one reaction.

A great many explanations of the Walden inversion have been suggested. Fischer and Werner, for example, assumed that the first stage is the formation of an additive product, the configuration of which determines the course of the final substitution. If, for example, the compound C(*abcd*) is treated with a reagent, XY, the latter is attracted to the face *adc*, or to that of one of the other three faces of the tetrahedron, according to the nature of the interacting compounds. When now the second stage of the reaction occurs and *d* is displaced from the molecule, if the substituent is in

one of the positions close to *d*, it will take the place of *d* and no inversion will occur; if, however, the substituent is in position on the distant face *abc*, one of the atoms or groups *a*, *b*, or *c* may slip into the position previously occupied by *d*, and its place will then be taken by X so that a Walden inversion results.

Another suggestion was made by Holmberg (*Ber.* 1926, 125) which does not assume the formation of an additive compound, but supposes that the course of the reaction is determined by the length of the molecule of the substituting reagent, X—Y. When this is large compared with the distance C—*d*, and Y removes *d*, one of the atoms or groups *a*, *b*, *c* will be nearer than X to the *d* corner and will slip into the unoccupied space, while X takes up the new position which has been vacated. In this case a Walden inversion will occur, whereas if the distance X—Y is small compared with C—*d*, X takes the place of *d* and there will be no change in configuration.

Theories of this kind were the only ones possible at that time and it was only after the mechanism of substitution in aliphatic compounds in general had been more fully studied that a satisfactory explanation could be given.

It has already been pointed out that in an S_N2 reaction,

$$A+RB \longrightarrow RA+B,$$

the entering group A approaches RB towards the face of the tetrahedron remote from B; when B leaves the transition state there is therefore an inversion of configuration by a sort of "umbrella turning inside out effect", as shown in the accompanying figure representing the action of an alkyl halide with ammonia (Mills, 1932),

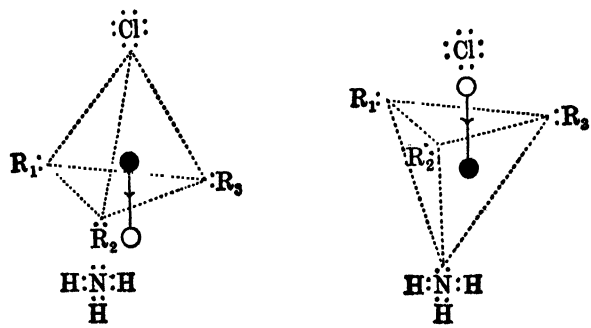


Fig. 30

That this is in fact the case has been shown by Hughes and his co-workers (*J.* 1935, 1525) who studied the reversible reaction between 2-n-*octyl iodide* and sodium iodide containing radioactive iodine (indicated by an asterisk) in acetone solution,

$$C_8H_{17}I + \overset{*}{I}^- \rightleftharpoons C_8H_{17}\overset{*}{I} + I^-,$$

and the racemisation of d-2-n-*octyl iodide* by sodium iodide in acetone, which is caused by a similar reversible interchange of iodine atoms of the alkyl halide with iodide ions. Assuming that every individual substitution gives inversion of configuration the rate of iodine exchange was calculated from the rate of racemisation ; this rate was found to be equal to the measured rate of exchange using radioactive iodine. In this particular case, therefore, the S_N2 reaction leads to inversion and it is now assumed that this is always so.

In an S_N1 reaction the *carbonium ion*, R^+, is planar and when union with A^- occurs there is an equal chance of A^- combining on either side of this plane : equimolecular amounts of the two configurations will be formed and complete racemisation results. In fact the situation is not quite so simple because if B^- has not moved far from R^+ before the approach of A^-, the latter will tend to be at the side remote from B^- and inversion will occur with some racemisation.

Another complication is present if the group R^+ contains certain *configuration holding* groups, the most important of which is the α-COO^- ion. This group is electron repelling and therefore promotes S_N1 substitution and as soon as B^- has been split off a weak bond, a sort of lactone, is formed between the carbon atom which B^- has left and the -COO^- ion on the side remote from that occupied previously by B^- ; this side is therefore protected from attack by A^- which must wait until B^- has moved sufficiently far for A^- to take its place. Reaction therefore occurs with retention of configuration,

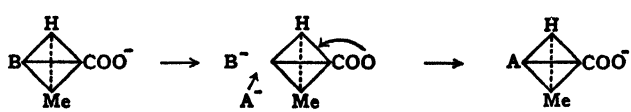
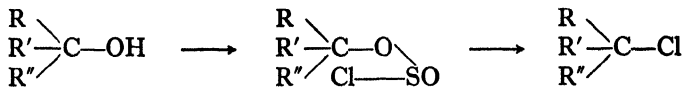


Fig. 31

Another way of regarding a reaction of this sort is that it consists of two successive S_N2 processes each involving inversion : the first

leads to the formation of the lactone and the second to its decomposition by the group A. It is clear that two inversions will reproduce the original configuration.

Reaction can occur with retention of configuration in another way as is illustrated by the action of thionyl chloride on an alcohol: an intermediate may be formed which then decomposes by an internal reaction in which the chlorine atom takes the place of the hydroyxl group,

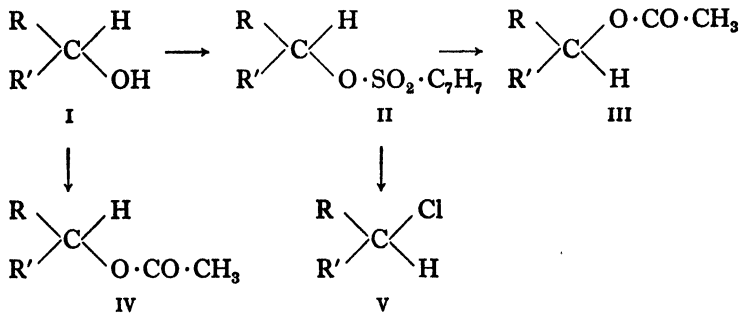


the thionyl chloride is acting as a configuration holding reagent. It is possible that this is the mechanism of the action of thionyl chloride on *β-phenyl-β-hydroxypropionic acid* (p. 752), which, as will be seen later, does not involve an inversion; thionyl chloride, however, does not always act in this way and in some cases causes inversion.

The other examples of the Walden inversion given all involve compounds which contain a carboxyl group as one of the four different groups of the asymmetric centre and it is now clear why the phenomenon was first observed in such cases. If the result of two successive reactions is to convert a *d-* into its *l*-antimer one of the changes must involve inversion, and one retention, of configuration; the commonest way in which the latter can occur is with an S_N1 reaction with a configuration holding group. Without such a group two successive S_N2 reactions would both give inversion and the final product would be identical in configuration with the starting material; or if either reaction were S_N1, racemisation with possibly some inversion would occur at each such step.

The next matter to consider is in which of the two reactions involved in converting a *d-* into an *l*-antimer or *vice versa* does the actual change of configuration occur. Kenyon and Phillips and their co-workers approached this problem as follows. When an alcohol, (I), is converted into its *p*-toluenesulphonate, (II), by the action of *p*-toluenesulphonyl chloride the carbon-oxygen link of the alcohol is not broken and it can be assumed that no change of configuration occurs in the asymmetric group; if it is similarly assumed that conversion of an alcohol into an acetate, (IV), by acetic anhydride also produces no change in configuration, it

follows that the alcohol, its *p*-toluenesulphonate and its acetate all have the same configuration. It is not, of course, obvious that the action of acetic anhydride, like that of *p*-toluenesulphonyl chloride, involves no break in the carbon-oxygen linkage, but a careful study of esterification has shown that the assumption is justified (p. 695*k seq.*). Now it was found that when an optically active alcohol was converted directly into its acetate the sign of rotation of the latter was opposite to that of the acetate, (III), obtained from the *p*-toluenesulphonate by the action of potassium acetate; inversion of configuration must therefore have occurred in this last change (II⟶III), by an S_N2 reaction,



Assuming that a similar inversion occurs in the analogous reaction of the *p*-toluenesulphonate with lithium chloride to give the chloride, (V), this chloride will be opposite in configuration to the original alcohol.

In many other cases it can be shown by kinetic investigations that reactions are of the S_N2 type and assuming that this always gives inversion, relative configurations can be determined; if, for example, a dextrorotatory halide is converted by an S_N2 hydrolysis into a laevorotatory hydroxy-compound, the halide and alcohol of like rotations are of the same configuration and so on. Working in this way it has been shown that substances of the same configuration have the signs of rotation as indicated:

	X=Cl	Br	OH	NH_2
$HOOC\cdot CH_2\cdot CHX\cdot COOH$	+	+	+	+
$CH_3\cdot CHX\cdot COOH$	+	+	−	−
$Ph\cdot CHX\cdot CH_2\cdot COOH$	+	+	+	

It is thus clear that in the examples on pp. 751-752, the reactions of caustic potash on the halides, of phosphorus pentachloride on the alcohols and of ammonia on the halides all occur with inversion of configuration, whereas those of silver oxide on the halides and of nitrosyl bromide on the amines do not involve such a change. In some of the reactions, such as those of phosphorus pentachloride on alcohols, which do not admit of kinetic investigation, the mechanism may be S_N2 or S_N1 involving predominant inversion : the silver oxide reaction is S_N1 with a configuration holding group. The schemes on pp. 751-752 have been so arranged that all the changes represented by horizontal arrows involve inversion, whilst those shown vertically do not.

The foregoing considerations also explain facts such as the following, which were very puzzling to earlier workers : although *d*-alanine gives *l*-bromopropionic acid with nitrosyl bromide (no inversion), its ethyl ester gives an ester of the *d*-bromo-acid (inversion) ; this is due to the configuration holding power of the carboxyl group which is not shown by the carbethoxy-radical. Again, when sodium α-bromopropionate is hydrolysed with concentrated alkali in aqueous solution an S_N2 reaction with inversion occurs, but with dilute alkali the configuration is retained by an S_N1 configuration holding reaction.

Other examples of the Walden inversion are encountered in the carbohydrates (p. 880) and the sterols, and the theories outlined above apply equally to all fields of organic chemistry where optical activity is due to asymmetric carbon-groups ; it is possible, therefore, to correlate the absolute configuration of a particular group of this kind in any compound with that in related substances.

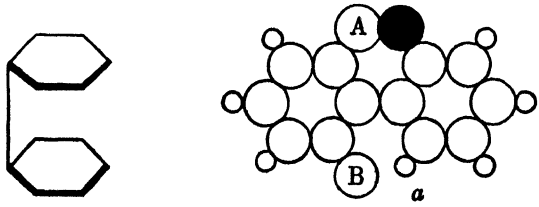
Optically Active Diphenyl Derivatives and the Phenomenon of Restricted Rotation

As the benzene molecule is planar (p. 1001), the configuration of diphenyl should presumably be represented by two plane rings, capable of free rotation about their point of union. Various compounds obtained from benzidine, $NH_2 \cdot C_6H_4 \cdot C_6H_4 \cdot NH_2$, however, appeared to be formed by reactions which required the proximity of the two *p*-amino groups; in consequence Kaufler (1907) proposed for diphenyl the configuration (I, Butterfly formula),

in which the two rings are situated in parallel planes, and the two *p*-amino-groups are closer together than in other possible configurations.

The experimental evidence on which Kaufler's suggestion had been based was afterwards found to be valueless, and his formula has also been disproved by measurements of the dipole moments of *pp'*-diphenyl derivatives, $X \cdot C_6H_4 \cdot C_6H_4 \cdot X$, which give values almost the same as those of the corresponding *p*-derivatives of benzene, and, in particular, when X = Cl or Br, the dipole moment is zero (p. 705): the Kaufler formula would require a relatively large moment in the case of *pp'*-dichlorodiphenyl.

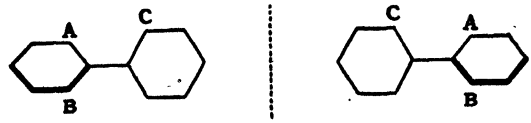
In the meantime, however, it had been shown by Christie and Kenner that certain simple substitution products of diphenyl could be resolved into optically active forms. This fact might be accounted for on the basis of Kaufler's formula, but an alternative explanation was put forward almost simultaneously by Turner and Le Fèvre, Bell and Kenyon, and Mills, who suggested that, in certain diphenyl derivatives, the free rotation of the phenyl groups was in some way prevented. This view is now established: when a diphenyl derivative contains sufficiently large substituents in the *o*-positions to the junction of the rings, these substituents cannot pass one another (provided the molecule is sufficiently rigid), but clash or collide when either of the rings is turned around the C—C axis; free rotation is therefore blocked.



I II

Fig. 32

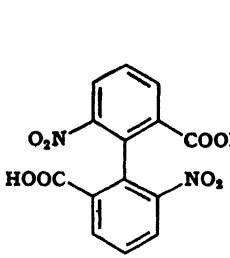
Thus in the case of a compound, (II), containing three substituents, A, B, and C, when C (the dark disc) cannot pass either A or B, the two benzene rings cannot be, or become, co-planar. Whatever their position, therefore, the compound will exist in two enantiomorphously related forms, (III), in both of which the rotation of either ring is confined to an arc of less than 180°.



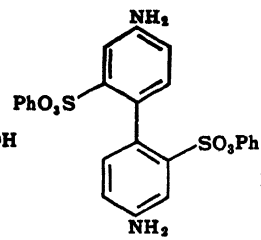
III

The first example of optical isomerism of this kind was observed in the case of 2:2′-*dinitro*-6:6′-*diphenic acid*, (IV), which was resolved by Christie and Kenner; since then many analogous compounds, including 2-*nitro*-6:6′-*diphenic acid*, have been proved to exist in optically active forms, as indicated in (III).

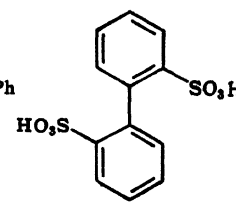
Later Lesslie and Turner (*J.* 1932, 2021, 2394) resolved *diphenyl benzidine*-2:2′-*disulphonate*, (V), and also *diphenyl*-2:2′-*disulphonic acid*, (VI); in which the groups in the 2- and 2′-positions are sufficiently large to clash with the *o*-hydrogen atoms of the nuclei indicated by (*a*) in (II), Fig. 32.



IV

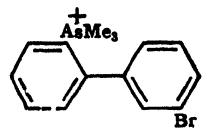


V



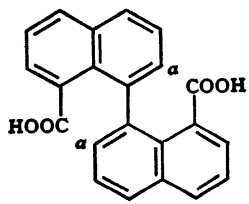
VI

d-Diphenyl-2:2′-disulphonic acid is racemised at 100° C., a fact which shows that the obstruction is not very large and the molecule not completely rigid. The compound (VII) has also been resolved; here restricted rotation is due to the clashing of the Me_3As group with the *o*-hydrogen atoms only, and the bromine atom causes dissymmetry.

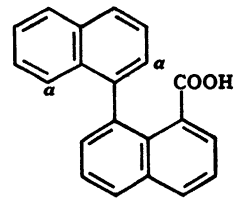


VII

Similar phenomena have been observed in the case of certain dinaphthyl derivatives. 1:1′-*Dinaphthyl*-8:8′-*dicarboxylic acid*, (VIII), has been resolved by the crystallisation of its brucine salt, but the sodium salt of the active acid slowly racemises in aqueous solution. 1:1′-*Dinaphthyl*-8-*carboxylic acid*, (IX), gives a brucine salt which, when crystallised from ethyl acetate, gives *either* the salt of the *d*- or that of the *l*-acid, and finally the whole acid may be deposited in the form of one component ; either salt can be obtained by ' seeding ' the solution with a crystal of the *d*- or *l*-isomeride. The sodium



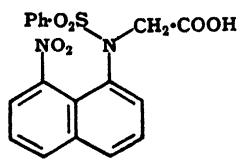
VIII



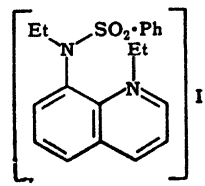
IX

salt racemises in aqueous solution. In (VIII) obstruction is caused by the hydrogen atoms (*a*) at 2 and 2′, and in (IX) by those at 2′ and 8′.

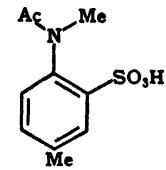
Mills and his co-workers have also demonstrated restricted rotation in *peri*-derivatives of naphthalene, (X), and quinoline, (XI), and in *o*-derivatives of benzene, (XII) and (XIII) :



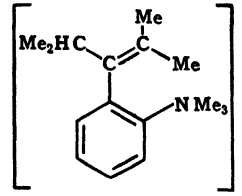
X



XI

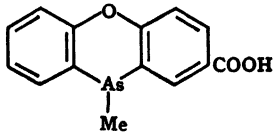


XII

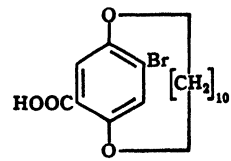


XIII

Lesslie and Turner (*J.* 1934, 1170) have resolved 10-*methylphenoxarsine-2-carboxylic acid*, (XIV); the dissymmetry is here ascribed to a folding of the molecule along a line joining the oxygen and the arsenic atoms:



XIV

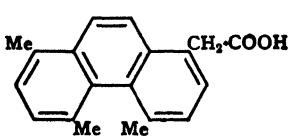


XV

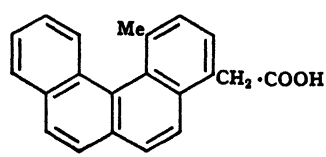
Dipole moment measurements indicate similar folded molecules for those analogues of the above in which the MeAs< group is displaced by an oxygen or a sulphur atom.

A final example of optical activity due to restricted rotation is that of (XV); here the full rotation of the benzene ring is prevented by its 2:5-substituents which clash with the large 1:4-ring.

In 1947 Newman showed that the acid (XVI) could be obtained



XVI



XVII

optically active; solutions of the brucine salt deposited the salt of the *d*-acid only and the optically active acid racemised easily. The activity of this acid proves that its molecule cannot be planar. A model of the molecule shows that there is no room for the two

methyl groups at 4- and 5- if the phenanthrene system and the methyl groups all lie in one plane, as would be expected. Either one or both the methyl groups must be forced out of the plane of the ring by this overcrowding, or the ring is buckled. The acid (XVII) has also been obtained optically active.

Stereochemistry of Quaternary Ammonium Compounds

For many years after the formulation of Le Bel and van't Hoff's hypothesis in 1874, the only compounds which were optically active in solution were those which contained in their molecules one or more asymmetric carbon-groups. In 1891, Le Bel prepared *methylethylpropylisobutylammonium chloride*, NMeEtPrBuCl, and, on the supposition that the quaternary salt might exist in enantiomorphously related forms, he attempted to obtain one of these by leaving a solution of the compound in contact with *Penicillium glaucum* (p. 306). In this way he obtained a solution which was very feebly laevorotatory, but which lost its activity when it was kept during a short time.

Pope and Peachey (*J.* 1899, 1127) prepared *methylallylphenylbenzylammonium iodide*, a compound which had been studied by Wedekind (*Ber.* 1899, 517), and heated it in acetone-ethyl acetate solution with silver *d*-camphor-β-sulphonate (p. 932); after the silver iodide had been separated, the salt in the solution was fractionally crystallised, and the more sparingly soluble fraction was found to have $[M]_D$+208° in aqueous solution. Since the acid ion has $[M]_D$+51·7°, it was concluded that the salt had been resolved and that the ammonium radical in the salt was dextrorotatory, having *approximately* $[M]_D$+156° in aqueous solution (p. 744). The first conclusion was confirmed by converting the camphorsulphonate into the iodide, which in acetone-methyl alcoholic solution gave $[M]_D$+192°.[1] The original mother liquors from the salt of the *d*-base gave finally the camphorsulphonate of the *l*-base, not quite free from the *d*-isomeride, having $[M]_D$−87° in aqueous solution; from this impure preparation the pure iodide of the *l*-base was prepared and found to correspond with that of the *d*-base. It was thus proved that a compound $NR_1R_2R_3R_4X$ exists in optically active, enantiomorphously related forms.

[1] As the $[M]_D$ of this salt was not determined in aqueous solution, its value is not that of the substituted ammonium radical, but rather that of the molecule of the salt.

The manner in which the five radicals in such compounds are arranged in space had previously given rise to much discussion. Willgerodt had suggested that they occupied the corners of a double pyramid on a triangular base (I, Fig. 33), with the acid radical situated at an apex. Other postulated arrangements were that the five groups occupied positions at certain corners of a cube (II, van't Hoff) or at the corners of a square pyramid (III, Bischoff). In each case the nitrogen atom was regarded as being situated at the centre of the given figure.

Later (1906) Werner suggested a tetrahedral configuration, (IV), for the four non-acidic groups, with the acidic ion not concerned in the spatial arrangement. This view gradually became more generally accepted with the development of the electronic theory of valency, but even in 1925, although (I) and (II) had been discarded, no definite decision had been made between (III) and (IV), both of which provided an explanation of the facts known at that time.

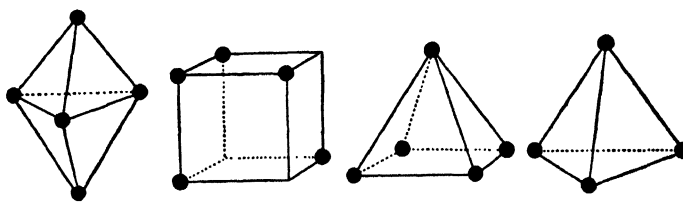
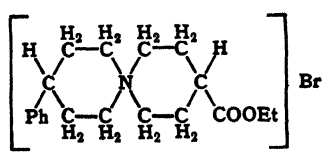


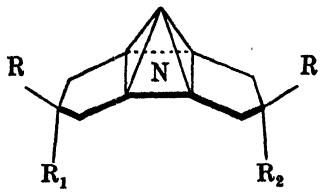
Fig. 33

The resolution of 4-*phenyl*-4'-*carbethoxy*bis*piperidinium*-1:1'-spiran *bromide*,

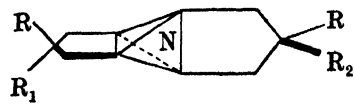


by Mills and Warren (*J.* 1925, 2507) finally disposed of the pyramidal configuration. It will be clear from the diagrams, Fig. 34, that if the pyramidal structure, (III), represents the molecule and the acidic ion occupies the apex of the pyramid, the two hydrogen atoms, the phenyl, and the carbethoxy-groups (RR_1RR_2) all lie in one

plane and the compound has a plane of symmetry : in the tetrahedral arrangement, (IV), on the other hand, the four groups occupy the corners of an irregular tetrahedron and enantiomorphously related forms should exist :



III



IV

Fig. 34

It can therefore be regarded as established that the four co-valently linked atoms or groups of quaternary ammonium compounds are arranged tetrahedrally round the nitrogen atom, a conclusion fully confirmed by X-ray crystal analysis.

Many nitrogen derivatives of the type $NR_1R_2R_3R_4X$ have now been resolved into their *d*- and *l*- isomerides, and an unstable optically active arsenic compound, $[AsMePhBz \cdot C_{10}H_7]I$ has been described by Burrows and Turner (*J.* 1921, 426).

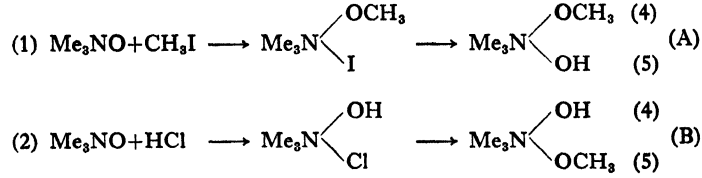
Optical Isomerism of Amine Oxides

When a tertiary amine is oxidised by hydrogen peroxide under certain conditions it affords an *amine oxide* of the type, R_3NO. Meisenheimer (*Ber.* 1908, **41**, 3966) oxidised methylethylaniline in this way and obtained a crystalline substance, MeEtPhNO, which gave salts, $[NMeEtPh \cdot OH]X$; the *d*-camphorsulphonate of this base was fractionated, and the base was thus resolved into optically active forms. Since that time many other amine oxides containing three different alkyl or aryl radicals have been resolved. In these compounds the three hydrocarbon groups and the oxygen atom are arranged tetrahedrally round the nitrogen atom.

A compound of phosphorus, MeEtPhPO, analogous to the amine oxides, has been resolved by Meisenheimer and Lichtenstadt (*Ber.* 1911, 356), and a derivative of arsenic, $MeEt(C_6H_4 \cdot COOH)AsS$, by Mills and Raper (*J.* 1925, 2479).

Before any very definite conclusions had been drawn regarding

the arrangement in space of the atoms or groups in a quaternary salt, Meisenheimer had shown that two of the valencies of the nitrogen atom are not identical. He treated (1) trimethylamine oxide with methyl iodide, and from the salt so formed liberated the base with alkali, and (2) trimethylamine oxide with hydrochloric acid, and displaced the chlorine atom by —OMe with the aid of sodium methoxide :



If the two nitrogen valencies (distinguished above as 4 and 5) concerned in these changes are identical, the same result must clearly be obtained by the two series of reactions, but this was not so. The final products could not be isolated, but the properties of their solutions were not the same : when their aqueous solutions were evaporated, the substance (A) yielded trimethylamine, formaldehyde and water, while (B) gave trimethylamine oxide and methyl alcohol, and in each case the change was quantitative. Similar results were obtained with other isomerides of the same type, and also with those of the structure $Me_3N(OEt)OMe$.

That the two products A and B should be different is in accordance with the accepted tetrahedral configuration for the quaternary ammonium compounds ; in (A) the hydroxyl group is combined to the co-valent complex, $[Me_3N \cdot OMe]$, by an electro-valency, while in (B) the methoxyl group is so united to the complex, $[Me_3N \cdot OH]$, as shown below :



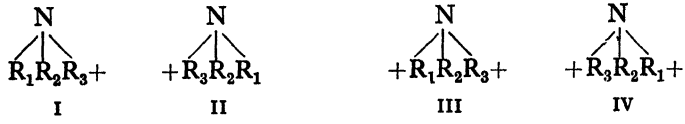
There is no experimental evidence, however, that either of these compounds is an electrolyte.

Stereochemistry of Tervalent Nitrogen

The disposition in space of the three nitrogen valencies in compounds, NR_3, has been the subject of much experimental work. If

the nitrogen atom, and the three atoms or groups to which it is united, do not lie in one plane, compounds of the type, $NR_1R_2R_3$, should exist in antimeric forms, but of the numerous attempts to resolve such substances (secondary and tertiary bases, alkylhydroxylamines, unsymmetrical hydrazines) by the crystallisation of their salts with optically active acids, none has succeeded. It is clear that in such experiments the compounds actually examined are derivatives of ' quinquevalent ' nitrogen, $[NR_1R_2R_3H]X$, and it is very remarkable that *salts* of this type, where X is an optically active radical, have not been obtained in diastereoisomeric forms, *d*B*d*A and *l*B*d*A, corresponding with those of the type, $[NR_1R_2R_3R_4]X$. For, even if the molecule, $NR_1R_2R_3$, is planar, it would appear to be necessary that, during its conversion into a salt, the original directions of the valencies of the tervalent nitrogen would be changed, giving the tetrahedral configuration. On the other hand, the liberation of the amine from its salt would probably be accompanied by a reversal of this change in configuration ; so that even if salts, *d*B*d*A and *l*B*d*A, could be separated, they might give the same planar base, $NR_1R_2R_3$, or the same inactive mixture of non-planar isomerides.

In view of this difficulty attempts have been made to obtain evidence of the disposition in space of the nitrogen valencies in another way (Kipping and Salway, *J.* 1904, 438). A base such as methylaniline or *p*-toluidine was treated with a *dl*-acid chloride (R_3), and was thus converted into a substituted amide, $NR_1R_2R_3$ (R_1 *or* R_2 may represent H), in which R_3 is either *d*-(+) or *l*-(−). If the three nitrogen valencies are not in one plane, the *d*-acid chloride would give the two diastereoisomerides, (I) and (II),

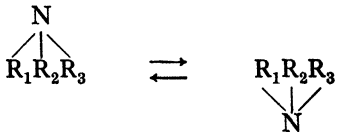


I II III IV

and the *l*-acid chloride would give the two corresponding *l*-derivatives, so that two different *dl*-substituted amides should be formed ; only one was obtained. An optically active base (i.e. a base in which R_1 is an optically active radical) such as *d*-indylamine or *l*-menthylamine was also treated with an optically active acid chloride (R_3) ; here again, two substituted amides, (III) and (IV), should have been formed, but only one was obtained.

Meisenheimer (*Ber.* 1924, 1744) also failed to resolve derivatives of anthranilic acid, $R_1R_2N \cdot C_6H_4 \cdot COOH$, by the crystallisation of their salts with optically active bases, although in such experiments no use is made of the salt-forming power of the $NR_1R_2R_3$ group.

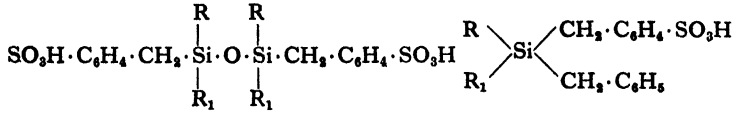
All these results seem to show that the three valencies of the tervalent nitrogen atom lie in a plane, and that the salts of tetrahedral configuration, $[NR_1R_2R_3H]X$, are either partially racemic (p. 307) in all cases which have been studied or are so easily racemised that only one salt, *d*B*d*A or *l*B*d*A, separates from the solution of the two, and gives both when it is redissolved. On the other hand, it is known (p. 705) that the molecule of ammonia is pyramidal so that the failure to resolve certain compounds is more probably due to the ease with which the nitrogen atom can pass through the plane of the three attached groups (p. 754), thus causing racemisation :



Stereochemistry of Tin and Silicon

Optically active methylethylpropylstannic iodide, MeEtPrSnI, was obtained by Pope and Peachey (*Proc. Chem. Soc.* 1900, 42 and 116). When the solution, prepared by treating the *dl*-iodide with silver *d*-camphorsulphonate, is evaporated, only the *d*A*d*B component is deposited, owing to the transformation of the *d*A*l*B salt into its diastereoisomeride ; this *d*A*d*B salt, treated with potassium iodide, gave an optically active iodide which, however, rapidly racemised (p. 751).

Silicon compounds of the two types shown below have been obtained in *d*- and *l*-forms (Kipping, *J.* 1907, 209 ; Challenger and Kipping, *J.* 1910, 755) :



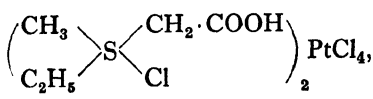
Nearly all the salts of the *dl*-acids with an optically active base are partially racemic, and the two compounds, *d*A*d*B and *l*A*d*B (or

*d*A*l*B and *l*A*l*B), are so similar that they cannot be easily distinguished (*J.* 1908, 457).

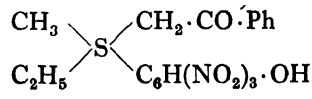
An optically active germanium compound, *phenylethylisopropylgermanium bromide*, has also been described (*Ber.* 1931, 2352).

Stereochemistry of Sulphur and Selenium Compounds

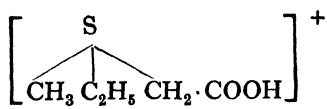
The first optically active sulphur compound, d-*methylethylthetine platinichloride*, was prepared by Pope and Peachey (*J.* 1900, 1072), and very shortly afterwards Smiles (*J.* 1900, 1174) obtained optically active picrates of *methylethylphenacylsulphine*. The structures of these substances were represented respectively by (I) and (II), in which the sulphur atom occupies the centre of a tetrahedron and is surrounded by four different groups :



I



II



III

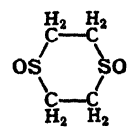
According to modern views, however, the acid radical is combined with the sulphur atom by an electro-valency, and the compound, (I), is regarded as a *sulphonium* salt, $[(CH_3)(C_2H_5)S(CH_2\cdot COOH)]_2PtCl_6$, in which the sulphur atom is tri-covalent and situated at one corner of a tetrahedron ; this view is expressed in (III).

An optically active selenium compound, *methylphenylselenetine bromide*, [PhMeSe($CH_2\cdot$COOH)]Br, was obtained by Pope and Neville (*Proc. Chem. Soc.* 1902, 198), and *phenyl*-p-*tolylmethyltelluronium iodide*, [PhMeTe$\cdot C_6H_4$Me]I, has also been resolved by Lowry and Gilbert (*J.* 1929, 2867) ; the configurations of these compounds are believed to be similar to that of a sulphonium salt.

Optically active derivatives of sulphur of a somewhat different character have been obtained by Phillips (*J.* 1925, 2552), who showed that when *ethyl* p-*toluenesulphinate*, $CH_3\cdot C_6H_4\cdot SO\cdot OC_2H_5$, (2 mol.) is heated with *l*-β-octanol (1 mol.) or *l*-menthol (1 mol.), and the product is then fractionated, a laevorotatory ethyl *p*-toluenesulph-

inate is obtained. This result shows that the ethyl ester exists in *d*- and *l*-forms which react with the optically active alcohol with different velocities, the ethyl group being displaced by an octyl or menthyl radical; when, therefore, the *unchanged* ethyl ester is separated, it no longer consists of equal quantities of the *d*- and *l*-forms, a partial resolution having been accomplished. This is another interesting example of the general phenomenon that *d*- and *l*-isomerides do not behave in the same way towards a given optically active compound (p. 747).

The optical activity of ethyl *p*-toluenesulphinate shows that the molecule is non-planar: the groups are probably arranged pyramidally, as in the sulphonium salts. Various sulphoxides, RR'SO (one of the radicals of which contains a basic or acidic group), and also sulphilamines, RR'SNR'', have been resolved. Further evidence supporting this view of the arrangement of the groups in such sulphur compounds was provided by the isolation of *cis*- and *trans*-isomerides of the *disulphoxide* of 1:4-*dithian* (Bell and Bennett, *J.* 1927, 1798); this result shows that the two oxygen atoms may lie either on the same or on different sides of the plane of the ring:



Stereochemistry of Organic Co-ordination Compounds

It has long been known that from aqueous solutions of mixtures of certain salts, well-defined crystalline products, such as the alums, $M_2'SO_4,M_2'''(SO_4)_3,24H_2O$, and sulphates, $M_2'SO_4,M''SO_4,6H_2O$, are deposited; similarly a solution of potassium chloride and platinic chloride gives a salt, K_2PtCl_6, and a mixture of potassium and ferrous cyanides gives $K_4Fe(CN)_6$. Such products were at one time regarded as having been formed by 'molecular association,' by an attraction between the molecules as such, without any change having occurred in their structures: it was thus implied that the atoms in the associated molecules retained their original state of combination. This view was clearly unsatisfactory, and it did not indicate the great differences which were shown by various so-called 'double salts' of this nature. The alums, for example, give the

reactions of the acid ion and those of both the constituent metal ions, whereas potassium ferrocyanide gives no reactions of the ferrous ion, but those only of potassium and of a complex ion, $Fe(CN)_6$; salts of the former kind, therefore, might be regarded as mere crystalline aggregates comparable with racemic substances, whereas those of the latter are certainly of a different type. Between these two extremes many ' double salts ' of an intermediate character could be recognised.

In 1893 Werner suggested that in such ' molecular compounds,' which exist in solution, the atoms, radicals, or molecules are arranged round a central atom, usually a metal, some combined by ordinary (principal) valencies, and others by ' residual affinity ' or auxiliary valencies. The formula of potassium chloroplatinate, for example, is then written $K_2[PtCl_6]$, to indicate that the platinum atom is combined with the six chlorine atoms by auxiliary valencies, while the potassium atoms are united to the platinum by principal valencies. The atoms or groups inside such a bracket are not, whereas those outside are, ionised in aqueous solution. The group in the bracket is known as the *co-ordination complex* or *co-ordinate group*, and the number of atoms, radicals, or molecules (any of which is possible) inside the co-ordinate group is known as the *co-ordination number* of the atom at the centre of such a group. This co-ordination number is not directly related to the ordinary valency of the atom, but is usually either four or six.

According to the electronic theory, the atoms or groups outside the bracket are held by electro-valencies or polar bonds, those inside by co-valencies or co-ordinate co-valencies. In the case of a complex having a co-ordination number four, the central atom has presumably an octet of electrons, but with a co-ordination number six, it has apparently twelve *shared* electrons.

Many compounds, known as *ammines*, have been prepared in which a metal is co-ordinated with ammonia or with amines; the compositions and relationships of these substances can be explained as follows:

Potassium chloroplatinate, $K_2[PtCl_6]$, ionises (as denoted by the brackets) into $2K^+$ and $PtCl_6^{--}$. If now an ammonia molecule is substituted for one of the chlorine atoms in the co-ordination complex, the electrons associated with the platinum atom are increased by one, because the chlorine takes out seven and the ammonia brings in a complete octet; the co-ordinate group, therefore, requires,

instead of two, only one electron to complete its stable arrangement and combines with only one potassium atom, giving the compound, $K[PtCl_5 \cdot NH_3]$. A repetition of this process produces $[PtCl_4 \cdot 2NH_3]$, which is a non-electrolyte.

The introduction of the next molecule of ammonia produces a group with one extra electron, which is lost to a negative element such as chlorine, forming $[PtCl_3 \cdot 3NH_3]Cl$, and so on, until all the six chlorine atoms have been displaced by ammonia molecules. The whole series of compounds is shown below in the second column; platinous *ammines* and corresponding derivatives of many other metals, such as cobalt and chromium, can also be obtained.

Platinous ammines Co-ordination number 4	Platinic ammines Co-ordination number 6	Cobaltic ammines Co-ordination number 6
$K_2[PtCl_4]$	$K_2[PtCl_6]$	$K_3[CoCl_6]$
$K[PtCl_3 \cdot NH_3]$	$K[PtCl_5 \cdot NH_3]$	$K_2[CoCl_5 \cdot NH_3]$
$[PtCl_2 \cdot 2NH_3]$	$[PtCl_4 \cdot 2NH_3]$	$K[CoCl_4 \cdot 2NH_3]$
$[PtCl \cdot 3NH_3]Cl$	$[PtCl_3 \cdot 3NH_3]Cl$	$[CoCl_3 \cdot 3NH_3]$
$[Pt \cdot 4NH_3]Cl_2$	$[PtCl_2 \cdot 4NH_3]Cl_2$	$[CoCl_2 \cdot 4NH_3]Cl$
	$[PtCl \cdot 5NH_3]Cl_3$	$[CoCl \cdot 5NH_3]Cl_2$
	$[Pt \cdot 6NH_3]Cl_4$	$[Co \cdot 6NH_3]Cl_3$

Cryoscopic and conductivity measurements with aqueous solutions of such compounds show that in every case the number of ions present in the solution is in agreement with the above formulae, and it should be noted that, as already stated, atoms, radicals, or molecules can form parts of the co-ordinated group.

In agreement with the general rule that co-valency is directional whilst electro-valency is not, the groups inside the co-ordination complex are arranged in a particular manner round the central metallic atom; consequently isomerism and stereoisomerism should be exhibited in certain cases.

Now long before Werner's hypothesis had been put forward, isomerism had, in fact, been discovered in compounds of this kind; $[PtCl_4 \cdot 2NH_3]$, for example, was shown by Cleve, in 1871, to exist in two isomeric forms, which he regarded as structural isomerides When, however, this complex salt is considered in the light of Werner's theory, it will be seen that in the case of an atom, M, with a co-ordination number six, there are at least four ways in which the co-ordinated groups might be arranged in space (Fig. 35).

namely at the corners of a hexagon, (I), a hexagonal pyramid, (II), a triangular prism, (III), or an octahedron, (IV) :

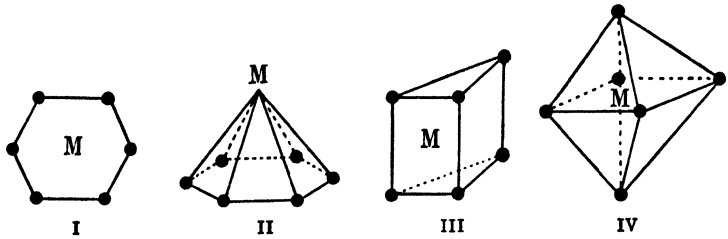


Fig. 35

In a complex of the formula, MA_2B_4, each of the arrangements (I), (II) and (III) gives *three* possible configurations for this group ; such a complex should therefore exist in three isomeric forms related to the *o*-, *m*-, and *p*- derivatives of benzene. The regular octahedral configuration, (IV), however, gives rise to only *two* isomerides, (V and VI, Fig. 36), which may be distinguished as *cis*- and *trans*-forms :

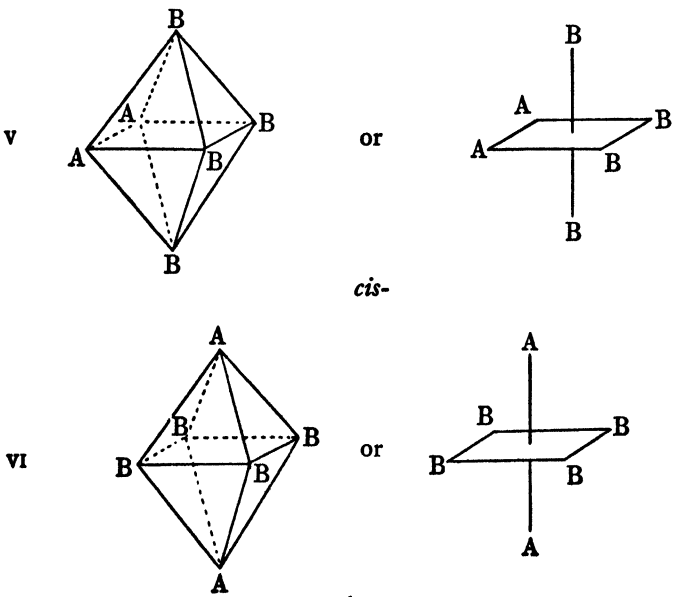
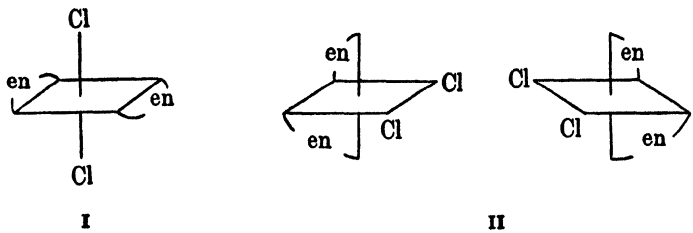


Fig. 36

The fact that only two isomerides have been isolated in the numerous cases examined, and the stereochemical evidence described below, seem to prove that such molecules have the octahedral arrangement, (IV).

Two molecules of ammonia in the ammines may be displaced by one molecule of a diamine, such as ethylenediamine (**en**), which then occupies two places in the co-ordinated complex; such a combination is known as a *chelate* (claw-like) group and may be formed by a dibasic acid (oxalic acid) as well as by a diacidic amine. Further, a compound $[Co\mathbf{en}_2Cl_2]Cl$, which contains two **en**-*chelate* groups, exists in two stereoisomeric forms, (I) and (II), related respectively to the *trans*- and *cis*-isomerides mentioned above:



I II

Fig. 37

A third form, in which one of the chelate groups would occupy extreme corners of the octahedron, probably does not exist, as the distance is too great to be bridged in this way.

Now a study of configurations (I) and (II) shows that whereas the *trans*-isomeride, (I), has a centre and several planes of symmetry, the *cis*-form, (II), has only an axis of symmetry and should therefore exist in the antimeric forms represented above.

A compound of this type, namely cis-*chloroamminodi(ethylenediamine)cobaltic dichloride* $[Co\mathbf{en}_2Cl\cdot NH_3]Cl_2$, was therefore investigated by Werner (1911), who resolved it into its optically active components by the fractional crystallisation of the corresponding *d*-α-bromocamphor-π-sulphonate. Since that time many organic substances of this type, including the cis-*dichlorodi(ethylenediamine)cobaltic chloride*, (II), shown above, have been obtained in optically active forms.

Complexes containing three chelate groups, as for example,

[$Coen_3$], also lack a plane or centre of symmetry and have been obtained in antimeric forms, indicated in Fig. 38.

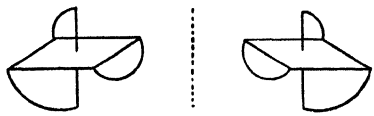
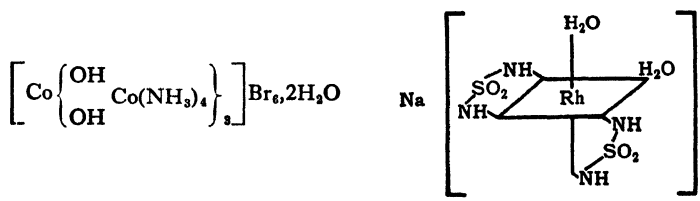


Fig. 38

Chelation has also been observed in the case of compounds such as 1:2:3-triaminopropane, which are capable of triple attachment to a single metallic atom (*tridentate* groups); *di*(1:2:3-*triaminopropane*)*cobaltic trichloride*, for example, has been prepared by Mann and Pope, and from *ββ′β″-triaminotriethylamine*, $N(CH_2 \cdot CH_2 \cdot NH_2)_3$, *dichloro*(*ββ′β″-triaminotriethylamine*) *platinic dichloride*, $[Cl_2PtN(CH_2 \cdot CH_2 \cdot NH_2)_3]Cl_2$, which contains a *quadridentate* group, has been obtained. The first entirely inorganic substance to be isolated in optically active forms was (III, Fig. 39), in which each $Co(NH_3)_4(OH)_2<$ plays the part of a chelate group; the molecular rotation of this compound is exceptionally high, namely $[M]_{5600}$ about $-47,500°$. Later Mann (*J.* 1933, 414) resolved a much more simple rhodium compound (IV, Fig. 39), in which sulphamide, $SO_2(NH_2)_2$, is used as the chelate group:



III IV

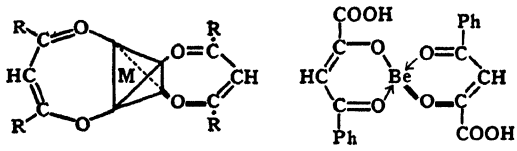
Fig. 39

Co-ordination compounds of the following elements, Al, Cr, Fe, Co, Ru, Rh, Ir, Pt, Ni, As, have now been obtained in optically active forms, in all of which the co-ordination number is six.

In a compound of an atom having a co-ordination number of four, either a square, or a tetrahedral spatial arrangement of the

co-ordinated group would appear to be probable, and in most cases of this kind the tetrahedral arrangement has been established by the resolution of suitable compounds.

The more important of these substances are the metallic derivatives of β-diketones. Metals displace one hydrogen atom from the enolic form of β-diketones (p. 823), giving salts, and, in particular cases, the metal then co-ordinates with the remaining ketonic oxygen atom ; in this way there is produced a partially co-ordinated complex, (I, Fig. 40), which is that of a spirocyclic compound (p. 723), since the metallic atom is common to the two rings. Mills and Gotts (*J.* 1926, 3121) have resolved such a compound, namely, the beryllium derivative of *benzoylpyruvic acid*, (II), by the fractional crystallisation



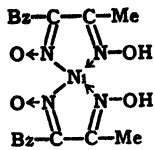
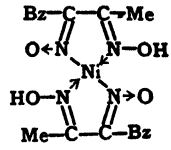
I II

Fig. 40

of its brucine salt. The existence of this substance in antimeric forms proves that the carbonyl oxygen atom is united to the metal ; if this were not so dissymmetry would not occur. Similar spirocyclic compounds of boron, palladium and platinum have been resolved.

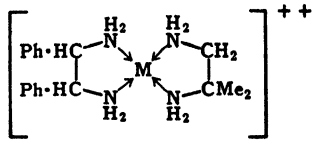
The tetrahedral arrangement for 4-covalent, and the octahedral one for 6-covalent elements has been confirmed by the examination of crystal structures, but in the case of some 4-covalent elements, there is conclusive evidence of a planar arrangement. A compound MA_2B_2, in which A_2 and B_2 all lie in one plane (whether co-planar with the metallic atom or not), will exist in *cis*- and *trans*-forms, and such isomerism has been observed in certain derivatives of 4-covalent platinum, palladium, and nickel. The compound, $Ptpy_2Cl_2$ (**py** = pyridine), for example, exists in two forms (as possibly does $Pdpy_2Cl_2$), which have the same molecular weight ; furthermore the results of X-ray analysis indicate a square arrangement of numerous 4-covalent derivatives of bivalent Ni, Pd, Pt, Cu and Ag, and of tervalent Au.

Sugden (*J.* 1932, 246) has obtained two isomeric compounds of nickel with *benzylmethylglyoxime*,

under conditions which appear to preclude any other explanation of their isomerism than that of different planar arrangements about the nickel atom. The compounds are diamagnetic, whereas a tetrahedral arrangement should give optical antimers, which would be paramagnetic. Similar derivatives of palladium have been prepared.

Proof of the planar distribution of the valencies of 4-covalent platinum and palladium has been provided by Mills and his co-workers : meso*diphenylethylenediamine* (1 mol.) and unsymmetrical *dimethylethylenediamine* (1 mol.) were combined in the complex shown, and this compound was then resolved :



If the valencies of the metal were directed towards the corners of a regular tetrahedron a resolution would be impossible, but with a planar arrangement the complex is dissymmetric.

CHAPTER 48

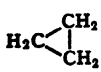
CYCLOPARAFFINS AND CYCLO-OLEFINES

It has been pointed out that benzene, and many other aromatic substances, can combine directly with hydrogen under suitable conditions (p. 406). The closed chain hydrocarbons which are formed from benzene and its derivatives in this way, and by many other methods, are classed as cyclo*paraffins* when they are fully saturated, and as cyclo-*olefines* when they are unsaturated. Hexahydrobenzene, C_6H_{12}, for example, is called *cyclo*hex*ane*, whereas tetrahydrobenzene, C_6H_{10}, is called *cyclo*hex*ene*, and dihydrobenzene, C_6H_8, is *cyclo*hexa*diene*.

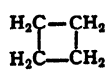
The terms *cyclo*paraffin and *cyclo*-olefine are also applied to corresponding compounds, the molecules of which contain closed chains of 3, 4, 5, 7, etc. carbon atoms. As already mentioned, it may be assumed that the carbon atoms of the simpler molecules lie in one plane, but as regards the higher members evidence to the contrary will be given later (p. 792).

Cyclo*paraffins and their Derivatives*

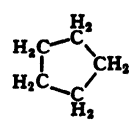
The *cyclo*paraffins are frequently referred to as the *polymethylenes*; their nomenclature may be illustrated by the following examples:



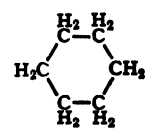
*Cyclo*propane (Trimethylene)



*Cyclo*butane (Tetramethylene)



*Cyclo*pentane (Pentamethylene)



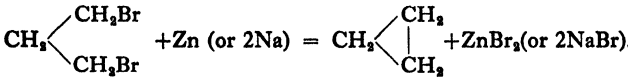
*Cyclo*hexane (Hexamethylene)

Derivatives of the hydrocarbons are named in the ordinary way, the positions of the substituents being shown by numbering the carbon atoms as usual, and using these numbers in the name of the compound; it is immaterial, of course, from which carbon atom the numbering starts, but as a rule it begins with one which is combined with some main substituent.

Preparation. Many of the reactions which bring about the union

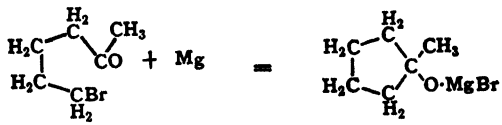
of carbon atoms of two *different* molecules, and result in the formation of an open chain compound, may be applied to bring about the union of two carbon atoms of one and the *same* molecule, to give a cyclic compound, as is illustrated by many of the following methods of preparation :

The lower cyclo*paraffins* may be prepared by treating certain $\alpha\omega$-dihalogen derivatives [1] of the paraffins with zinc or with sodium (Freund), but other dibromides, such as $CH_3 \cdot CHBr \cdot (CH_2)_n \cdot CH_2Br$, may also be employed,

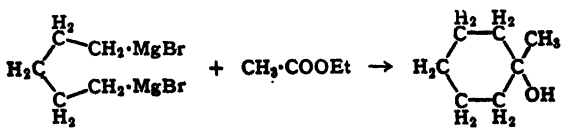


*Cyclo*propane is now manufactured by this reaction and is used as an anaesthetic.

Hydroxy-derivatives of the *cyclo*paraffins may be obtained by treating halogen derivatives of certain open chain ketones with magnesium, in the presence of ether ; δ-acetylbutyl bromide, for example, gives a Grignard compound, which with a dilute acid affords 1-*methyl*cyclo*pentan*-1-*ol*,



Similarly the Grignard reagent from 1:5-dibromopentane, with ethyl acetate, gives finally 1-*methyl*cyclo*hexanol*,[2]



Dihydroxy-derivatives may be prepared by reducing certain open

[1] The letter ω denotes a terminal position in any chain.

[2] When, as in this case, one substituent is not numbered, that particular group is in the 1-position.

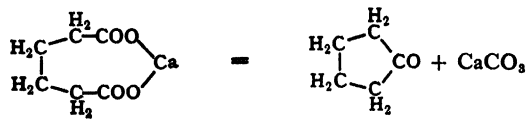
chain diketones (Perkin and Kipping); this reaction is analogous to that which occurs in the formation of pinacol from acetone,



2:8-Nonandione

1:2-Dimethyl*cyclo*heptan-1:2-diol

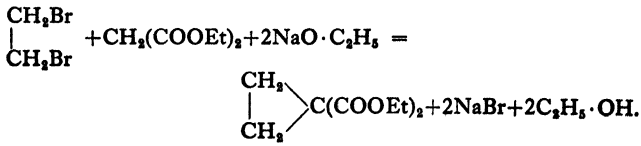
Keto-derivatives may be prepared by heating the calcium (or other) salt of certain dicarboxylic acids, a reaction which corresponds with that employed in the preparation of ketones from monocarboxylic acids (Wislicenus); the calcium salt of adipic acid, for example, gives cyclo*pentanone*,



This method of formation is referred to in more detail later (p. 784).

Adipic and pimelic anhydrides, on distillation, give carbon dioxide and cyclic ketones (Blanc, cf. p. 1089).

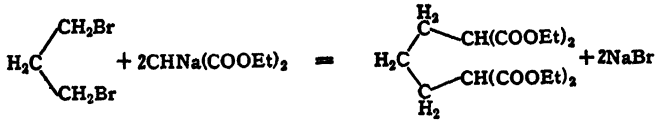
Carboxy-derivatives may be prepared by treating certain dihalides of the paraffins with the sodium derivative of diethyl malonate, ethyl acetoacetate, or cyanoacetate (Perkin),

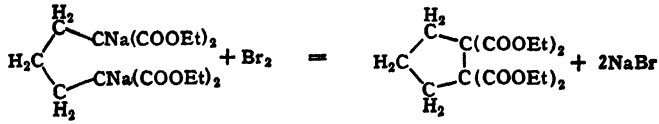


Diethyl *cyclo*propane-1:1-dicarboxylate

Such reactions occur in various stages, but for the sake of brevity are summarised in the one equation; the operations are carried out in much the same way as in the synthesis of open chain derivatives of ethyl acetoacetate and diethyl malonate. Another method is by treating certain dihalogen derivatives of the paraffins (1 mol.) with diethyl sodiomalonate (2 mol.), and then submitting the sodium

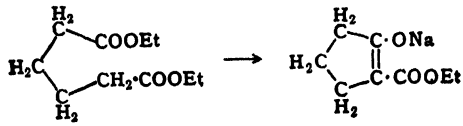
derivatives of the products to the action of bromine, iodine, or dihalides, such as methylene di-iodide or ethylene dibromide (Perkin):

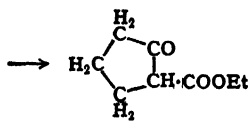




Tetra-ethyl *cyclo*pentane-1:1:2:2-tetracarboxylate

Carboxy-derivatives of *cyclic ketones* may be prepared by treating the esters of certain dicarboxylic acids with sodium,

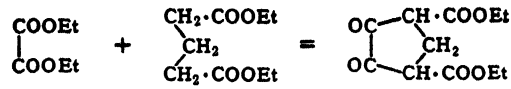




This reaction is Dieckmann's modification of a Claisen condensation (p. 827), and the sodium derivative of the enol is formed, as in the case of the preparation of ethyl acetoacetate; the product, treated with a dilute acid, gives the keto-isomeride, *ethyl* cyclo*pentan-2-onecarboxylate*.

Similar condensations occur with other dicarboxylic esters and keto-esters and give usually a five- or a six-membered ring; thus ethyl ε-acetylhexoate gives 2-acetyl*cyclo*hexanone.

Carboxy-derivatives of *cyclic diketones* (di*ones*) may be prepared in a somewhat analogous manner, by condensing the esters of certain dicarboxylic acids with diethyl oxalate, with the aid of sodium or of sodium ethoxide (compare p. 929),

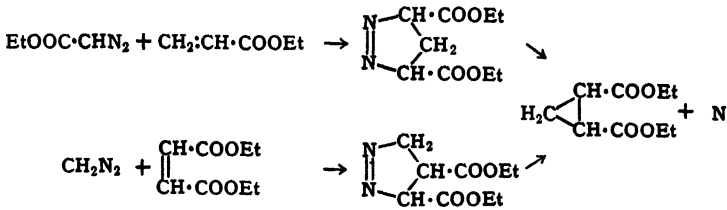


Diethyl *cyclo*pentan-1:2-dione-3:5-dicarboxylate

This reaction corresponds with that which occurs in the preparation of diethyl oxaloacetate and, like the preceding one, represents a Claisen condensation.

Diketones are also obtained by the destructive distillation of the salts of dibasic acids (p. 784).

*Cyclo*propanecarboxylic acids may be prepared from pyrazoline derivatives, produced from aliphatic diazo-compounds and unsaturated esters (p. 1053),



*Cyclo*paraffin rings may also be enlarged with the aid of these diazo-compounds.

Derivatives of *cyclo*butane are formed by the dimerisation of cinnamic acid and from ketene, etc. (pp. 718, 829); the Diels-Alder reaction is also an important method for obtaining 6-membered rings (p. 818).

A method of great general importance for the preparation of *cyclo*hexane and many of its derivatives is that of Sabatier and Senderens, already described (p. 405). Another method, particularly useful for the reduction of compounds which might be decomposed by heat, such as certain terpene derivatives, consists in treating the unsaturated compound with hydrogen in the presence of colloidal platinum or palladium. Under these conditions most *cyclo*-olefinic compounds unite with hydrogen rapidly at ordinary temperatures, and are transformed into the corresponding *cyclo*paraffin derivatives (p. 804).

Properties of the Cyclo*paraffins*. The *cyclo*paraffins and their derivatives usually boil at higher temperatures than the correspond-

ing normal saturated open chain compounds, as shown in the following table :

*Cyclo*pentane, C_5H_{10}	50°	Pentane, C_5H_{12}	37°
*Cyclo*hexane, C_6H_{12}	81°	Hexane, C_6H_{14}	71°
*Cyclo*butanol, $C_4H_7 \cdot OH$	123°	Butyl alcohol, $C_4H_9 \cdot OH$	117°
*Cyclo*propanecarboxylic acid, $C_3H_5 \cdot COOH$	183°	Butyric acid, $C_3H_7 \cdot COOH$	163°

In other physical properties, the two classes of compounds resemble one another rather closely ; the stereoisomerism of some *cyclo*paraffin derivatives has already been discussed (p. 716).

In certain chemical properties some of the *cyclo*paraffins and their derivatives differ considerably from the corresponding open chain compounds, inasmuch as they form additive products, the closed chain undergoing *fission*. Cyclo*propane*, for example, is slowly attacked by bromine at ordinary temperatures, yielding trimethylene dibromide (1:3-dibromopropane), but cyclo*butane* and the higher homologues are either unchanged or yield substitution products. Hydrogen bromide immediately converts *cyclo*propane into propyl bromide, but does not attack the higher homologues. *Cyclo*propane and *cyclo*butane are reduced by hydriodic acid, giving the corresponding paraffins, but the higher members are not attacked ; similarly *cyclo*propane is reduced by hydrogen in the presence of nickel more readily than is *cyclo*butane, and again the larger rings are not attacked.

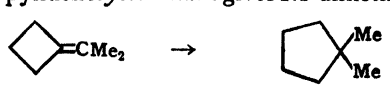
These results (which may vary greatly with the temperature) and other facts show that the stability of the closed chains increases with the number of carbon atoms in the ring up to five, and then remains almost constant (p. 791). It is noteworthy, however, that the stability of a *cyclo*paraffin derivative depends not only on the size of the closed chain, but also on the positions of the substituents. Thus, whereas cyclo*propane*-1:1-*dicarboxylic acid* is very readily attacked by hydrobromic acid, giving *β-bromoethylmalonic acid*, $CH_2Br \cdot CH_2 \cdot CH(COOH)_2$, the isomeric 1:2-dicarboxylic acid is not changed, even when it is heated with the halogen acid.

In nearly all those reactions which do not involve a fission of the closed chain, the *cyclo*paraffin derivatives behave like the corresponding open chain compounds. The cyclic *alcohols*, for example, may be oxidised to ketones, and obtained from the latter by reduction ; they may be converted into esters by the usual methods, and

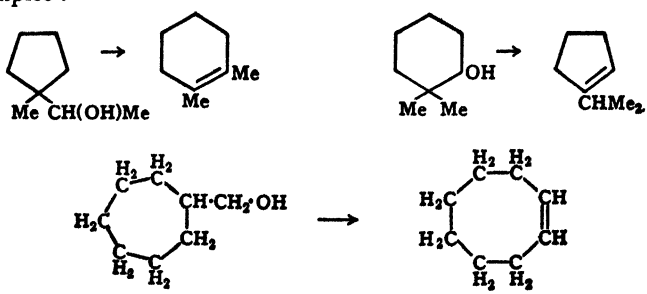
their halogen derivatives may form, and also react, with Grignard reagents. As a rule, however, halides cannot be converted into the corresponding cyanides, amines, etc., by the action of potassium cyanide, ammonia, etc. The cyclic *ketones* react with the usual ketonic reagents, and their oximes may be reduced to cyclic *amines*; on oxidation, the closed chain of a ketone undergoes fission and an aliphatic dicarboxylic acid is formed. It is thus possible to pass from one of the higher cyclic ketones to the next lower homologue. Cyclo*heptanone*, for example, is oxidised by potassium permanganate, giving pimelic acid, from the calcium salt of which cyclo*hexanone* may be obtained.

The *cyclo*paraffin *carboxylic acids* are very similar to the aliphatic acids in their reactions, and give salts, esters, amides, etc., in a normal manner. They may be converted into their α-bromo-substitution products, with the aid of bromine and red phosphorus, and from these compounds cyclic olefinic acids may be obtained; all the dicarboxylic acids which contain the group $>C(COOH)_2$ give monocarboxylic acids when they are heated alone or with water.

In a few cases the direct conversion of a closed chain of n carbon atoms into one containing $n-1$ or $n+1$ carbon atoms has been observed; when, for example, benzene is reduced with hydriodic acid at 250°, it yields *methyl*cyclo*pentane*, as well as *cyclo*hexane, and under similar conditions *iso*propylidene*cyclo*butane gives 1:1-dimethyl*cyclo*pentane,[1]

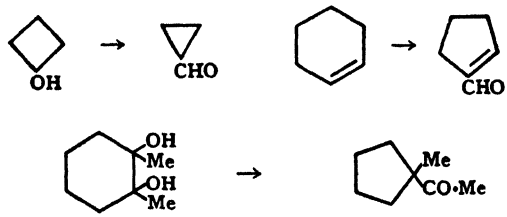


Changes in the size of the ring also occur when certain alcohols are heated with oxalic acid or zinc chloride, as shown in the following examples:

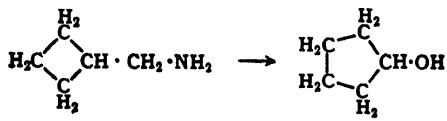


[1] These formulae are explained on p. 912.

Oxidation, combined with a pinacol-pinacolone transformation (p. 848), may produce similar changes :



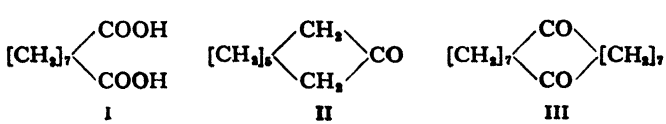
When cyclic amines, such as *cyclo*butylmethylamine, containing a $—CH_2 \cdot NH_2$ side chain, are treated with nitrous acid, they yield not only the corresponding alcohol, but also one containing another carbon atom in the ring (Demjanov),



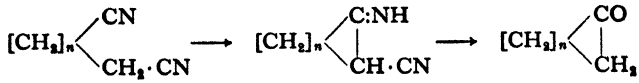
Large Ring Compounds

Before 1926 no pure compound containing a single ring of more than eight carbon atoms was known ; since that date substances containing 30 or more carbon atoms in a single closed chain have been obtained and the following methods are available for their preparation : (1) Certain salts of aliphatic dicarboxylic acids are distilled in a vacuum ; the yield of cyclic ketone is often much better if, instead of the calcium salt, the thorium or yttrium salt, mixed with copper filings, is employed, but even then the yield may be less than 4% of the theoretical (Ruzicka and co-workers).

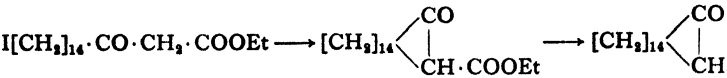
Symmetrical cyclic diketones are often formed together with the monoketones ; distillation of the thorium salt of azelaic acid, (I), for example, yields not only cyclo-*octanone*, (II), but also cyclo-*hexadecan*-1:9-*dione*, (III),



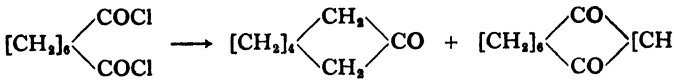
(2) Greatly improved yields result when a dinitrile undergoes condensation in *very dilute* solution in the presence of the alkali metal derivative, R_2NK, of a secondary amine, and the products are then hydrolysed (Ziegler and co-workers),



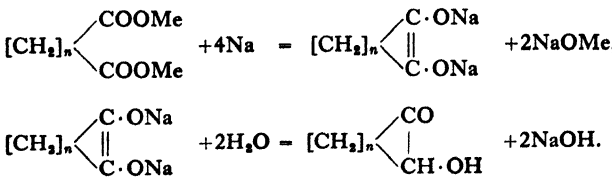
(3) ω-Iodo-derivatives of β-ketonic esters are treated with potassium methoxide in methylethyl ketone (Hunsdiecker); ethyl 2-keto-16-iodohexadecanecarboxylate thus yields finally cyclo*hexadecanone*



(4) A very dilute ethereal solution of the dichloride of a dibasic acid is slowly added to a gently boiling solution of triethylamine in ether: complex reactions occur in which cyclic ketones and diketones (and other products) are formed. Thus the dichloride of suberic acid gives cyclo*heptanone* and cyclo*tetradecan*-1:8-*dione* (Blomquist):



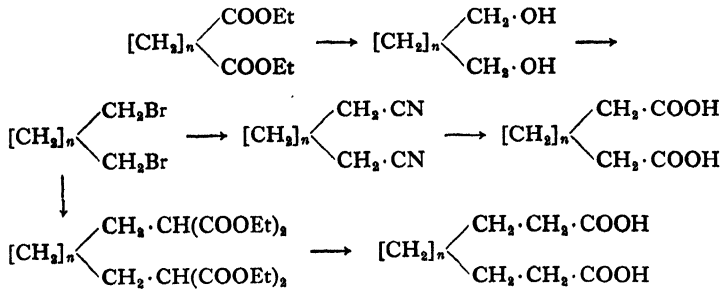
(5) Esters of the higher dibasic acids are treated with sodium in an inert solvent (xylene) in the complete absence of oxygen, and the resulting sodium compounds decomposed with water; cyclic α-hydroxyketones (*acyloins*) are thus formed:



This method does not require the high dilution of some of the other methods and the yields may be as high as 96% (Stoll and Prelog).

The dicarboxylic acids or dinitriles used in this work may be prepared

as follows : Esters of the higher dicarboxylic acids, $[CH_2]_n(COOH)_2$, are reduced with the aid of sodium and alcohol, giving dihydroxy-compounds, which are then converted into acids, $[CH_2]_{n+2}(COOH)_2$ and $[CH_2]_{n+4}(COOH)_2$, by the usual reactions for passing up a homologous series :



The dibromides (above) may also be converted into the (di) Grignard compounds, which react with chlorodimethyl ether, $ClCH_2 \cdot OMe$, giving ethers ; these products are decomposed with hydrobromic acid and the operations are repeated :

$$[CH_2]_n(CH_2 \cdot MgBr)_2 \rightarrow [CH_2]_n(CH_2 \cdot CH_2 \cdot OMe)_2 \rightarrow [CH_2]_n(CH_2 \cdot CH_2Br)_2$$

The dibromides are finally converted into acids as above.

The ω-iodo-derivatives required for method (3) are prepared as follows : The dimethyl ester of a dibasic acid is carefully hydrolysed to the monomethyl ester, the silver salt of which is treated with bromine in carbon tetrachloride solution,

$$MeOOC \cdot [CH_2]_n \cdot COOAg + Br_2 = MeOOC \cdot [CH_2]_n \cdot Br + CO_2 + AgBr.$$

The resulting ω-bromo-ester is converted into the acid chloride by the ordinary methods, and the latter treated with ethyl sodio-acetoacetate in ether : the product, hydrolysed with sodium methoxide, gives an ω-bromoketonic ester which is transformed into the iodo-compound in the usual way,

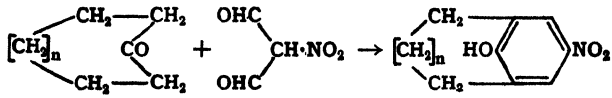
$$Br \cdot [CH_2]_n \cdot CO \cdot Cl \longrightarrow Br \cdot [CH_2]_n \cdot CO \cdot CH(CO \cdot CH_3) \cdot COOEt$$
$$\longrightarrow Br \cdot (CH_2)_n \cdot CO \cdot CH_2 \cdot COOEt$$

The cyclic monoketones obtained by such methods range from *cyclo*-octanone, $C_8H_{14}O$, up to about cyclo*nonacosanone*, $C_{29}H_{56}O$. Those containing 10, 11, and 12 carbon atoms have an odour of camphor, that with 13, a faint smell of cedar wood, which increases

with the size of the ring up to 18 atoms; when the vapour is more dilute, however, the substances containing 14, and especially 15 carbon atoms smell of musk, while those with 16, 17, and 18 carbon atoms respectively smell of civet. Cyclo*pentadecanone*, $C_{15}H_{28}O$, is manufactured under the name *Exaltone*, as a substitute for musk (below).

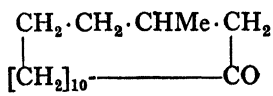
The rings containing more than 7 carbon atoms are as stable as those containing only 5 or 6; thus no change occurs when the ketones containing from 7 to 18 carbon atoms are heated with concentrated hydrochloric acid at 180–200°, or when the ketone, $C_{17}H_{32}O$, is passed over thoria heated at 400–420°; further, the cyclic hydrocarbons, $C_{15}H_{30}$ and $C_{17}H_{34}$, are unchanged by concentrated hydriodic acid at 250°.

The ketones, diketones, etc., show the usual chemical properties of such *cyclo*paraffin derivatives: in addition, when cyclic ketones containing from 8 to 30 atoms in the ring are shaken for some days with nitromalonodialdehyde in aqueous-alcoholic solution containing sodium hydroxide, a very interesting reaction gives *p*-nitrophenols bridged in the *m*-position.

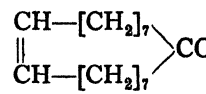


Compounds containing large rings in which some of the links are NH< groups have also been described.

Until 1926 no monocyclic compound containing a ring of more than 6 carbon atoms had been found in nature; *muscone*, or muskone, $C_{16}H_{30}O$, however, which occurs in vegetable musk, is now known to be *l*-3-*methylexaltone*, (IV), and *civetone*, $C_{17}H_{30}O$, a perfume obtained from civet, has been shown to be a *cyclo*-olefinic ketone, (V),



IV

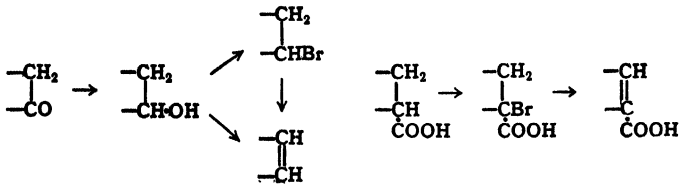


V

On reduction civetone yields cyclo*heptadecanone*, and on oxidation it gives azelaic acid as one of the products; its constitution, thus established, has been confirmed by synthesis

Cyclo-*olefines*

The *cyclo*-olefines are related to the *cyclo*paraffins just as the olefines are related to the paraffins. They may be prepared from ketones and alcohols of the *cyclo*paraffin series by reactions corresponding with those used in the formation of olefines from open chain compounds ; either of the following series of changes, for example, may be brought about by the usual methods :

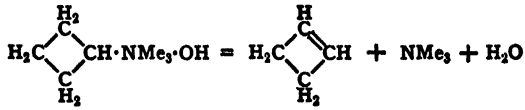


Derivatives of cyclo*hexene* may also be prepared from certain types of aromatic compounds which are first reduced to the corresponding *cyclo*hexane derivatives ; the latter may then be transformed into cyclo-oleinic compounds as above,

$$C_6H_5\cdot OH \longrightarrow C_6H_{11}\cdot OH \longrightarrow C_6H_{11}Br \longrightarrow C_6H_{10},$$
$$C_6H_5\cdot COOH \longrightarrow C_6H_{11}\cdot COOH \longrightarrow C_6H_{10}Br\cdot COOH \longrightarrow C_6H_9\cdot COOH.$$

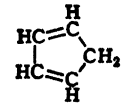
The *cyclo*-olefines, like ethylene, readily form additive products with bromine, hydrogen bromide, ozone, etc., and unlike the *cyclo*paraffins, they are very easily oxidised to acids, the closed chain undergoing fission. The more important *cyclo*-olefine derivatives are those of *cyclo*hexene, which are described later (p. 798) ; in addition the following are of interest.

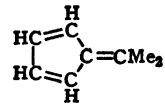
*Cyclo***butene**, a gas, may be obtained from *cyclo*butanecarboxylic acid, the amide of which, treated with bromine and alkali (Hofmann's reaction), gives *cyclo*butylamine ; when this compound is exhaustively methylated (p. 597) and the quaternary hydroxide is heated, *cyclo*butene is formed,



*Cyclo*butene is reduced by hydrogen in the presence of nickel, giving cyclo*butane*, b.p. 11–12°.

***Cyclo*pentadiene**, (I), is an interesting cyclic diolefine which occurs in coal-tar ; it boils at 41° and is extremely unstable, readily undergoing polymerisation at ordinary temperatures (p. 819). It reacts with aldehydes and ketones, in the presence of sodium ethoxide giving condensation products, which are derived from the unknown methylene derivative ($>C=CH_2$), and are termed *fulvenes* ; *dimethylfulvene*, (II), for example, is an orange-coloured liquid (b.p. 46°), whereas *diphenylfulvene* is a deep-red crystalline compound (m.p. 82°). The fulvenes are conjugated compounds

I 

II 

(p. 813), and, like the polyenes (p. 980), are examples of coloured hydrocarbons. *Cyclo*pentadiene in benzene solution gives a potassium derivative, C_5H_5K (p. 695*h*) and interesting compounds with other metals (p. 695*q*) also exist.

Cyclo-**octatraene** is described later (p. 1001).

The Strain Theory

In order to account for the graded stability of the *cyclo*paraffins and their derivatives known in his time, Baeyer (1885) proposed a *strain theory*, which was based on the arrangement in space of the four valencies of the carbon atom. The (normal) angle between any two such valencies is 109° 28′ ; when, therefore, a carbon atom forms part of a planar saturated closed chain, the directions of two of its valencies must be deflected, causing, presumably, a strain in the molecule, as can be demonstrated with the aid of the usual models. In that of *cyclo*ethane (ethylene), which may be regarded as the simplest closed chain, each of the two bonds must be deflected through an angle of 109° 28′/2, in order to bring them parallel with one another. In the model of cyclo*propane*, the bonds would form an equilateral triangle, and the deflection of each would be 109° 28′–60°/2. Similarly, in the cases of the models of closed chains composed of 4, 5, 6, etc. atoms, certain deflections of the bonds would occur. These angular deflections, which Baeyer regarded as measures of the strains set up in the molecules, are tabulated on the next page, the minus values indicating that the bonds are bent outwards instead of inwards ;

*Cyclo*ethane (ethylene) 54° 44′ (109° 28′/2)
*Cyclo*propane 24° 44′ (109° 28′−60°/2)
*Cyclo*butane 9° 44′ (109° 28′−90°/2)
*Cyclo*pentane 0° 44′ (109° 28′−108°/2)
*Cyclo*hexane −5° 16′ (109° 28′−120°/2)
*Cyclo*heptane −9° 33′ (109° 28′−128° 34′/2)
Cyclo-octane −12° 51′ (109° 28′−135°/2)

It is evident from the above values that the deflection is greatest in *cyclo*ethane ; this molecule, therefore, should be the least stable, since ring-formation is accompanied by the greatest strain. In accordance with this view, the *cyclo*ethane ring (the ethylenic bond) is readily broken—as, for example, when ethylene combines with bromine or with hydrogen bromide. From the other deflections (strains) given in the table, it would also be inferred that the relative stabilities of the *cyclo*paraffins gradually increase up to *cyclo*pentane, and then decrease again.

The great difference in behaviour between α-, β-, γ-, δ-, etc. hydroxy-acids, as regards the readiness with which they form *lactones*, and of dicarboxylic acids, as regards the readiness with which they form *inner anhydrides*, is also accounted for by the strain theory ; in molecules, such as those of γ-valerolactone and succinic anhydride, which are very readily formed, there is presumably a smaller strain than in those which contain similar smaller closed chains. The facility with which various types of closed chains are produced from certain *o*- and *peri*-derivatives, but not usually from *m*- or *p*-compounds, is also accounted for in a similar manner ; and in general, the strain theory may also be applied to heterocyclic rings, provided that the valencies of the oxygen, nitrogen, or other atom, which form links in the closed chain, are normally directed at an angle of about 109°, as in the case of carbon.

The most definite information regarding the relative stabilities of analogous molecules is afforded by their heats of combustion (p. 706), and the data given in the following table agree on the whole with Baeyer's theory ; as the strain diminishes the heat of combustion calculated for each $>CH_2$ group becomes smaller up to *cyclo*pentane, but does *not* increase again, as was to be expected, and *cyclo*heptane, which ought to have the same heat of combustion as *cyclo*butane, has, in fact, a smaller one.

Number of atoms in ring	2	3	4	5	6	7	8
Heat of combustion per CH_2 group (Cal.)	170	168	165	158·7	157·4	158·3	158·6
Angle of valency deflection	54° 44′	24° 44′	9° 44′	0° 44′	−5° 16′	−9° 33′	−12° 51′

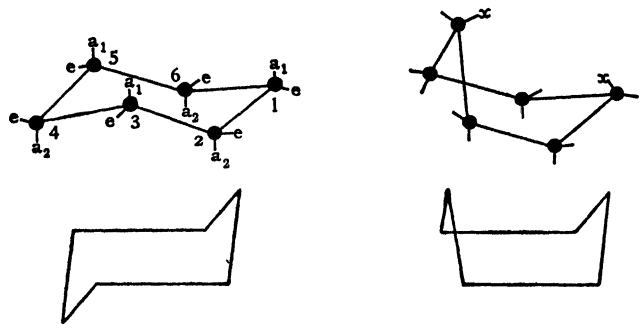
The Theory of Strainless Ring Structures

Although Baeyer's strain theory thus seemed to correlate and account for many facts, it was not, as just shown, altogether satisfactory, and, as time went on, it became untenable in its original form. The work of Ruzicka, for example, had shown that even closed chains of 32 carbon atoms can be obtained, and are remarkably stable (p. 787), whereas, according to the strain theory, they should be highly unstable.

Now it had been suggested by Sachse in 1890 (before the existence of such compounds was known) that if, in the case of those rings from *cyclo*hexane upwards (where there is an outward deflection), it is assumed that the carbon atoms may take up a *multiplanar* arrangement, all strain might be avoided ; cyclic molecules containing 6, 7, 8, 9 and more carbon atoms might then be as stable as *cyclo*pentane. This suggestion of the existence of *strainless* systems led to the further assumption that the strainless molecules might exist in two or more stereoisomeric forms. *Cyclo*hexane, for example, might have either of the forms shown (Fig. 41, p. 792), known respectively as the *chair* and *boat* forms ; and similarly in the cases of the higher *cyclo*paraffins, two (or more) strainless arrangements might be possible.

When models of the two forms of *cyclo*hexane are constructed it will be found, however, as pointed out by Mohr, that they can be converted into one another, without breaking any bonds, by very gentle pressure, suitably applied. These two stereoisomeric forms differ in configuration in a special way. Stereoisomeric substances such as *d*- and *l*-lactic acids, maleic and fumaric acids, glucose and mannose, *d*-α-glucose and *d*-β-glucose, etc. also differ respectively in configuration, but cannot be interconverted merely by twisting or rotating single bonds or by alteration of valency angles as in the case of the forms of *cyclo*hexane : stereoisomerides which can be so interconverted are said to differ in *conformation*. Conformational isomerides are usually so readily interconvertible that their isolation is impossible, but nevertheless important consequences follow from

their study: the *d*- and *l*-forms of those substances which owe their optical activity to restricted rotation about a single bond are examples of stable compounds which differ in conformation.



Cyclohexane

Fig. 41

In the diagrams (Fig. 41) the carbon atoms are, for clarity, drawn too far apart and if a scale model of the boat (bed) form is constructed it will be found that the hydrogen atoms (not shown in the Fig.) attached to the valencies in the 1:4-position within the boat so to speak (*x*, *x*, Fig. 41) are very close together: it is now thought that *cyclo*hexane and its derivatives exist almost entirely in the chair form to avoid this crowding, which, of course, would be worse with larger atoms than hydrogen attached at *x*. There is experimental evidence for this view from X-ray data, electron diffraction spectra and dipole moments of *cyclo*hexane and its derivatives.

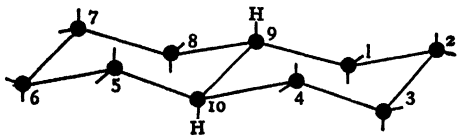
Further examination of the chair form shows that three of the carbon atoms (1:3:5) lie in one plane and three (2:4:6) in another very near (and parallel to) the first. The hydrogen atoms lie in three groups: three at a_1 above the mean plane of the carbon atoms, six at *e* nearly in this plane and three at a_2 below it. Those at a_1 and a_2 are known as *axial* (attached by axial bonds) and those at *e* as *equatorial* (attached by equatorial bonds): the term *polar* has been used instead of axial, but to avoid confusion with the electrochemical use, the term is no longer employed.

A substituent in *cyclo*hexane may occupy either an axial or an equatorial position and this often has an important bearing on its chemical reactions, as, for example, the ease of dehydration of a cyclic alcohol. Furthermore in a *cis*-1:2-disubstituted *cyclo*hexane

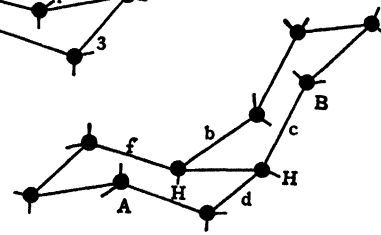
one substituent must be axial and one equatorial, whereas in the *trans*-form both must be either axial or equatorial, and the latter is usually the preferred arrangement as the substituents then have more room. It is to be noted that none of the above considerations affect the number of possible stable position or stereoisomerides of *cyclo*hexane derivatives, or the existence or otherwise of optical activity in these compounds as previously discussed (Chapter 45). For such purposes the ring may still be regarded as planar, as it is sufficiently flexible for any one chair form to change into another: when such a change occurs it will be found that the axial bonds become equatorial and *vice versa*. The geometrical considerations just described have also been applied to heterocyclic compounds, such as the pyranose sugars.

Now when two such strainless rings are condensed together, as in decahydronaphthalene, two stable stereoisomerides should exist. The one might be regarded as having been formed by a *cis*- addition, the other by a *trans*-addition, of hydrogen to the carbon atoms common to the two rings of naphthalene; further, in both compounds the two rings are so interlocked that the stereoisomerides cannot be converted one into the other, except by a fission of one of the closed chains.

Figures of the models of the strainless *cis*- and *trans*-forms of decahydronaphthalene (decalane) are given below:



trans-Decalane



cis-Decalane

Fig. 42

It is to be noted that in *both* forms of decalane *both cyclo*hexane systems are chair forms. In *trans*-decalane the rings are joined entirely by equatorial bonds leaving the axial bonds of the two carbon atoms common to the two rings to carry the *trans*-hydrogen

atoms (the only two shown in the figure): it is also clear that *trans*-decalane is a very flat molecule in which there are roughly three planes of atoms:

(*a*) axial hydrogen atoms at 2:4:5:7:9,

(*b*) all the carbon atoms and the equatorial hydrogen atoms,

(*c*) axial hydrogen atoms at 1:3:6:8:10.

In *cis*-decalane union of the two rings is accomplished by one axial and one equatorial bond in each case: with reference to ring A bond b is equatorial and c axial, while for ring B bond d is equatorial and f axial. It is also seen that *cis*-decalane is not a flat molecule as is the *trans*-form. Mohr, who first pointed out that the rings would be locked in the dicyclic systems (1918) assumed that *cis*-decalane was made up of two boat forms of *cyclo*hexane and it was Bastiansen and Hassel (1946) who suggested the above modification of the theory.

Experimental evidence of the existence of such *cis*- and *trans*-forms of a dicyclic structure had already been afforded by Baeyer, who had found that both *cis*- and *trans*-hexahydrophthalic acids gave anhydrides. The behaviour of the *trans*-acid, however, was regarded as abnormal, because the *cyclo*hexane ring was then assumed to be planar, and anhydride formation would involve considerable strain. If, however, the ring is in the chair form the two carboxyl groups are equidistant from one another in the *cis*- and *trans*-acids, and anhydride formation can occur with both.

Further evidence of a similar kind was provided by Windaus, Hückel, and Reverey (*Ber.* 1923, 91), who found that both the *cis*- and the *trans*-isomerides of *2-carboxycyclohexylacetic acid*, $HOOC \cdot C_6H_{10} \cdot CH_2 \cdot COOH$ (hexahydrohomophthalic acid), gave its own anhydride; here again, if the *cyclo*hexane ring is planar, the two carboxyl groups in the *trans*-acid are widely apart, but in the chair form the two carboxyl radicals are brought into such positions that both acids can form anhydrides.

The existence of stable *cis*- and *trans*-forms of a dicyclic structure was fully established by the results of Hückel's work on decalane and its derivatives. It had been found that *β-decalol*, $C_{10}H_{17} \cdot OH$, prepared by reducing β-naphthol, existed in stereoisomeric forms, but this, of course, was to be expected. In a dicyclic structure, such as that of decalane, it was assumed that the two rings were inclined to one another at an angle of 109° 28′, and the hydroxyl group in decalol might therefore be situated either within or without

this angle, as indicated in Fig. 43 (in which the symbols for the two hydrogen atoms of the $\geqslant CH$ groups are omitted):

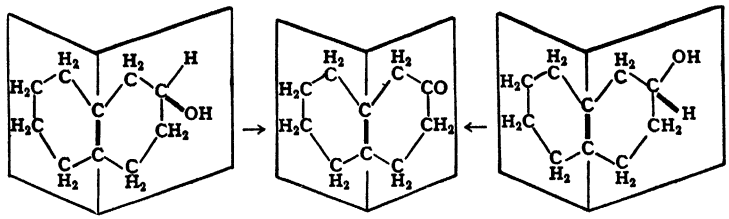


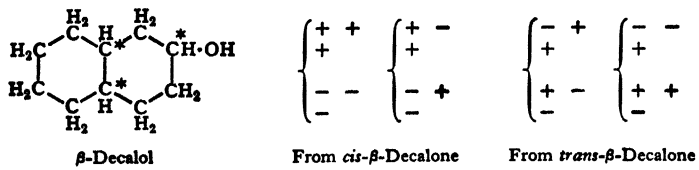
Fig. 43

But the isomeric decalols gave *different* ketones (decalones) on oxidation, whereas, had they been merely *cis*- and *trans*-forms which were related as indicated above, they must have been converted into one and the same decalone, when the H—C—OH and HO—C—H groups were converted into >C=O. The existence of the two decalones, therefore, proved the existence of two decalanes, which can differ in configuration only; moreover, one of the decalones must be derived from the *cis*- and the other from the *trans*-decalane. In accordance with this view, one of the decalones, on oxidation, gave the *cis*-, and the other the *trans*-form of 2-*carboxy*cyclo*hexyl-propionic acid*, $HOOC \cdot C_6H_{10} \cdot CH_2 \cdot CH_2 \cdot COOH$. These results are summarised below, and they are all readily accounted for by the theory described above:

cis-Decalane ⟶ *cis*-β-Decalone ⟶ { *cis* (*cis*)-β-Decalol; *cis* (*trans*)-β-Decalol }

trans-Decalane ⟶ *trans*-β-Decalone ⟶ { *trans* (*trans*)-β-Decalol; *trans* (*cis*)-β-Decalol }

It will thus be seen that four decalols should be obtainable, and since each of these is a *dl*-compound, eight optically isomeric forms of β-decalol should be capable of existence. These optical isomerides



may be indicated as on p. 795, the configurations of the groups attached to the carbon atoms marked by asterisks being distinguished by the positive and negative signs.

The four *dl*-forms have been obtained, and also the four corresponding dl-*β-decalylamines* (reduction products of β-naphthylamine); analogous isomerides have also been prepared from α-naphthol. Further, it has been shown that *cis*- and *trans*-forms of *hydrindane* and of 0,3,3-*dicyclo*-octane (cf. p. 820) are capable of existence.

Configurations of Open Chain Compounds

If one of the methyl groups of ethane is rotated relative to the other an infinite number of different conformations are possible: there is, however, only one compound C_2H_6 and this can be explained by assuming either that rotation is perfectly free or that the molecule exists in one stable position, which will be that having the least energy of all possible forms produced by rotation. The hydrogen atoms of one methyl group may, for example, start directly over those of the other (*eclipsed* position) and gradually rotate until the bonds joining carbon to hydrogen in one methyl group bisect the angle between similar bonds in the other group (*staggered* position). All other positions lie between these two extremes. It is now believed that mutual repulsion of the C—H bonds causes the staggered position to be preferred. In ethylene dichloride it has been shown by infra-red and Raman spectral measurements that the *anti*- (staggered) form in which the chlorine atoms are as far apart as possible is the most stable: it should be pointed out that the energy differences between forms of this sort are too small (1-2 Cal. per mole) to allow any hope of separating such isomerides.

The heat of combustion per CH_2 group of *cyclo*hexane is less than that of *cyclo*pentane (p. 791) which indicates a greater strain in the latter hydrocarbon. This is possibly explained when it is realised that in the chair form of *cyclo*hexane all C—H bonds are staggered (and indeed *cyclo*hexane is the only *cyclo*paraffin in which this can be so) whereas if *cyclo*pentane is planar all C—H bonds are eclipsed. Thermal and spectral data suggest that *cyclo*pentane is not planar, and therefore strained, presumably in order to avoid the eclipsed positions of the hydrogen atoms. The larger heat of combustion of *cyclo*heptane, as compared with *cyclo*hexane, is probably due to similar causes.

Reduction Products of Aromatic Compounds
Cyclo*hexane and its Derivatives*

*Cyclo*hexane, *cyclo*hexene, *cyclo*hexadiene, and their derivatives may all be regarded as reduction products of aromatic substances and classed as *hydroaromatic* compounds. *Cyclo*hexane and some of its homologues occur in large proportions in Caucasian petroleum, and are sometimes known as *naphthenes*.

*Cyclo***hexane**, C_6H_{12} (*hexahydrobenzene, hexamethylene*), was first obtained by Berthelot in an impure state by the reduction of benzene with hydriodic acid and red phosphorus ; at the high temperature which is required, the closed chain of six atoms undergoes an isomeric change, to a certain extent, and some *methyl*cyclo*pentane* is also formed. It was not until 1893 that the pure hydrocarbon was prepared by Baeyer (p. 798) ; later, it was obtained by Perkin by the action of sodium on *hexamethylene dibromide* (1:6-*dibromohexane*), and it is now easily prepared commercially by the reduction of benzene with nickel and hydrogen.

*Cyclo*hexane boils at 83–84° and is very stable : it is not attacked by potassium permanganate solution, or by bromine at ordinary temperatures, but it is oxidised by hot nitric acid, giving adipic acid.

The stereoisomerism of hexachloro*cyclo*hexane, $C_6H_6Cl_6$, has already been described (p. 720) ; the α-isomeride has been shown to be capable of optical activity by treating it with half the amount of brucine required to convert it completely into trichlorobenzene. The base reacts more rapidly with the *d*-form and the unattacked hexachloride is laevorotatory. This is an interesting example of how different rates of reaction may be used to show optical activity.

*Cyclo***hexanol**, $C_6H_{11}\cdot OH$, is now prepared on a large scale by the reduction of phenol with hydrogen and nickel at about 170°. It boils at 161° (m.p. 15°), does not react with sodium hydroxide, and with hydrobromic acid gives cyclo*hexyl bromide*, $C_6H_{11}Br$. On oxidation it first gives cyclo*hexanone* and then adipic acid. The Grignard reagents obtained from the *cyclo*hexyl halides are used for the preparation of many *cyclo*hexyl derivatives.

*Cyclo***hexan-1:4-diol**, $C_6H_{10}(OH)_2$ (*quinitol*), may be obtained by reducing quinol with hydrogen and nickel, and was first prepared from *cyclo*hexandione (p. 798) ; it exists in *cis*- and *trans*-forms, melting at 102° and 139° respectively, both of which are oxidised by chromic acid, giving benzoquinone.

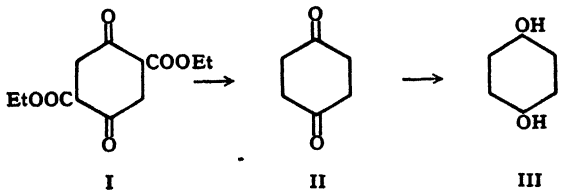
***Cyclo*hexanpentol**, $C_6H_7(OH)_5$, is an interesting compound which occurs in nature. A dextrorotatory form, *quercitol*, (m.p. 235°), is found in acorns, and a laevorotatory isomeride (m.p. 174°) in the leaves of *Gymnema sylvestre*, but obviously the two stereoisomeric alcohols are not enantiomorphously related.

***Cyclo*hexanhexol**, $C_6H_6(OH)_6$ (*inositol*), exists theoretically in eight stereoisomeric forms (p. 719), one of which is a *dl*-substance. The *d*-compound occurs in the sap of certain pine trees in the form of its monomethyl ether, and an *l*-ether is found in *quebracho* bark; *meso*inositol (fourth configuration, p. 720) occurs in human muscle, in various plants, and sometimes in the urine, and another non-resolvable inositol is present in certain fish and plants.

***Cyclo*hexanecarboxylic acid**, $C_6H_{11}\cdot COOH$ (*hexahydrobenzoic acid*), may be obtained by reducing benzoic acid with sodium amalgam and water; it melts at 31°, and its bromide $C_6H_{11}\cdot COBr$, gives an α-bromo-substitution product, $C_6H_{10}Br\cdot COBr$.

Cyclo*hexene*, Cyclo*hexadienes*, *and their Derivatives*

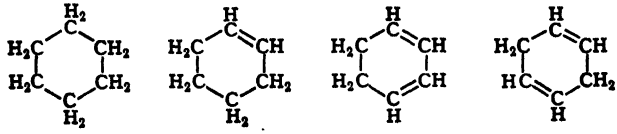
Many important reduction products of benzene were obtained synthetically by Baeyer from diethyl succinate. When this ester (2 mol.) is heated with sodium it gives *diethyl succinylosuccinate* (1 mol.) and sodium ethoxide, as the result of a Claisen condensation. Diethyl succinylosuccinate or *diethyl* 1:4-cyclo*hexandione*-2:5-*dicarboxylate*, (I), affords on hydrolysis a β-ketonic acid, which, like acetoacetic acid, readily loses carbon dioxide, giving 1:4-cyclo*hexandione*, (II); this diketone may be reduced with sodium amalgam and water, and is thus converted into 1:4-*cyclo*hexandiol (quinitol), (III),



I II III

When quinitol is heated with hydriodic acid it gives a di-iodide, which is reduced by zinc-dust and acetic acid to *cyclo*hexane. With cold hydriodic acid it gives an iodohydroxy-compound, which can

be reduced to *cyclo*hexanol; if this alcohol is converted into *cyclo*hexyl bromide, and the product heated with quinoline, cyclo*hexene* or *tetrahydrobenzene* is formed, whereas 1:4-*dibromo*cyclo*hexane*, prepared directly from quinitol and treated in a similar manner, gives a mixture of two structurally isomeric cyclo*hexadienes* (*dihydrobenzenes*). The following four compounds were thus synthesised from diethyl succinate:



*Cyclo*hexane *Cyclo*hexene Δ-1:3- and Δ-1:4-*Cyclo*hexadienes

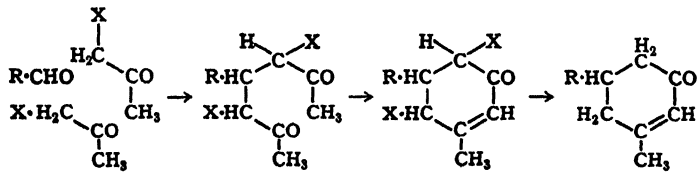
***Cyclo*hexene**, C_6H_{10}, usually obtained by treating *cyclo*hexanol with sulphuric acid, boils at 83–84°; it combines directly with bromine, with nitrosyl chloride (p. 914), and with ozone, and is readily oxidised, giving adipic acid. Its ozonide (m.p. 75°) is decomposed by water giving adipic acid and adipic aldehyde.

Δ-1:3- and Δ-1:4-*Cyclo*hexadienes, C_6H_8, have practically the same boiling-point (81–82°), and both readily undergo polymerisation; they differ, however, in their behaviour towards bromine, inasmuch as the Δ-1:3-isomeride (a conjugated compound, p. 815) is mainly converted into a 1:4-dibromide (1:4-*dibromo*-Δ-2-cyclo*hexene*), whereas the Δ-1:4-cyclic di-olefine gives a saturated tetrabromide (*tetrabromo*cyclo*hexane*).

All these reduction products of benzene differ fundamentally from the parent hydrocarbon, and do not show the characteristic reactions of aromatic compounds towards halogens, nitric acid, and sulphuric acid.

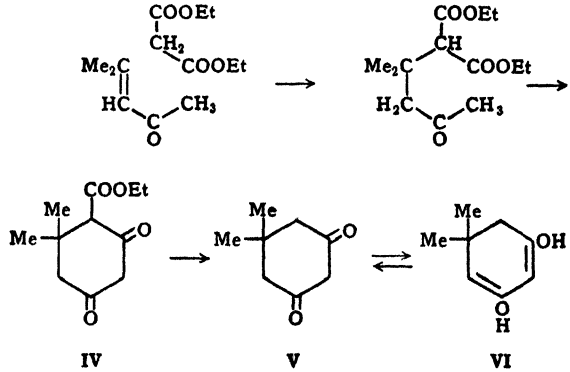
Many derivatives of *cyclo*hexene and *cyclo*hexadiene may be obtained from open chain aliphatic compounds. When ethyl acetoacetate, diethyl acetonedicarboxylate, or similar β-ketonic compounds are treated with aldehydes, or di-iodides, $RCHI_2$, in the presence of diethylamine or piperidine, derivatives of 1:5-diketones are formed (Knoevenagel). These compounds, (I, X= COOEt, when ethyl acetoacetate is used), readily undergo inner condensation with the loss of the elements of water, yielding derivatives of *cyclo*hexene, (II); the latter, treated with dilute acids,

undergo hydrolysis and then lose carbon dioxide (2 mol.).[1] The product, (III), obtained in this way from acetaldehyde (R = CH_3) and ethyl acetoacetate is 2:4-*dimethyl*-Δ-1-cyclo*hexen*-6-*one*, or, if in the enolic form, 2:4-*dimethyl*-Δ-1:5-cyclo*hexadien*-6-*ol*, that is to say it may be regarded either as a keto-derivative of *cyclo*hexene or as a hydroxy-derivative of *cyclo*hexadiene, and its properties accord with these structures.



I II III

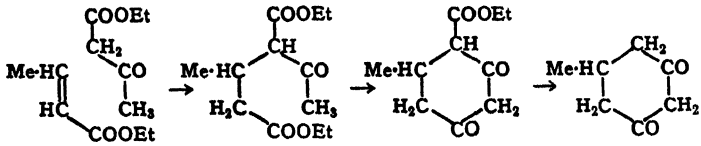
Diketo-derivatives of *cyclo*hexane may be obtained by the condensation of diethyl sodiomalonate or of ethyl sodioacetoacetate with αβ-unsaturated ketones, such as mesityl oxide, or analogous esters (Vorländer), an application of the Michael reaction (p. 807); when the product, (IV), is hydrolysed, the resulting β-ketonic acid loses carbon dioxide, giving a cyclic diketone, (V), which in the dienolic form is 1:1-*dimethyl*-Δ-3:5-cyclo*hexadien*-3:5-*diol* or 5:5-*dimethyl-dihydroresorcinol*, (VI):



IV V VI

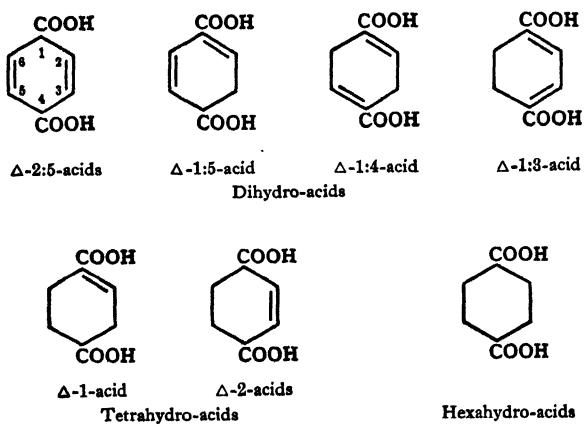
[1] One of the carboxyl groups in the hydrolysis product is β to a carbonyl radical and the other part of a group —CO·CH:CR·CHR′·COOH; both such groups readily lose carbon dioxide.

In a similar manner the condensation of ethyl sodioacetoacetate with ethyl crotonate finally leads to the synthesis of a *methyl*cyclo*hexandione*, which, in the enolic form, is 5-*methyldihydroresorcinol* :



Cyclo*hexene- and* Cyclo*hexadiene-dicarboxylic Acids*
Reduction of the Phthalic Acids

The reduction products of phthalic, *iso*phthalic, and terephthalic acids formed the subject of a long investigation by Baeyer, who obtained the di-, tetra-, and hexa-hydro-derivatives of all the three isomerides ; his results may be illustrated by a short summary of those obtained in the case of *terephthalic acid*, the reduction products of which are represented by the following seven structural formulae :



Of the above the Δ-2:5-dihydro-, the Δ-2-tetrahydro-, and the hexahydro-acid exist in *cis*- and *trans*-forms (p. 716) and some of them are *dl*-compounds.

When terephthalic acid in alkaline, neutral, or acid solution is reduced with sodium amalgam at various temperatures, it yields

different dihydro-acids, according to the experimental conditions. It was ultimately proved that the first reduction product is a mixture of the *cis*- and *trans*-forms of the Δ-2:5-acid, formed by the addition of hydrogen to the two carbon atoms in the 1:4-position. In the molecules of these acids the double bindings in the $\beta\gamma$-position are labile, and, whether present in an open or a closed chain structure, pass into the $\alpha\beta$-position when they are heated with aqueous alkalis (p. 838):

$$—CH{:}CH\cdot\overset{|}{C}H\cdot COOH \longrightarrow —CH_2\cdot CH{:}\overset{|}{C}\cdot COOH$$

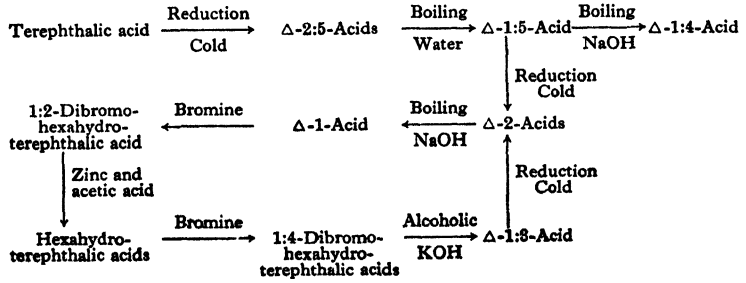
One such change takes place even when the Δ-2:5-acid is boiled with water, and the Δ-1:5-acid, which is thus produced, then undergoes a similar transformation when its alkaline solution is boiled, with the formation of the Δ-1:4-acid.

The Δ-1:3-acid is prepared from hexahydroterephthalic acid which is converted into 1:4-*dibromo*cyclo*hexane*-1:4-*dicarboxylic acid* (*αα'-dibromohexahydroterephthalic acid*); this product, treated with boiling alcoholic potash, loses two molecules of hydrogen bromide and gives Δ-1:3-dihydroterephthalic acid.

Both the *cis*- and *trans*-Δ-2-tetrahydro-acids are produced by the reduction of Δ-1:3- or Δ-1:5-dihydroterephthalic acid with sodium amalgam and cold water; they both undergo isomeric change when they are boiled with a solution of sodium hydroxide, the double binding passing from the $\beta\gamma$- to the $\alpha\beta$-position in the usual manner, with the formation of the Δ-1-acid.

A mixture of the cis- and trans-*hexahydroterephthalic acids* is produced when the tetrahydro-acids are combined with bromine and the dibromo-additive products are reduced with zinc-dust and acetic acid.

These relationships are tabulated below:



The structures of the various di- and tetra-hydro-acids were determined from their methods of formation, their behaviour towards alkalis, the results of their oxidation with permanganate, and in several other ways. Thus, one of the tetrahydroterephthalic acids must be the Δ-2-compound since it isomerises, giving the Δ-1-compound when it is heated with aqueous alkali; also it combines with bromine, and the additive product, with alcoholic potash, is converted into a stable dihydroterephthalic acid which must be the Δ-1:3-compound. The latter is thus distinguished from the other stable dihydro-acid, which, therefore, is the Δ-1:4-isomeride.

From all the results obtained with the three phthalic acids, it was found that sodium amalgam and water reduce a double binding only when it is in the $\alpha\beta$-position to a carboxyl group. Further, terephthalic acid, instead of giving a Δ-3:5-dihydro-derivative, as might have been expected if hydrogen were added to the carbon atoms 1 and 2, gave the Δ-2:5-compound, *one* hydrogen atom only combining with each of the $\geqslant$C·COOH groups, just as if the two carbon atoms 1 and 4 were directly united; a rearrangement of the two remaining ethylenic bindings had also occurred. This and other reactions of *conjugated systems* are considered later (p. 813).

W: . . ., working with *pure* sodium amalgam (a reagent very different from that used by Baeyer), found that the first reduction product of terephthalic acid which can be isolated is the Δ-2-acid. These discordant results may be due to the different lengths of time during which the initial product is exposed to the action of the alkali hydroxide.

CHAPTER 49

OLEFINIC COMPOUNDS

SOME of the more important methods of preparation and additive reactions of the $>C=C<$ group of olefines and certain olefinic derivatives have already been described (pp. 85, 337); the following account amplifies what is there given.

All olefinic groups combine with hydrogen, but not under the same conditions; hydrogen in the presence of catalysts (Ni, Pt, Pd, etc.) reduces all olefinic (also in many cases aromatic) compounds (p. 405), but nascent hydrogen (from sodium amalgam and water, etc.) does not combine with ethylene (or benzene). On the other hand, derivatives of ethylene, such as acrylic and maleic acids (and aromatic acids), are reduced by sodium amalgam and water, as the properties of the ethylenic group are profoundly modified by the substitution of carboxyl for hydrogen (p. 816).

Olefinic compounds which cannot be reduced with nascent hydrogen can generally be converted into saturated compounds by first adding halogen or halogen acid (HBr, HI) to the molecule and then displacing the halogen by hydrogen with reducing agents (p. 802).

The combination of olefines with halogens (Cl_2, Br_2) is a general property, to which, however, there are important exceptions; tetraphenylethylene and 1:2-dibromo-1:2-diphenylethylene, for example, as well as certain aliphatic olefinic compounds, such as tetrachloroethylene and dimethyl- and dibromo-fumaric acids, do not react with bromine; the symbol, $>C=C<$, in such cases may therefore be misleading.

The addition of a molecule of a halogen acid to an olefine usually takes place more slowly than that of a halogen, and the rule which summarises the usual course of the reaction for hydrocarbons (Markownikoff, p. 95) is not invariable, as the nature of the product depends largely on the experimental conditions; in the absence of oxygen or peroxides, such as benzoyl peroxide or perbenzoic acid, propylene unites slowly with hydrogen bromide, giving β-bromopropane (normal reaction), but in the presence of

oxygen or peroxides combination occurs much more rapidly and α-bromopropane is formed by an abnormal addition (Kharasch, McNab and Mayo, *J. Am. Chem. Soc.* 1933, 2531).

Similarly allyl bromide and vinyl bromide show slow normal (Markownikoff) additions with hydrogen bromide in the absence of oxygen or peroxides, giving αβ-dibromopropane and ethylidene dibromide ; but in the presence of peroxides rapid *abnormal* reactions give αγ-dibromopropane and ethylene dibromide respectively. Many further examples of this interesting *peroxide effect* have been observed, and in molecules which do not contain a strongly directing group either the normal or the abnormal reaction can be induced by suitable conditions ; in some cases it is necessary to add an anti-oxidant, such as hydrogen, catechol, quinol or diphenylamine, in order to suppress the abnormal reaction.

In the combination of an αβ-unsaturated acid with a halogen acid Markownikoff's rule does not apply. The usual behaviour is that the halogen unites with that carbon atom of the olefinic group which is the further removed from the carboxyl group ; thus acrylic and crotonic acids with hydrogen bromide give only β-bromo-derivatives, but in the acids, $CH_2{:}CH\cdot[CH_2]_n\cdot COOH$, the carboxyl group has little effect on the reaction, and normal or abnormal effects are observed.

Hydrogen fluoride, chloride and iodide, unlike hydrogen bromide, do not show abnormal reactions catalysed by oxygen or peroxides.

It has been shown that the mechanism of a normal reaction with hydrogen bromide is probably the addition of a proton followed by that of a bromide *ion* (p. 695*p*) :

$$CH_3{-}CH=CH_2 + HBr \longrightarrow$$

$$CH_3{-}\overset{+}{C}H{-}CH_3 + \overset{-}{Br} \longrightarrow CH_3{-}CHBr{-}CH_3.$$

In an abnormal reaction, the oxygen or peroxide liberates a bromine *atom* from the hydrogen bromide and this atom then combines with the olefine,

$$CH_3{-}CH{=}CH_2 + Br^{\cdot} \longrightarrow CH_3{-}\dot{C}H{-}CH_2Br;$$

a reaction with hydrogen bromide follows with the liberation of

another bromine atom and so on, leading to a rapid homolytic chain reaction (p. 695*i*) :

$$CH_3—\dot{C}H—CH_2Br+HBr \longrightarrow CH_3—CH_2—CH_2Br+\dot{B}r.$$

In the presence of an anti-oxidant, which combines with bromine atoms, the chain is readily broken and a normal slow addition occurs. Abnormal reactions do not occur with the other halogen acids, as hydrogen fluoride and chloride are not attacked by oxygen or peroxides, and iodine atoms produced from hydrogen iodide do not react with olefines.

Although the complex, (I), usually gives additive products with halogens, numerous cases are known in which the methylene group is preferentially attacked. If, for example, one of the two olefinic carbon atoms is not combined with hydrogen, halogens at ordinary temperatures may give substitution ; thus *iso*butylene with chlorine gives β-methylallyl chloride and bromine displaces hydrogen of the methyl group in triphenylmethylethylene :

$$>C=\underset{\text{I}}{\overset{|}{C}}—CH_2— \qquad CH_2{:}C<^{CH_3}_{CH_3} \longrightarrow CH_2{:}C<^{CH_2Cl}_{CH_3}$$

$$Ph_2C{:}C<^{CH_3}_{Ph} \longrightarrow Ph_2C{:}C<^{CH_2Br}_{Ph}$$

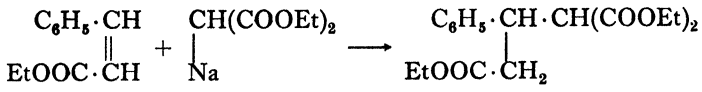
Even very simple olefines often undergo substitution at high temperatures, propylene, for example, at 300–600° gives allyl chloride (p. 246).

N-chloro-substituted anilides such as *N*-chloro-4-chloroacetanilide, $C_6H_4Cl\cdot NCl\cdot CO\cdot CH_3$, and *N*-chloro-2:4-dichloroacetanilide, $C_6H_3Cl_2\cdot NCl\cdot CO\cdot CH_3$, are very useful reagents for substituting chlorine for hydrogen in groups such as (I, above) ; *N*-bromosuccinimide reacts similarly, and, with *cyclo*hexene, for example, gives a good yield of 1-bromo-Δ-2-*cyclo*hexene.

Hydrogen cyanide does not combine with olefines, but it reacts with $\alpha\beta$-unsaturated aldehydes and ketones giving either cyanohydrins, or cyano-derivatives of the saturated compound. Cinnamic aldehyde, for example, gives a cyanohydrin, but mesityl oxide is converted into the *cyanide*, $CN\cdot CMe_2\cdot CH_2\cdot CO\cdot CH_3$ (p. 816). Other compounds which unite directly with olefines are HOCl, NOCl, N_2O_3, and N_2O_4 ; some of the additive products so formed

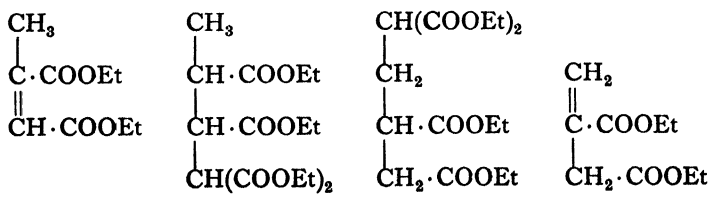
from nitrosyl chloride are of considerable importance in the study of the terpenes (pp. 914, 925).

The addition of alkali metals, and of metallic alkyls, to certain types of olefinic compounds is described later (pp. 1038-39). Of much greater practical importance is the addition to $\alpha\beta$-unsaturated esters and $\alpha\beta$-unsaturated ketones of the sodium derivative of diethyl malonate or of ethyl acetoacetate (Michael reaction). Diethyl sodiomalonate, for example, combines with ethyl cinnamate, giving a sodium derivative, which is immediately decomposed by dilute acids, the sodium atom being displaced by hydrogen:



The tricarboxylic acid obtained from this ester, like all such derivatives of malonic acid, decomposes when it is heated, with the formation of *β-phenylglutaric acid.*

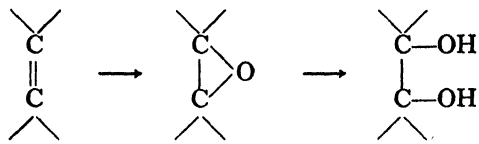
Other examples of this most useful general reaction have been given (p. 800), and it should be noted that when addition takes place the sodium atom of the ester *seems* to unite with that carbon atom, which is directly combined with the —COOEt or >CO group. The course of the reaction depends, however, on the nature of the unsaturated ketone or ester, and also on the experimental conditions. From *diethyl citraconate*, (I), for example, with diethyl sodiomalonate, both the compounds, (II) and (III), may be obtained, and the *same* two esters may also be produced from *diethyl itaconate*, (IV), under the same conditions, probably because the two olefinic esters are tautomeric in the presence of sodium ethoxide (Hope, *J.* 1912, 892 ; Ingold, Shoppee, and Thorpe, *J.* 1926, 1477).



The polymerisation of olefines is considered later (p. 960) and also the isomeric change of olefinic acids (p. 838).

Oxidation of Olefines

The oxidation of olefines with potassium permanganate and chromic acid has already been mentioned (p. 95), but there are many other reagents which oxidise such compounds in various ways. With perbenzoic acid or monoperphthalic acid (p. 813), for example, olefines usually give cyclic oxides (*epoxides*) which can be hydrolysed to 1:2-glycols,



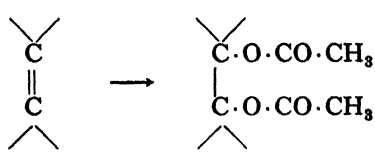
Hydrogen peroxide, in alkaline solution, often effects a similar change, especially with $\alpha\beta$-unsaturated ketones.

In the presence of catalysts, such as osmium tetroxide or pervanadic acid, a solution of hydrogen peroxide in ether or acetone, may convert an olefine either into an oxide, as shown above, a glycol, or a mixture of carbonyl compounds.

The glycol formed in this (or in other) ways may be oxidised to the carbonyl compounds with a solution of lead tetra-acetate in acetic acid (*Criegee's* reagent),[1]

$$\begin{matrix} >C\cdot OH \\ | \\ >C\cdot OH \end{matrix} + Pb(O\cdot CO\cdot CH_3)_4 = \begin{matrix} >CO \\ \\ >CO \end{matrix} + 2CH_3\cdot COOH + Pb(O\cdot CO\cdot CH_3)_2,$$

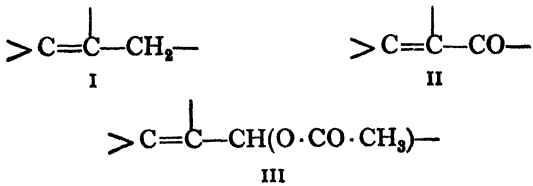
which often attacks olefines directly giving the diacetate of the diol,



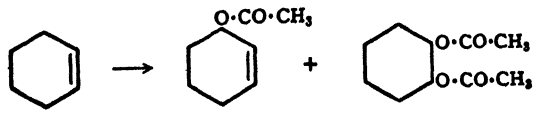
Just as the group (I) may undergo substitution instead of addition,

[1] The oxidation of glycols with periodic acid is discussed later (p. 895).

so may it be oxidised abnormally to (II), by selenium dioxide or chromic acid, and by Criegee's reagent to (III):



*Cyclo*hexene, for example, with the last-named reagent, gives a mixture of acetates which can then be hydrolysed to the unsaturated alcohol and saturated diol respectively,



Ozonides and Ozonolysis

As previously stated (p. 96) an essential step in the determination of the structure of an olefinic compound is to ascertain the position in the molecule of the double bond; for this purpose oxidation with an alkaline solution of permanganate is very commonly employed. Another highly important method, the various stages of which are summarised in the term *ozonolysis*, involves the preparation of the *ozonide* of the unsaturated compound.

The ozonides (p. 96) were first investigated by Harries, who found that ozone combined directly with olefinic and acetylenic compounds, one molecule of ozone uniting with each unsaturated binding of the substance. They may be prepared by dissolving the unsaturated compound in an inert solvent, such as chloroform, and passing into the cooled solution ozonised oxygen, diluted with carbon dioxide if it is necessary to moderate the reaction. Under such conditions ethylene, allyl alcohol, mesityl oxide, and oleic acid, for example, give mono-ozonides, whereas diallyl and other di-olefinic derivatives give di-ozonides.

The ozonides of the simpler olefines may be distilled in a vacuum, but most ozonides are very explosive; they behave like peroxides, liberating iodine from potassium iodide, and they are decomposed

by water (yielding aldehydes, ketones, acids, etc., p. 811) in such a way that the carbon atoms, originally united by a double bond, are completely separated from one another. The formation of an ozonide, followed by its decomposition with water, is therefore a most valuable method (*ozonolysis*) of determining the positions of the double bindings in all types of unsaturated compounds ; for such a purpose the isolation of the ozonide is unnecessary, and the process may often be carried out by treating the compound with ozone in aqueous or acetic acid solution.

Ethylene ozonide, decomposed with water, gives formaldehyde and formic acid ; diallyl ozonide gives succindialdehyde and/or succinic acid, together with formic acid and/or formaldehyde :

$$\begin{array}{ccc} CH_2{=}CH_2 & & CH_2{=}CH{-}CH_2{-}CH_2{-}CH{=}CH_2 \\ \downarrow & & \downarrow \\ CH_2O \quad CH_2O_2 & & CH_2O_2 \quad CHO{\cdot}CH_2{\cdot}CH_2{\cdot}CHO \quad CH_2O_2 \end{array}$$

The ozonides of oleic acid and elaidic acid (p. 710) yield nonylic aldehyde (or acid), and azelaic acid (or semialdehyde),

$$\begin{array}{c} CH_3{-}[CH_2]_7{-}CH{=}CH{-}[CH_2]_7{-}COOH \\ \downarrow \\ CH_3{\cdot}[CH_2]_7{\cdot}CHO \quad COOH{\cdot}[CH_2]_7{\cdot}COOH \end{array}$$

and those of crotonic acid and *iso*crotonic acid (p. 709) give acetaldehyde and glyoxylic acid ; the two stereoisomerides are thus proved to be structurally identical in both cases. Similarly the ozonides of *stearolic acid*, $CH_3{\cdot}[CH_2]_7{\cdot}C{:}C{\cdot}[CH_2]_7{\cdot}COOH$, and *phenylpropiolic acid*, $C_6H_5{\cdot}C{:}C{\cdot}COOH$, are decomposed by water, the former giving pelargonic (nonylic) and azelaic acids, and the latter, benzoic and oxalic acids.

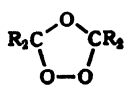
Cyclo-olefines yield ozonides which are relatively stable towards water ; *cyclo*hexene ozonide, C_6H_{10},O_3, for example, is only slowly decomposed even at 100°. Aromatic hydrocarbons also give ozonides : benzene forms a *tri-ozonide*, $C_6H_6,3O_3$, which explodes with warm water, but decomposes more slowly with cold water, yielding glyoxal,

$$C_6H_6,3O_3+3H_2O = 3C_2H_2O_2+3H_2O_2.$$

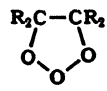
Naphthalene yields a *diozonide* only.

Ozonolysis was first used by Harries in his investigation of the constitution of rubber, and is now a process of great importance in the study of olefinic compounds in general; in the case of some diolefinic derivatives, one only of the double bonds may undergo fission, if graded ozonolysis is applied, and further information as to the structure of the compound is thus obtained.

Various structural formulae might be assigned to a given ozonide, if valency alone is considered and it is assumed that oxygen may be di- or quadri-valent, but most of them need not be discussed. According to Staudinger the action of ozone on an ethylenic compound, $R_2C{=}CR_2$, leads finally to the formation of an ozonide, (I):

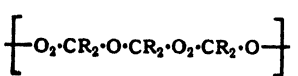


I

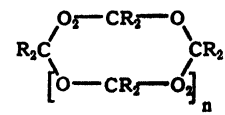


II

All the relatively stable mono-ozonides seem to have this structure, because on reduction they yield ketones (or aldehydes), and not glycols, as would be the case if they were represented by (II), as suggested by Harries. Many ozonides, however, undergo polymerisation, giving viscous or solid amorphous *polyozonides*,

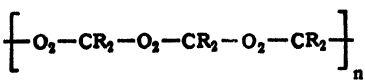


or



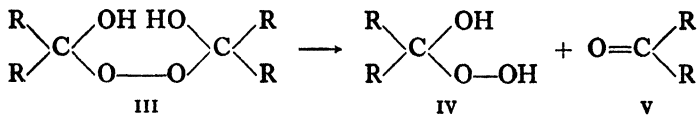
the molecular weights of which in benzene solution range from about 3000 to 6000.

Oxozonides are sometimes formed by the combination of ozonides with oxygen, and are probably polymerides of the structure,



The initial decomposition of an ozonide, (I), by water is a fission of one of the links of $—CR_2{\cdot}O{\cdot}CR_2—$ giving a dihydroxydialkyl

peroxide, (III), which is then converted into a monohydroxyalkyl hydrogen peroxide, (IV), and a ketone, (V);



III IV V

the former then decomposes into a ketone and hydrogen peroxide. When, however, either of the radicals, R, represents hydrogen, (V) is an aldehyde instead of a ketone, and (IV) gives an acid, R·COOH, and water instead of a ketone and hydrogen peroxide. Sometimes the products of decomposition are obtained in the form of their peroxides (p. 966).

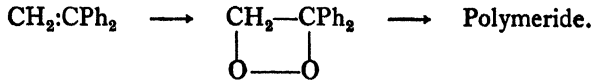
Ozonolysis of acetylenic compounds usually gives (a mixture of) acids,

$$R\cdot C{:}C\cdot R' + O_3 + H_2O = R\cdot COOH + R'\cdot COOH.$$

The importance of the process of ozonolysis can hardly be overrated; in addition to its use in the case of mono-, di-, and poly-olefinic compounds (compare citral, sesquiterpenes, and polyenes), it has been employed in attempts to determine the structures of unstable olefinic enols. The ozonide of the enolic form of *benzoyl-acetone*, $C_6H_5\cdot CO\cdot CH_2\cdot CO\cdot CH_3$, for example, with water gives methylglyoxal, benzoic acid, and hydrogen peroxide; it may therefore be concluded that the enol probably has the structure, $C_6H_5\cdot C(OH){:}CH\cdot CO\cdot CH_3$.

Ozone also reacts with certain types of saturated compounds; it oxidises primary alcohols to aldehydes and then to acids, and converts di-*iso*amyl ether, for example, into iso*amyl* iso*valerate*, $C_4H_9\cdot COOC_5H_{11}$.

Many unsaturated compounds combine slowly with oxygen in the dark, more quickly in the light, yielding *peroxides*; the changes involved are probably as indicated below:



Acetyl peroxide, $CH_3\cdot CO\cdot O\cdot O\cdot CO\cdot CH_3$, *benzoyl peroxide*, $C_6H_5\cdot CO\cdot O\cdot O\cdot CO\cdot C_6H_5$, and many analogous compounds are obtained by the action of metallic peroxides on anhydrides, acid chlorides, etc.; the former is a thick explosive liquid, but the latter

is crystalline and relatively stable, and is used as an oxidising agent and disinfectant.

When benzoyl peroxide is treated with sodium methoxide it yields sodium perbenzoate and methyl benzoate, and the salt, with dilute sulphuric acid, gives *perbenzoic acid*,

$$(Ph\cdot CO)_2O_2+MeONa = Ph\cdot CO_3Na+Ph\cdot COOMe.$$

Monoperphthalic acid, $C_6H_4(COOH)\cdot CO\cdot OOH$, is obtained by treating phthalic anhydride with alkaline hydrogen peroxide and liberating the acid at a low temperature.

Conjugated Systems

Of the two di-olefinic hydrocarbons, isoprene and diallyl, which have already been briefly described (p. 105), the latter may be said to show a normal behaviour : that is to say its chemical properties might have been foretold from its structural formula, inasmuch as each of its olefinic bindings behaves on the whole like that of ethylene. Isoprene, however, under various conditions, gives certain additive products which were at first regarded as abnormal, and many other di-olefines and their derivatives behave in this respect like isoprene.

Such unexpected reactions were first observed by Fittig (1885) in the case of piperic acid (p. 601) ; on reduction with sodium amalgam and water this compound gave the $\beta\gamma$-unsaturated acid shown below, instead of one of the expected products, which would have been formed by the normal addition of two hydrogen atoms to one, or to both of the olefinic bonds :

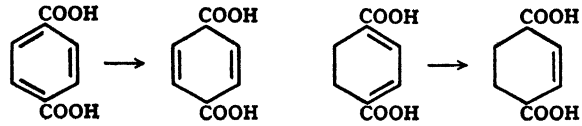
$$CH_2<^{O}_{O}>C_6H_3\cdot CH{:}CH\cdot CH{:}CH\cdot COOH+2H =$$

$$CH_2<^{O}_{O}>C_6H_3\cdot CH_2\cdot CH{:}CH\cdot CH_2\cdot COOH.$$

It will be seen that in this reaction *both* the original double bonds are changed by combination with hydrogen, but a new one is formed in a different position in the molecule.

Baeyer's work on the reduction of the phthalic acids afforded other examples of the same kind ; terephthalic acid, (I), for example, gave a Δ-2:5-dihydro-derivative, (II), and Δ-1:3-dihydroterephthalic acid, (III), gave the Δ-2-tetrahydro-acid, (IV), the two hydrogen

atoms having been added in the 1:4-position, with the formation of a new double binding in both cases (p. 802) :



I II III IV

In order to obtain further information regarding these reactions, Baeyer examined the reduction of open chain di-olefinic acids, having a Δ-1:3-structure analogous to that of terephthalic acid. *Muconic acid* may be obtained by condensing glyoxal with malonic acid in the presence of pyridine and then heating the tetracarboxylic acid so formed ; it has the structure, (V), given below, and is reduced by sodium amalgam and cold water to dihydromuconic acid, (VI). The constitution of dihydromuconic acid is shown by the fact that it yields malonic acid on oxidation ; also, when heated with alkali, it undergoes isomeric change, and the double bond passes from the $\beta\gamma$- to the $\alpha\beta$-position (p. 838), with the formation of (VII), which, on oxidation, gives a mixture of oxalic and succinic acids :

V $HOOC \cdot CH{:}CH \cdot CH{:}CH \cdot COOH$
VI $HOOC \cdot CH_2 \cdot CH{:}CH \cdot CH_2 \cdot COOH$
VII $HOOC \cdot CH_2 \cdot CH_2 \cdot CH{:}CH \cdot COOH$

It is clear from these results that the behaviour of terephthalic acid on reduction is strictly comparable with that of a Δ-1:3- open chain di-olefinic acid, and that in both cases hydrogen atoms are added in the 1:4-position with the formation of a *new* double binding. Further investigations by various workers proved that other di-olefinic acids behaved in the same way. *Cinnamylidenemalonic acid* (p. 529), for example, gave on reduction the product shown below :

$$Ph \cdot CH{:}CH \cdot CH{:}C(COOH)_2 \longrightarrow Ph \cdot CH_2 \cdot CH{:}CH \cdot CH(COOH)_2$$

This phenomenon of 1:4-addition is not confined to acids, but is observed in the case of many di-olefinic compounds of a *particular type* ; thus both 1-phenylbutadiene and symmetrical 1:4-diphenylbutadiene, with nascent hydrogen, yield 1:4-dihydro-derivatives,

$$Ph \cdot CH{:}CH \cdot CH{:}CH_2 + 2H = Ph \cdot CH_2 \cdot CH{:}CH \cdot CH_3,$$
$$Ph \cdot CH{:}CH \cdot CH{:}CH \cdot Ph + 2H = Ph \cdot CH_2 \cdot CH{:}CH \cdot CH_2 \cdot Ph.$$

Similarly, pyrrole is reduced to pyrroline (p. 588).

It will be seen later that 1:6-, and even 1:10-addition may take place in the case of certain polyenes (p. 982).

In order to account for all the reactions of this nature, which were then known, Thiele suggested that the atom-fixing powers of the two carbon atoms in an olefinic group are not completely exhausted or satisfied by the combined affinities of the atoms forming that group : that the two unsaturated carbon atoms have some ' residual affinity,' to which their reactivity is due. If, in the following scheme, these residual affinities, or *partial valencies*, are represented by dotted lines, the combination of an olefinic derivative with hydrogen may be represented thus :

$$\underset{\vdots\ \vdots}{\text{R—CH:CH—R}} + \text{H}_2 = \underset{\vdots\ \vdots}{\text{R—CH:CH—R}} \longrightarrow \text{R—CH}_2\cdot\text{CH}_2\text{—R}.$$
$$\text{H}\quad\text{H}$$

In the case of a molecule, which contains the group —CH:CH · CH:CH—, it may be supposed that the partial valencies of the two central carbon atoms neutralise one another, those of the end carbon atoms remaining free, as indicated below, (I) ; 1:4-addition then takes place because of the two partial valencies of the two terminal carbon atoms of the system, with the formation of a new olefinic bond, (II, Thiele's rule) :

$$\underset{\vdots\qquad\vdots}{\text{—CH:CH·CH:CH—}} + 2\text{H} \longrightarrow \underset{\vdots\ \vdots}{\text{—CH}_2\cdot\text{CH:CH}\cdot\text{CH}_2\text{—}}$$
$$\text{II}$$

An arrangement of alternate double and single bonds of this kind is known as a **conjugated system.**

The addition of bromine (1 mol.) to a conjugated system may also follow Thiele's rule : *Cyclo*pentadiene, for example, and Δ-1:3-dihydrobenzene (*cyclo*hexadiene) form 1:4-dibromo-additive products, but 1:2-addition often occurs ; in most reactions of this kind, however, a mixture of 1:4- and 1:2-dibromo-derivatives is formed although one type of addition may predominate. Thus butadiene and 1:3-, 2:3-, and 1:4-dimethylbutadienes all give mixtures of 1:2- and 1:4-derivatives ; (symmetrical) 1:4-diphenylbutadiene gives the former only but yields a 1:4-additive product with nitrogen peroxide.

In general, the course of such reactions of conjugated systems depends both on the nature of the unsaturated substance and on

that of the addendum ; thus 1:4-addition occurs so generally with nascent hydrogen, in various types of compounds, that it is possible to infer the presence or absence of a conjugated system from the behaviour of a compound on reduction. In the case of the addition of bromine or an unsymmetrical compound such as hydrogen bromide, however, the results are very irregular ; the exceptions to Thiele's rule gradually became so numerous that the rule lost its value.

According to modern ideas in a conjugated compound such as butadiene forms such as $^{+}CH_2 \cdot CH{:}CH \cdot CH_2^{-}$ contribute to the mesomeric state of the molecule and the fact that the length of the central (single) carbon-carbon bond in butadiene is 1·46 A.U. as compared with the length of 1·5 A.U. of an unconjugated single bond confirms this view. The central bond thus has some double bond character. If this form of butadiene is the most reactive the first attack by an electrophilic reagent leads to the addition of, for example, Br^+ or H^+ to one end of the conjugated system and to the formation of an ion which is mesomeric and thereby stabilised,

$$CH_2{:}CH \cdot CH{:}CH_2 + Br^+ \longrightarrow CH_2{:}CH \cdot \overset{+}{C}H \cdot CH_2Br / CH_2 \cdot CH{:}CH \cdot CH_2\overset{+}{B}r,$$

$$CH_2{:}CH \cdot CH{:}CH_2 + H^+ \longrightarrow CH_2{:}CH \cdot \overset{+}{C}H \cdot CH_3 / CH_2 \cdot CH{:}CH \cdot \overset{+}{C}H_2.$$

An ion formed by addition of bromine or hydrogen to one of the central carbon atoms, $CH_2{:}CH \cdot CHBr \cdot CH_2^+$ or $CH_2{:}CH \cdot CH_2 \cdot CH_2^+$ cannot be stabilised by mesomerism. That this view is correct is supported by the fact that the final product of addition as found experimentally, is always one during the formation of which such a mesomeric ion may be assumed ; with butadiene, for example, no 1-bromobut-3-ene, $CH_2{:}CH \cdot CH_2 \cdot CH_2Br$, is formed with hydrogen bromide, and with 1-phenylbutadiene similarly the product is $Ph \cdot CH{:}CH \cdot CHBr \cdot CH_3$ and not $Ph \cdot CH{:}CH \cdot CH_2 \cdot CH_2Br$ while 1:4-dimethylbutadiene and hydrogen bromide give a mixture of $Me \cdot CH_2 \cdot CHBr \cdot CH{:}CH \cdot Me$ and $Me \cdot CH_2 \cdot CH{:}CH \cdot CHBr \cdot Me$.

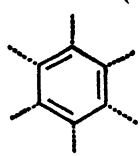
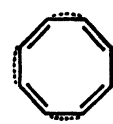
The second stage of the reaction is the combination of the bromide ion with the mesomeric cation and the final product depends on various factors : the structure of the first formed product depends on the relative rates of addition of Br^- at the two possible positions and that isomeride which is the more rapidly formed will predominate. This compound may, however, ionise again and if there is sufficient time the final product will consist mainly or entirely of the more stable isomeride. Whether the first formed addition

compound re-ionises or not depends on the structure of the original conjugated substance, the solvent in which addition is taking place, the temperature, etc. and the composition of the final mixture may also depend on the time of reaction. The case of 1-phenylbutadiene may be cited as an example of the control of addition by very different stabilities of the final products; $Ph \cdot CH{:}CH \cdot CHBr \cdot CH_3$ is more stable than $Ph \cdot CHBr \cdot CH{:}CH \cdot CH_3$ as in the former compound the ethylenic linkage is conjugated with the aromatic ring whereas in the latter it is not; the former, as already stated, is the sole product of reaction of hydrogen bromide with 1-phenylbutadiene.

When an ethylenic linkage is conjugated with a carbonyl group, $>C{=}CR{-}CR'{=}O$, certain nucleophilic additions to the former, which do not occur with an isolated double bond, are possible; additions to unsaturated aldehydes and ketones of hydrogen cyanide (CN^-), and of diethyl malonate($^-CH(COOEt)_2$), the Michael reaction, have already been mentioned (pp. 806-807) and the reactions with ammonia, hydroxylamine and Grignard reagents (R^-) are described later (p. 825). In these reactions the carbonyl group causes the β-carbon atom to assume a positive charge by mesomeric change and that carbon atom is active towards nucleophilic reagents,

$$CH_2{=}\overset{\curvearrowright}{CH}{-}CH{=}\overset{\curvearrowleft}{O}.$$

It is interesting to recall that Thiele applied his views to explain the great stability of benzene, in comparison with that of olefinic compounds; he suggested that the molecule of benzene, represented by the Kekulé formula, may be regarded as an extended conjugated system, (I), in which the partial valencies neutralise one another, as indicated in (II); corresponding symbols may be written for

I  II  III 

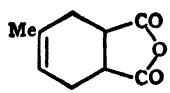
naphthalene and other benzenoid compounds, as well as for heterocyclic compounds, such as pyridine. Such explanations, however, are found wanting when further cases are considered. *Cyclo*-octatetrene, for example, may be represented by the symbol, (III), in which, as in (II), all the partial valencies are neutralised, but this hydrocarbon is very reactive and olefinic in character; thus, it

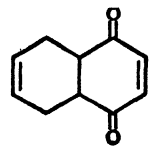
reduces permanganate, combines readily with bromine, is decomposed when it is heated, and gives tarry products with nitric acid.

Modern views explain the difference between the two hydrocarbons, benzene and *cyclo*-octatetrene (p. 1001).

The Diels-Alder Reaction

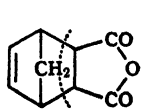
Very interesting additive reactions have been described by Diels, Alder, and their collaborators, who found that substances containing the group, —CH=CH—CO—, such as maleic anhydride, ethyl acrylate, and *p*-benzoquinone, unite directly with conjugated systems, the addition always occurring in the 1:4-position. Isoprene and

I 

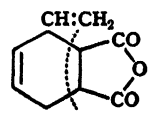
II 

maleic anhydride, for example, give the anhydride of 4-*methyl*-Δ-4-cyclo*hexene*-1:2-*dicarboxylic acid*, (I, *methyltetrahydrophthalic anhydride*); similarly butadiene and quinone give a hydronaphthalene derivative, (II). Maleic anhydride, acetylenedicarboxylic acid (or its ester), and certain other unsaturated substances, also react with cyclic conjugated systems giving bridged ring compounds (p. 819).

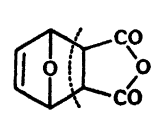
Thus the products of the combination of maleic anhydride with *cyclo*pentadiene, (III), hexatriene, (IV), and furan, (V), and those of acetylenedicarboxylic acid (or ester) with anthracene, (VI, X = COOH), *cyclo*pentadiene, (VII), and furan, (VIII), are shown below; the dotted lines indicate where combination has taken place.



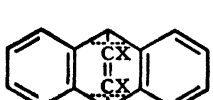
III



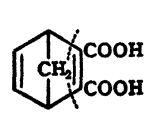
IV



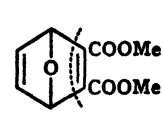
V



VI



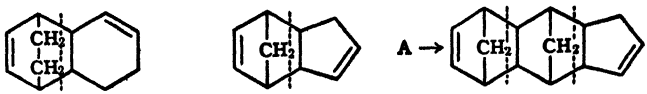
VII



VIII

Reactions with maleic anhydride, such as those indicated above, are so general that this compound may be used for determining the presence or absence of a conjugated system in di- and poly-olefines of unknown structure, such as members of the terpene and sesquiterpene groups ; additional very interesting examples of the Diels-Alder reaction are given later (pp. 1028, 1035).

Two or more molecules of a given conjugated hydrocarbon may also unite by 1:4-addition (Alder and Stein, *Ann*, **496**, 197). Δ-1:3-*Cyclo*hexadiene, for example, undergoes polymerisation, giving (IX), and two molecules of *cyclo*pentadiene give the hydrocarbon, (X), which may then combine with a third molecule (A) forming the compound (XI) :



IX X XI

Benzene, however, does not undergo polymerisation in this way, and does not react with maleic anhydride, facts which, like many others, show the unique character of the molecular structure of this hydrocarbon.

Polymerides are often termed *dimerides*, *trimerides*, etc., according to the number of molecules of the original substance from which they are formed.

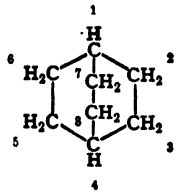
Nomenclature and Stereochemistry of Bridged Ring Compounds

In the structural formulae of many of the polycyclic compounds just considered, one or more carbon atoms of one of the rings may be regarded as forming a link or *bridge* between two of those of another ring; such molecules are said to have a *bridged ring* structure, of which many more examples are found among the dicyclic terpenes and their derivatives (p. 924).

In the systematic nomenclature of such compounds the presence of the bridge is denoted by the prefix *meso* (Bredt) or *endo* (Diels), followed by the name of the group which forms the bridge across the *higher* membered or parent ring ; this latter is numbered, starting from one of the carbon atoms common to all three rings,

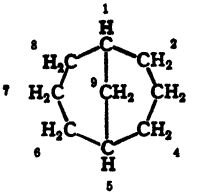
and the position of the bridge is then indicated by numerals as shown:

I



1:4-*Meso*ethylene*cyclo*hexane
1:4-*Endo*ethylene*cyclo*hexane

II

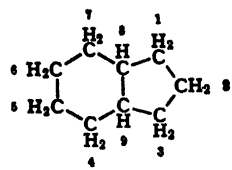


1:5-*Meso*methylene*cyclo*-octane
1:5-*Endo*methylene*cyclo*-octane

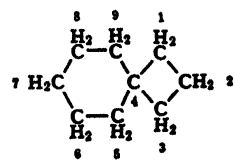
An alternative system names the compound as a derivative of that *dicyclic* hydrocarbon which contains the same number of carbon atoms as the entire bridged ring structure (all substituents excluded); the number of carbon atoms forming the bridge, followed by that of each of the links which connects the two carbon atoms common to the three rings is then given before the name. Thus (I) is 2,2,2-di*cyclo*-octane and (II) 1,3,3-di*cyclo*nonane, the first figure in each case indicating the number of carbon atoms in the bridge.

Systematic names may now be given to the compounds mentioned on p. 818: (V), for example, is 1:4-*meso*-oxy-Δ-5-*cyclo*hexene-2:3-dicarboxylic anhydride and (VII) is 1:4-*meso* (or *endo*) methylene-2:5-*cyclo*hexadiene-2:3-dicarboxylic acid, or 1,2,2-di*cyclo*hepta-2:5-diene-2:3-dicarboxylic acid.

The second system of nomenclature (above) can be applied to decahydronaphthalene, hydrindane and other structures of a similar type, which may be regarded as bridged rings; decalane, for example, would then be 0,4,4-di*cyclo*decane and hydrindane 0,3,4-di*cyclo*nonane since the bridges here are bonds and do not contain carbon atoms. In the latter case the numbering starts with the *smaller* ring and finishes with those carbon atoms common to the two rings.



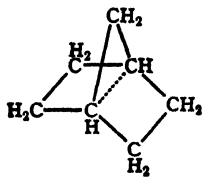
Hydrindane



Spiro-3,5-nonane

The nomenclature and numbering of spirocyclic compounds (p. 723) may also be seen from the above example.

It has already been seen that the molecule of decalane is not planar (p. 793): similarly bridged ring compounds are rigid tridimensional structures, as indicated in the case of 1,2,2-di*cyclo*heptane, (I); the planes of the three rings (two of four and one of three atoms) which would be formed if certain atoms were joined as indicated by the dotted line are inclined to one another and meet at that line. The same structure is indicated in a somewhat different way in (II). The stereochemistry of such tridimensional structures is therefore very complex.



I



II

CHAPTER 50

KETONES, KETONIC ACIDS, AND KETENES

Ketones

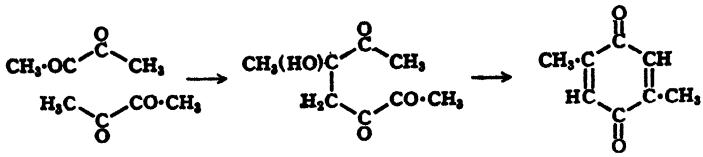
THE symbol $>C{=}O$ which occurs in the formulae of various types of compounds, as already mentioned, does not represent or summarise a constant set of properties or reactions, since this group, like $>C{=}C<$, behaves very differently according to the nature of the atoms or radicals with which it is combined. When, for example, it is directly united to —OH, —OEt, —NH_2, or —Cl, as well as to a carbon atom, it is very inert, and its properties are quite different from those which it shows in ketones and in aldehydes, probably because of resonance (p. 517); in the two types just mentioned the carbonyl group is highly reactive, and, in consequence, the study of its reactions in such compounds is of importance.

In addition to the simple mono-ketones, di-, tri-, etc., ketones are known. The *diketones* are classed according to the relative positions of the two carbonyl groups, and are distinguished as α- or 1:2-, β- or 1:3-, γ- or 1:4-, etc., diketones; a more systematic nomenclature is illustrated below.

Diacetyl, $CH_3{\cdot}CO{\cdot}CO{\cdot}CH_3$ (*dimethylglyoxal*, *butandione*), is the simplest 1:2-diketone and is obtained by the hydrolysis with dilute sulphuric acid of its monoxime, iso*nitrosomethylethyl ketone*,[1] which is prepared by the interaction of methylethyl ketone, amyl nitrite, and hydrochloric acid:

$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3 \longrightarrow CH_3{\cdot}CO{\cdot}C(:N{\cdot}OH){\cdot}CH_3 \longrightarrow CH_3{\cdot}CO{\cdot}CO{\cdot}CH_3.$$

Diacetyl is a *yellow*, volatile liquid, b.p. 87–89°, with a characteristic quinone-like smell; with alkalis it yields first *diacetylaldol* and then p-*xyloquinone*:



[1] The group, $>C{:}N{\cdot}OH$, if produced from $>CO$ and hydroxylamine, is usually called the *oximino*-group, but when formed from $>CH_2$ and nitrous acid, as in this case, it is called the iso*nitroso*-group.

It condenses with *o*-phenylenediamine, yielding *dimethylquinoxaline* (p. 1060), a reaction which is shown by most substances containing the —CO·CO— group, and it reacts with hydroxylamine and with phenylhydrazine, as do other 1:2-diketones, such as benzil, in a normal manner.

Dimethylglyoxime, $CH_3 \cdot C(:N \cdot OH) \cdot C(:N \cdot OH) \cdot CH_3$ (*diacetyldioxime*), is prepared by the interaction of *iso*nitrosomethylethyl ketone and hydroxylamine, and melts at 234°. It is used in the detection and estimation of nickel, as it yields an almost insoluble red compound, $(C_4H_7O_2N_2)_2Ni$, with nickel salts in neutral solution.[1] On reduction the dioxime yields a mixture of meso- and dl-2:3-*diaminobutanes*.

Acetylacetone, $CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3$ (2:4-*pentandione*), is a 1:3-or β-diketone, and is prepared by the condensation of acetone and ethyl acetate in the presence of sodamide (Claisen condensation),

$$CH_3 \cdot COOEt + CH_3 \cdot CO \cdot CH_3 = CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3 + Et \cdot OH.$$

It boils at 139°, and is decomposed into acetone and acetic acid when it is heated with water: like ethyl acetoacetate, it forms a sodium derivative which reacts with alkyl halides and many other halogen compounds. Derivatives of acetylacetone with metals such as beryllium, copper, zinc, and aluminium are remarkably stable, and many of them can be vapourised unchanged. They have therefore been used for the determination of the atomic weight and valency of various metals. They are regarded as partly co-ordinated compounds rather than as mere salts because of their volatility and from stereochemical evidence (p. 775). The behaviour of acetylacetone and other 1:3-diketones towards hydroxylamine and phenylhydrazine is described later (pp. 1052, 1057).

Many other 1:3-diketones may be prepared by the condensation of esters with ketones, as in the case of acetylacetone; thus a mixture of ethyl benzoate and acetone, or of ethyl acetate and acetophenone, gives *benzoylacetone*, $C_6H_5 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3$, which closely resembles acetylacetone in its reactions.

Acetonylacetone, $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CO \cdot CH_3$ (2:5-*hexandione*), is a 1:4-diketone, prepared by treating ethyl sodioaceto-

[1] α-Benzildioxime also reacts with nickel salts and gives a precipitate, which is so sparingly soluble in water that one part of the metal in two million parts of water can thus be detected (compare p. 776).

acetate with iodine, and submitting the product, *diethyl diacetylsuccinate*, to ketonic hydrolysis :

$$\begin{matrix}CH_3\cdot CO\cdot CHNa\cdot COOEt\\ CH_3\cdot CO\cdot CHNa\cdot COOEt\end{matrix} \longrightarrow \begin{matrix}CH_3\cdot CO\cdot CH\cdot COOEt\\ |\\ CH_3\cdot CO\cdot CH\cdot COOEt\end{matrix} \longrightarrow \begin{matrix}CH_3\cdot CO\cdot CH_2\\ |\\ CH_3\cdot CO\cdot CH_2\end{matrix}$$

It can also be obtained from ethyl acetoacetate in another way (p. 211). It boils at 192°, and has no acidic properties, as its molecule does not contain the active group, —CO·CH_2·CO— ; it reacts normally with one or with two molecules of hydroxylamine or phenylhydrazine.

Acetonylacetone and other 1:4-diketones are of very considerable importance owing to the great readiness with which they form five-membered heterocyclic compounds (p. 589).

Derivatives of δ- or 1:5-diketones are formed by the condensation of aldehydes with ethyl acetoacetate, but these products undergo inner condensation and are converted into derivatives of *cyclo*hexenone (p. 799).

Triketones and tetraketones are known ; dibenzoylacetylmethane is described later (p. 832), and triketoindane has already been mentioned (p. 556).

Pentantrione, $CH_3\cdot CO\cdot CO\cdot CO\cdot CH_3$ (*triketopentane*), has been obtained by condensing acetylacetone with *p*-nitrosodimethylaniline and hydrolysing the product, $CAc_2{:}N\cdot C_6H_4\cdot NMe_2$; it is an orange liquid, and condenses with acetylacetone to give the hydroxytetraketone,

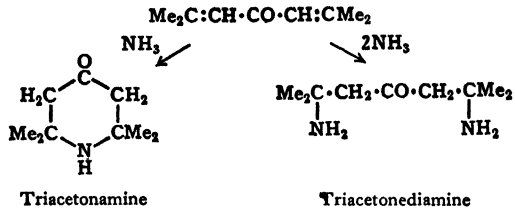
$$\begin{matrix}CH_3\cdot CO\cdot C(OH)\cdot CO\cdot CH_3\\ |\\ CH_3\cdot CO\cdot CH\cdot CO\cdot CH_3\end{matrix}$$

Most of the reactions of simple aldehydes have already been given and the tautomerism of hydroxyaldehydes is discussed later (p. 834) ; both the —CHO groups of dialdehydes, such as glyoxal and succindialdehyde show, as a rule, the normal behaviour.

Many of the higher aldehydes of the $C_nH_{2n}O$ series, from heptylaldehyde upwards, are used in perfumery.

αβ-Unsaturated ketones are readily prepared by the condensation of ketones either alone or with aldehydes ; acetone, for example, gives mesityl oxide and phorone, whereas acetone and benzaldehyde in the presence of sodium hydroxide give ***benzylideneacetone***, $C_6H_5\cdot CH{:}CH\cdot CO\cdot CH_3$.

$\alpha\beta$-Unsaturated ketones are conjugated substances (p. 816) and readily give additive products; from mesityl oxide and ammonia, diacetonamine is formed (pp. 148, 606), whereas phorone and ammonia give triacetonamine (p. 605) and *triacetonediamine*,



Triacetonamine Triacetonediamine

Mesityl oxide reacts with hydroxylamine, giving a hydroxylamino-additive compound and an oxime,



$\alpha\beta$-Unsaturated ketones may also form ethylenic additive products with hydrogen cyanide, instead of cyanohydrins (p. 806) and may combine similarly with Grignard reagents, such as phenyl magnesium bromide,



Ketonic Acids

It has already been pointed out (p. 210) that β-ketonic acids and their esters differ from the corresponding α- and γ-ketonic compounds in certain very important respects. Ethyl acetoacetate is a β-ketonic ester of exceptional interest and the mechanism of its formation by the action of sodium on ethyl acetate, as well as its structure, were at one time widely discussed. It was first assumed by Frankland and Duppa that sodium displaced hydrogen from the molecule of ethyl acetate, giving $CH_2Na \cdot COOEt$, which then reacted with unchanged ethyl acetate. Much later, Claisen suggested that in the first place sodium ethoxide was formed, from traces of alcohol contained in the ethyl acetate or produced by its decomposition, and that this compound gave, with ethyl acetate,

an additive product, which then condensed with unchanged ester, as shown below :

$$CH_3\cdot COOEt+NaOEt = CH_3\cdot C(ONa)(OEt)_2,$$

$$CH_3\cdot C(ONa)(OEt)_2+CH_3\cdot COOEt = CH_3\cdot C(ONa){:}CH\cdot COOEt+2Et\cdot OH.$$

In accordance with this view it was found that benzyl benzoate and sodium methoxide gave the same compound as methyl benzoate and sodium benzyloxide :

$$C_6H_5\cdot CO\cdot OCH_2\cdot C_6H_5+CH_3\cdot ONa \rightarrow C_6H_5\cdot C(ONa)(OCH_3)(O\cdot CH_2\cdot C_6H_5)$$

$$C_6H_5\cdot CO\cdot OCH_3+C_6H_5\cdot CH_2\cdot ONa \rightarrow$$

It was also shown that when the ethyl acetate, used in the preparation of ethyl acetoacetate, is free from alcohol, the reaction with sodium is very slow at first, but becomes more rapid as soon as some alcohol (sodium ethoxide) has been formed, in accordance with Claisen's view.

Michael disputed the existence of Claisen's intermediate product, and Nef assumed the formation of a sodium compound of an enolic form of ethyl acetate, which combines with ethyl acetate,

$$CH_2{:}C(ONa)(OEt)+CH_3\cdot COOEt = CH_3\cdot C(ONa)(OEt)\cdot CH_2\cdot COOEt;$$

the additive compound so formed might then lose a molecule of alcohol, giving $CH_3\cdot C(ONa){:}CH\cdot COOEt$. This explanation has been slightly modified by Arndt and Eistert (*Ber.* 1936, 2381) : a small proportion of an anion which is the mesomeric form of (I) and (II) is first produced by the action of the sodium (or sodium ethoxide) on ethyl acetate,

I $\left[\bar{C}H_2\cdot C(=O)OEt\right]$ II $\left[CH_2{:}C(O^-)OEt\right]$

A reversible reaction then occurs between (I) and an active form of ethyl acetate, (III), to give an anion, (IV), which loses alcohol and affords (V, one of the contributors of a mesomeric ion) :

III $\overset{+}{C}(CH_3)(OEt)(O^-)$ IV $\left[EtOOC\cdot CH_2\cdot C(CH_3)(OEt)(O^-)\right]$ $\rightarrow$ V $\left[EtOOC\cdot CH{:}C(CH_3)(O^-)\right]$

A sodium derivative of ethyl acetate has been isolated by Scheibler.

Whatever may be the mechanism of the reaction between ethyl acetate and sodium, it is known that many analogous condensations may be brought about; two molecules of the same or of different esters of monocarboxylic acids (below), or one molecule of an ester and one molecule of a ketone (p. 823), or two molecules of the esters of different dicarboxylic acids (p. 781), may condense in the presence of sodium, sodium ethoxide, or sodamide, giving ketonic esters or diketones; such reactions, of which many examples have been given, are described as *Claisen condensations*. In most of the cases already considered only the final stage of the change is indicated.

Ethyl benzoylacetate, $C_6H_5 \cdot CO \cdot CH_2 \cdot COOEt$, can be prepared by the condensation of ethyl benzoate with ethyl acetate in the presence of sodium or alcohol-free sodium ethoxide. It boils at 148° (11 mm.) and closely resembles ethyl acetoacetate in its chemical behaviour; its sodium derivative reacts with alkyl halides as does ethyl sodioacetoacetate, and the products undergo acid and ketonic hydrolysis; the ester is therefore of service in the synthesis of many aromatic ketones and other compounds.

Ketenes

Ketenes are compounds which contain the group $>C{:}CO$, and the simplest **ketene**, $CH_2{:}CO$, was first obtained by decomposing acetic anhydride with a white-hot platinum wire (Wilsmore),

$$\begin{matrix} CH_3 \cdot CO \\ CH_3 \cdot CO \end{matrix} \!\!>\!O = 2CH_2{:}CO + H_2O.$$

It is more conveniently prepared by passing the vapour of acetone through a tube, partially filled with earthenware, at a dull red heat,

$$CH_3 \cdot CO \cdot CH_3 = CH_2{:}CO + CH_4.$$

Ketene, and some of its homologues, may be obtained by treating a solution of an α-bromoacyl bromide with zinc,

$$(CH_3)_2CBr \cdot COBr + Zn = (CH_3)_2C{:}CO + ZnBr_2;$$

dialkylketenes are formed when dialkylmalonic anhydrides (obtained

from the acid chlorides with pyridine and sodium carbonate solution) are heated,

$$(C_2H_5)_2C\begin{matrix}CO\\ \diagup\ \diagdown\\ CO\end{matrix}O = (C_2H_5)_2C{:}CO + CO_2.$$

Ketenes are usually *yellow*, mobile liquids with a characteristic odour. Ketene is a gas (b.p. −56°), and *diethyl ketene*, $CEt_2{:}CO$, a liquid (b.p. 92°). Ketenes do not show the reactions characteristic of ketones, but they combine directly with many compounds, addition taking place to the ethylenic linkage; thus with acetic acid, for example, ketene gives acetic anhydride,

$$CH_2{:}CO + CH_3\cdot COOH = (CH_3\cdot CO)_2O,$$

which is thus prepared on the large scale. With water, alcohol, and ammonia or amines, ketenes yield acids, esters, and amides respectively, the group $>C{:}CO$ in these reactions behaving like the —N:CO group of the carbimides,

$$CH_2{:}CO + R\cdot OH = CH_3\cdot CO\cdot OR,$$
$$CH_2{:}CO + NH_3 = CH_3\cdot CO\cdot NH_2.$$

With bromine, bromo-acid bromides are formed, and halogen acids give acyl halides.

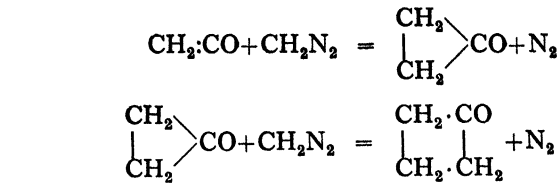
Dimethyl ketene combines with tertiary bases, such as pyridine, forming additive compounds, which are decomposed by boiling hydrochloric acid, yielding the base and *iso*butyric acid, by the addition of the elements of water.

Ketenes are oxidised to peroxides by oxygen; they combine directly with olefines, and with various other substances which contain double linkages, as, for example, with ketones and with Schiff's bases (p. 499),

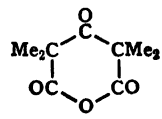
$$R_2C{:}CO + R'_2CO = \begin{matrix}R_2C—CO\\ |\quad\ |\\ R_2'C—O\end{matrix}$$

$$R_2C{:}CO + R'\cdot CH{:}NR'' = \begin{matrix}R_2C\ —\ CO\\ |\quad\ |\\ R'CH—NR''\end{matrix}$$

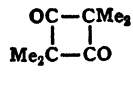
When ketene is passed into a dry ethereal solution of diazomethane, it gives cyclo*butanone*, probably in two stages,



The great reactivity of ketenes is shown by the fact that dimethyl ketene combines with carbon dioxide at low temperatures, giving products such as $2(CH_3)_2C{:}CO,CO_2$, $3(CH_3)_2C{:}CO,2CO_2$, and $4(CH_3)_2C{:}CO,3CO_2$. The first of these three compounds is crystalline and is *tetramethylacetonedicarboxylic anhydride*, (I), since, on hydrolysis, it is decomposed into dimethylmalonic acid and *iso*butyric acid, and it is formed when dimethylmalonic anhydride is heated with a little methylamine ; in the latter reaction it may be assumed that the anhydride is first decomposed giving dimethyl ketene and carbon dioxide, which then combine again, but in different proportions. When dimethylmalonic anhydride is heated alone it is converted into *tetramethyl*cyclo*butandione*, (II), and carbon dioxide, the diketone being formed by the polymerisation of dimethyl ketene :

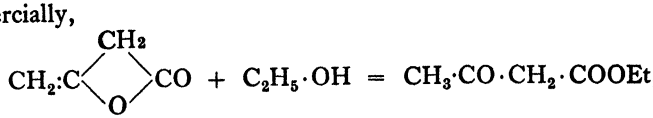


I



II

Most ketenes polymerise with great facility, either spontaneously or in the presence of a catalyst. Ketene, for example, gives *diketene*, which melts at $-6{\cdot}5°$, boils at 127°, and is stable at very low temperatures ; in the presence of acids, diketene combines with alcohols, giving esters of acetoacetic acid, which are thus prepared commercially,



and on reduction it gives β-butyrolactone, a reaction which confirms the given structure. Under ordinary conditions diketene gives a dark tarry polymeride.

In benzene solution in the presence of pyridine, ketene or diketene is converted into dehydracetic acid (p. 984), which, like tetramethyl-*cyclo*butandione, might be classed as a *polyketene*, $(CR_2{:}CO)_n$.

Diphenyl ketene, $Ph_2C{:}CO$, prepared by treating diphenylchloroacetyl chloride with zinc, is a reddish-yellow liquid, boiling at 146° (12 mm.); unlike the aliphatic ketenes, it does not undergo polymerisation, but it shows the general reactions of those compounds. It was the first ketene to be obtained, and was discovered by Staudinger in 1905.

Carbon suboxide, C_3O_2 (p. 276), boils at 7° and polymerises to a red solid. Its chemical behaviour is similar to that of the ketenes.

CHAPTER 51

ISOMERIC CHANGE

Keto-enol Tautomerism

THE phenomenon of keto-enolic tautomerism, a type of dynamic isomerism, of which some account has already been given (pp. 203-205), is shown by many substances, such as β-ketonic esters (ethyl acetoacetate, diethyl oxaloacetate, diethyl acetonedicarboxylate) and β-diketones, the molecules of which contain the group, —CO—CH_2—CO— or —CO—CHR—CO—, and it has been very extensively studied by many chemists, among whom may be mentioned Knorr, Claisen, W. Wislicenus, Kurt Meyer, and Dimroth.

From the *allelotropic* mixture of the ketonic and enolic forms of ethyl acetoacetate the two *desmotropes* (p. 205) have been isolated; they are both stable in the pure condition, but are readily converted into an equilibrium mixture by various catalysts.

This change was discussed by Laar, who introduced the term tautomerism, as long ago as 1885; he suggested that the molecule of ethyl acetoacetate contained a very mobile hydrogen atom, which oscillated perpetually between the two positions represented in the isomeric structures. According to present views the first change is probably the separation of a proton from the molecule, giving the resonance or mesomeric form of the anions, (I), (II), and (III); the proton can then recombine with the anion in either one of two ways:

$$\left.\begin{array}{l} CH_3\cdot CO\cdot CH_2\cdot COOEt \\ CH_3\cdot C(OH){:}CH\cdot COOEt \end{array}\right\rightleftharpoons \left\{\begin{array}{ll} CH_3\cdot CO\cdot \bar{C}H\cdot COOEt & \text{I} \\ CH_3\cdot C(\bar{O}){:}CH\cdot COOEt & \text{II} \\ CH_3\cdot CO\cdot CH{:}C(\bar{O})\cdot OEt & \text{III} \end{array}\right.$$

The resonance of the ion is an essential feature of all such tautomeric changes. This view of the mechanism is supported by the fact that the change is catalysed by ions and does not occur in the solid or vapour state. The resonance of the ion may also account for the fact that in some reactions the ester gives *C*-, and in others *O*-derivatives. Thus when ethyl acetoacetate is treated with benzoyl chloride in the presence of pyridine it gives an *O*-benzoyl derivative, $CH_3\cdot C(O\cdot CO\cdot C_6H_5){:}CH\cdot COOEt$, but when its sodium derivative

reacts with benzoyl chloride or with alkyl halides, a *C*-derivative, $CH_3 \cdot CO \cdot CHR \cdot COOEt$, is produced. The alkali derivatives of such tautomeric substances are mainly ionic compounds in which the metal is associated with the mesomeric form of analogues of (I), (II), and (III). The copper, beryllium and other metal derivatives of β-diketones are, however, co-valent and chelated (p. 775), as, indeed, are the enolic forms themselves (p. 833).

Some other interesting examples of the phenomenon of desmotropism are given below.

Dibenzoylacetylmethane, $CH_3 \cdot CO \cdot CH(CO \cdot C_6H_5)_2$ (*dibenzoylacetone*), is prepared by treating an ethereal solution of benzoylacetone (p. 823) with benzoyl chloride in the presence of sodium carbonate, and decomposing an aqueous solution of the sodium derivative thus formed with acetic acid. The precipitated impure enolic form melts at 80–85°, but the liquid slowly solidifies and melts again at 99–101° (equilibrium mixture). The enol gives an immediate colouration with ferric chloride in alcoholic solution and is immediately soluble in alkalis. The ketonic form melts at 150°, and only gives these reactions after it has passed into the enol.

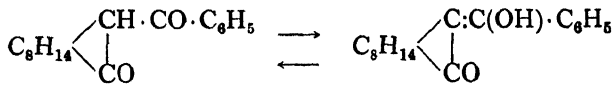
When either isomeride is dissolved in hot anhydrous alcohol and the solution is *rapidly* cooled, the deposit is a mixture of both, but when the solution of the enol in aqueous alcohol evaporates *slowly* at ordinary temperatures, the pure keto-form is deposited. In the latter case the solution becomes saturated with the keto-isomeride, and, as this form then separates in crystals, the equilibrium is disturbed and more keto-isomeride is produced, until finally the change is complete.

Diethyl diacetylsuccinate, $EtOOC \cdot CHAc \cdot CHAc \cdot COOEt$, prepared from ethyl sodioacetoacetate (p. 824), may be a *dl*- or a *meso*-compound in its diketonic form, because the molecule contains two asymmetric carbon-groups of identical structure, but these two forms, which melt at 30° and 90°, are in equilibrium in solution owing to keto-enol change. The mono-enolic form, which owing to chelation (p. 833) would not be expected to exhibit *cis-trans*-isomerism, is a *dl*-compound and the di-enolic form (m.p. 45°) is probably doubly chelated. Two mono-enolic forms have been described; one is a liquid, the purity of which is doubtful, and the other melts at 20°.

Diethyl dibenzoylsuccinate, $EtOOC \cdot [CH(COPh)]_2 \cdot COOEt$, obtained from ethyl sodiobenzoylacetate (p. 827), also exists in

desmotropic ketonic and enolic forms, and the two types show considerable differences in their absorption spectra.

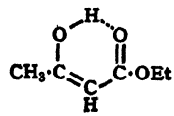
Benzoylcamphor has also been obtained in two crystalline desmotropic forms, which may be represented as below, but the enol is probably chelated (below):



Owing to the readiness with which tautomeric change usually occurs in the presence of traces of alkalis or acids, attempts to determine the proportion of the tautomerides in any given allelotropic mixture by colorimetric methods with ferric chloride, by titrating the enol with bromine, or by precipitating it with cupric acetate (p. 200), give only approximate results, which, however, may sometimes be supplemented by a study of the physical properties of the mixture (density, molecular refraction, etc.).

It has thus been found that the proportion, keto : enol, in the case of a given allelotropic mixture, usually varies considerably with the temperature; but in the case of ethyl acetoacetate, the equilibrium is practically unaltered by changes of temperature, even up to the boiling-point of the ester. When in solution, the nature of the solvent and the concentration of the solution also influence the proportion of the isomerides; in general, the percentage of enol is low in water, formic acid, and acetic acid, [illegible] in the order given, and is greatest in non-dissociating solvents such as benzene and hexane. It has already been seen that the boiling-point of the enol is lower than that of the keto-form (p. 205).

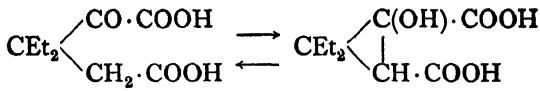
These facts, which at first sight appear to be anomalous, are accounted for by the assumption that the enol is not a hydroxy-compound, but resembles rather an ether, owing to the occurrence of chelation (p. 489):



chelation would also explain the stabilities of the enolic forms of 1:3-diketones, which can give a practically strainless six-atom ring containing two double bonds.

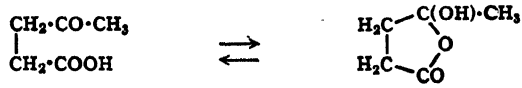
Keto-enolic tautomeric change of a modified type may take place

even when the —CO— and —CH_2— groups are separated from one another by one or more carbon atoms ; the two acids,

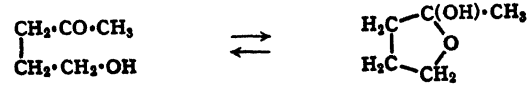


for example, are converted one into the other by concentrated alkali and the same equilibrium mixture is obtained from either compound ; as the hydroxy-form is not an unsaturated alcohol (enol), this change is known as *keto-cyclol* tautomerism.

Keto-lactol tautomerism, in which a hydrogen atom passes from a carboxyl to a carbonyl group, with the formation of a lactone, also involves ring closure ; laevulic acid, for example, behaves like a ketone in most of its reactions, but gives an acetyl derivative of the hydroxy- or lactol form,

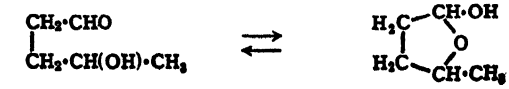


Keto-cyclo-tautomerism, in which a hydrogen atom passes from a hydroxyl group to a carbonyl oxygen atom, with the formation of a closed chain, is of particular interest (Helferich and Malkomes, *Ber.* 1922, 702). *γ-Acetylpropyl alcohol*, (I), for example, prepared by the ketonic hydrolysis of *ethyl β-bromoethylacetoacetate*, $CH_3 \cdot CO \cdot CH(COOEt) \cdot CH_2 \cdot CH_2Br$, gives an oxime, but in other reactions it behaves as if it had the structure of the tetrahydrofuran derivative, (II),

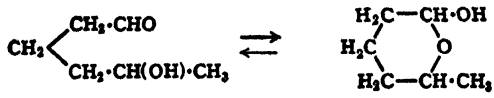


I II

Similarly *γ-hydroxy*-n-*valeraldehyde*, (III), is tautomeric with *methylhydroxytetrahydrofuran*, (IV), and δ-*hydroxycaproaldehyde*, (V), with *methylhydroxytetrahydropyran*, (VI) :



III IV



V VI

Both these substances, (III) and (V), give the reactions of aldehydes, but do so only slowly, and judging from their physical properties (molecular refraction), their allelotropic mixtures consist almost entirely of the closed chain structures, (IV) and (VI); both of them, like a sugar, can be methylated with methyl alcohol and hydrogen chloride, a reaction which does not occur in the case of a simple alcohol.

Keto-cyclo-tautomeric changes, strictly analogous to the above, are observed in the molecules of the polyhydric ketones and aldehydes, that is to say, in the sugars; the ketonic or aldehydic form apparently exists in solution in equilibrium with the furanose or pyranose structure (pp. 874, 873). In all such cases, two (α- and β-) diastereoisomeric forms of the closed chain molecule are possible, so that the solution contains an equilibrium mixture of three compounds, of which the ketonic or aldehydic form is probably present in small proportions only.

It was at one time believed that the mutarotation of certain sugars was due to the conversion of the α- into the β-form, or *vice versa*, by the addition to, and subsequent elimination of a molecule of water from, the carbonyl group, but the study of the keto-cyclo-tautomerism of simple ketones and aldehydes seems to show that such an assumption is unnecessary; the two epimeric sugars may be regarded as keto-cyclo-tautomeric forms of the hydroxy-aldehyde or ketone, and it has been found that the conversion of one into the other may occur in the absence of water.

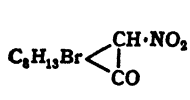
Desmotropes of simple mono-ketones are rare, or unknown, and their molecules seem to exist almost entirely in the ketonic form; nevertheless, such compounds may show tautomerism and give derivatives of both isomerides. Acetone, for example, forms a sodium derivative and behaves towards bromine like an enol; *cyclo*-hexanone gives an acetyl derivative of the enolic form with acetic anhydride, and methylindanone (p. 749) is doubtless partly converted into the enol by alkali; in all these cases the liquid substance is probably an allelotropic mixture, consisting almost entirely of the carbonyl form.

On the other hand, phenols, naphthols, etc., exist as enols owing to the stability of the benzene ring; if they passed into ketonic modifications, unstable dihydro-aromatic rings would be produced. Phloroglucinol, a tri-enol, however, can form a non-olefinic triketo-*cyclo*hexane and derivatives of both forms are known (p. 493); in the solid state phloroglucinol is probably an enol.

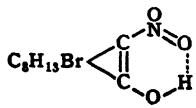
The Tautomerism of Nitro-compounds

The tautomerism of primary and secondary nitroparaffins has already been mentioned (p. 194). In the case of phenylnitromethane, the isolation of the normal, $Ph \cdot CH_2 \cdot NO_2$, and aci-forms, $Ph \cdot CH{:}NO \cdot OH$, has been described (p. 437); the former is an oil and gives no colour with ferric chloride, whereas the latter melts at 84°, gives a red colour with ferric chloride and is an electrolyte.

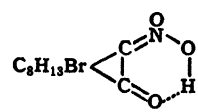
π-Bromo-α-nitrocamphor has also been obtained in two forms. The one melts at 142° and has $[\alpha]_D + 188°$, the other melts at 108° and has $[\alpha]_D - 51°$; both compounds show mutarotation and the equilibrium mixture from either has $[\alpha]_D - 39°$ (all the specific rotations refer to a benzene solution). When either of the desmotropes is dissolved in chloroform and the solution is evaporated at ordinary temperatures, the deposit finally contains both forms, an unusual phenomenon, due to the slowness with which the one is converted into the other in the absence of any added catalyst (p. 833); in alcoholic solution in the presence of ferric chloride, however, the change is very rapid, and both forms give an immediate colouration. These observations may be accounted for by assuming that the structure, (I), is tautomeric with a chelated form, (II), or (III):



I



II



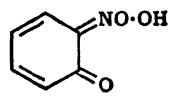
III

α-Nitrocamphor also shows mutarotation in the presence of traces of catalysts, but is known in only one form.

It was at one time considered that optically active β-nitrobutane, $Et \cdot CHMe \cdot NO_2$, and β-nitro-octane, $C_6H_{13} \cdot CHMe \cdot NO_2$, yielded optically active sodium salts; if this were so the salts could not

have the structure [RR'C:NO·O]Na because the anion would not then show optical activity. As it now seems probable that these salts are not in fact optically active, the structures given above still serve to explain all the facts.

According to Hantzsch, tautomerism is also observed in the case of *o*- and *p*-nitrophenols. *o*-Nitrophenol, which has a light yellow colour, and *p*-nitrophenol, which is colourless, give highly coloured salts; from the alkali metal salts, with alkyl halides, colourless alkyl derivatives, $NO_2 \cdot C_6H_4 \cdot OR$, are produced, but in certain cases from the silver salts and alkyl halides, intensely coloured unstable alkyl compounds are formed. The latter are believed to be esters of quinonoid acids, (IV), which are formed from the nitrophenols by a complex tautomeric change, but their nature is still unsettled. The chelation of *o*-nitrophenols has already been mentioned (p. 489).



IV

p-*Nitrosophenol*, prepared from phenol and nitrous acid, or from *p*-nitrosodimethylaniline (p. 451), would seem to be represented by $NO \cdot C_6H_4 \cdot OH$, but as the same compound is formed by the action of hydroxylamine on quinone, it might be *quinone monoxime*, $HO \cdot N{:}C_6H_4{:}O$. It crystallises from ether in green plates, but can also be obtained in colourless crystals from aqueous solution; both forms give the same green solution in these solvents, and as the compound gives the reactions of both the above structures, it is regarded as tautomeric. From a comparison of the absorption spectra of *p*-nitrosophenol with that of *p*-nitrosoanisole, $NO \cdot C_6H_4 \cdot OMe$ and the *O*-methyl ether of quinone monoxime, $MeO \cdot N{:}C_6H_4{:}O$, it has been inferred that *p*-nitrosophenol exists as quinone monoxime.

Tautomerism similar to that just described is shown by other nitrosophenols, as for example α-nitroso-β-naphthol, but here presumably chelation is also possible.

Other examples of isomeric change in which atoms or groups pass from the 1- to the 4-position in the benzene nucleus are given later (p. 844).

Lactam-lactim Tautomerism

The phenomenon of *lactam-lactim* tautomerism, expressed by —CO·NH—⇄—C(OH):N—, is observed in many ring compounds (pp. 580, 634, 1052, 1058), and indeed the first recorded case of tautomerism was that of isatin (Baeyer). As a rule such substances seem to have the lactam structure in the solid state, but usually give alkyl derivatives of both the forms ; the *O*-alkyl derivatives are hydrolysed by acids, but the *N*-alkyl compounds are not, so they are easily distinguished. Even simple amides, such as acetamide, give sodium salts and from urea, *methylisourea*, $NH_2 \cdot C(OMe):NH$, may be obtained by the action of dimethyl sulphate.

Imino-ethers, R·C(OR′):NH, are derived from the aci-forms of amides ; they may sometimes be obtained by treating the silver derivative of an amide with an alkyl halide, but more conveniently, by the interaction of a cyanide and an alcohol in the presence of hydrogen chloride,

$$R \cdot CN + R' \cdot OH = R \cdot C(OR'):NH.$$

Amidines, R·C(NHR′):NH, are also derived from aci-amides, and may be obtained by the action of ammonia, or of an amine, on an imino-ether, or by heating an amide with an amine and phosphorus pentachloride ; in the latter reaction the amide is converted into the dichloro-derivative, $R \cdot CCl_2 \cdot NH_2$, and then, by the loss of hydrogen chloride, into the *imino-chloride*, R·CCl:NH, which with the amine gives R·C(NHR′):NH.

The anions of the alkali metal salts of imides, —CO·NH·CO—, such as succinimide and phthalimide, probably exist in mesomeric forms,

$$—CO \cdot \bar{N} \cdot CO— \quad \text{or} \quad —C\bar{O}:N \cdot CO— \quad \text{or} \quad —CO \cdot N:C\bar{O}—,$$

which with alkyl halides give *N*-alkyl derivatives. Similarly sulphonamides, $R \cdot SO_2 \cdot NHR'$, and disulphones, $R \cdot SO_2 \cdot CH_2 \cdot SO_2 \cdot R'$, both of which are soluble in alkali, probably give mesomeric anions.

Three-carbon-atom Tautomerism

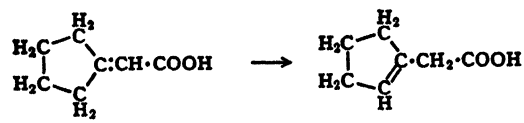
It was found by Fittig that various $\beta\gamma$-unsaturated acids, $R \cdot CH:CH \cdot CH_2 \cdot COOH$, which are stable under most conditions,

are converted into the $\alpha\beta$-isomerides when their solutions in aqueous alkali are heated; during his study of the reduction products of the phthalic acids, Baeyer observed several cases of a similar kind, in which a $\beta\gamma$- is transformed into an $\alpha\beta$-isomeride, sometimes even by boiling water (p. 802). The resulting $\alpha\beta$-unsaturated acid, like the $\beta\gamma$-compound, is usually stable, both in the solid and in the dissolved state, except that it may be partially reconverted into the $\beta\gamma$-compound by boiling aqueous alkalis, and equilibrium between the two forms is then established; the reaction, therefore, is a reversible one, and is an example of *three-carbon-atom tautomerism*,

$$—CH{:}CH\cdot CH_2— \rightleftarrows —CH_2\cdot CH{:}CH—$$

In the case of such unsaturated acids, however, the alkaline solution does not contain a simple allelotropic mixture; the salts of the two acids are in equilibrium with that of the β-hydroxy-acid, which is formed by the addition of the elements of water to the $\alpha\beta$-unsaturated compound.

Some aromatic $\beta\gamma$-olefinic acids, such as *β-benzylidenepropionic acid*, $C_6H_5\cdot CH{:}CH\cdot CH_2\cdot COOH$, change into the $\alpha\beta$-isomeride only very partially, and the latter, *γ-phenylcrotonic acid*, is almost completely converted into the $\beta\gamma$-acid when it is merely warmed with pyridine. Certain $\alpha\beta$-olefinic acids, derived from *cyclo*-paraffins, are also practically completely converted into the $\beta\gamma$-*cyclo*-olefinic isomerides by alkalis (Kon and Linstead, *J.* 1925, 616, 815), as in the example given below,



Particularly facile tautomerism of this type is shown by glutaconic acid derivatives, $HOOC\cdot CR{:}CH_2\cdot CHR'\cdot COOH$.

Three-carbon-atom isomeric change is also shown by various allyl derivatives of benzene, in which the group $—CH_2\cdot CH{:}CH_2$ passes into $—CH{:}CH\cdot CH_3$, when the compound is treated with alcoholic potash at high temperatures; *eugenol*, for example, is converted into iso*eugenol* and *safrole* into iso*safrole*, in this way (p. 951). These changes, however, seem to be non-reversible.

The Tautomerism of Diazoamino-compounds

The group, —N:N·NH—, of diazoamino-compounds, undergoes tautomeric change, which may be compared with that of the three-carbon-atom system. When phenyldiazonium chloride is treated with *p*-toluidine the same compound is obtained as when *p*-tolyldiazonium chloride is treated with aniline :

$$C_6H_5\cdot N_2Cl + NH_2\cdot C_6H_4\cdot CH_3 = C_6H_5\cdot N{:}N\cdot NH\cdot C_6H_4\cdot CH_3 \quad \text{I}$$
$$C_6H_5\cdot NH_2 + ClN_2\cdot C_6H_4\cdot CH_3 = C_6H_5\cdot NH\cdot N{:}N\cdot C_6H_4\cdot CH_3 \quad \text{II}$$

As two different products, having respectively the structures shown above, might be expected if the reaction is merely an elimination of a molecule of hydrogen chloride, it must be inferred that one of the forms passes into the other by an isomeric change. On hydrolysis with acids, this product yields aniline, *p*-toluidine, phenol, and *p*-cresol, and on reduction it gives aniline, *p*-toluidine, phenylhydrazine and *p*-tolylhydrazine ; it thus behaves as if it were a mixture of (I) and (II), which, therefore, are tautomeric. Tautomerism of this kind, in which both tautomerides are of the same type, is sometimes known as *virtual tautomerism.*

The group, R—N:CH·NH—R′, also undergoes tautomeric change into R—NH·CH:N—R′ (p. 1051).

Anionotropic Changes

In all the above cases it is a hydrogen atom (or proton) which migrates and the changes may be termed *prototropic* ; many examples are known, however, in which a negative group migrates and such reactions are known as *anionotropic.* Thus the *p*-nitrobenzoate of phenylvinyl carbinol, $Ph\cdot CH(OH)\cdot CH{:}CH_2$, in boiling acetic acid solution gives the corresponding ester of γ-phenylallyl alcohol, $Ph\cdot CH{:}CH\cdot CH_2\cdot OH$, whereas under other conditions an equilibrium mixture of the two esters is produced. Similar changes often occur during reactions of allyl compounds as in the following examples,

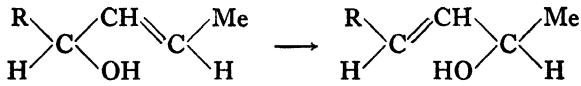
$$CH_3\cdot CH{:}CH\cdot CH_2OH \xrightarrow{HBr} CH_3\cdot CH{:}CH\cdot CH_2Br + CH_3\cdot CHBr\cdot CH{:}CH_2,$$

$$Me\cdot CH{:}CH\cdot CHR'\cdot O\cdot CO\cdot R \xrightarrow{NaOH} Me\cdot CH{:}CH\cdot CHR'\cdot OH + Me\cdot CH(OH)\cdot CH{:}CHR',$$

and another case has already been mentioned (p. 816).

The conversions of linalool into geraniol (p. 942) and of nerolidol into farnesol (p. 947) are also of this type.

A very interesting example described by Kenyon and his co-workers is that shown below, and in many cases, if the original alcohol is optically active, activity is also shown by the product although it is due to a different asymmetric group.



Reversible and Irreversible Isomeric Change

In the preceding examples some of the substances which show tautomerism give allelotropic mixtures with great rapidity at ordinary temperatures in the presence of catalysts, and the mixtures may contain considerable proportions of both forms. In other cases the change is brought about only slowly even by concentrated reagents, the one form may be present in the equilibrium mixture in very small proportions, and the only evidence of its presence is that some of its derivatives can be isolated ; the unknown, unstable, or *labile* isomeride is then called the *pseudo-form* (p. 437). There are also many cases in which a compound can be transformed into an isomeride with the aid of heat, or reagents, or both, but this isomeride cannot be reconverted into the original compound under the same, or other, conditions ; the isomeric change is *complete* and *irreversible*. When, for example, a ketoxime undergoes the Beckmann transformation, and is converted into a substituted amide, the latter cannot be reconverted into the oxime. Similarly, when hydrazobenzene is transformed into benzidine, the latter is not reconverted into the parent substance, when it is heated with strong acids or treated in other ways.

All grades of behaviour between clearly defined examples of dynamic equilibrium on the one hand, and completed irreversible isomeric changes on the other, are known, and in many cases it is difficult to decide under which heading the change should be classed. Ammonium cyanate is stable in the dry state, but when it is dissolved in water or gently heated, it is almost completely transformed into urea ; the latter is also stable in the dry state and *seems* to crystallise from water unchanged, but in fact, at 100°, in aqueous solution,

4–5% of the urea is converted into ammonium cyanate. The apparently irreversible completed change,

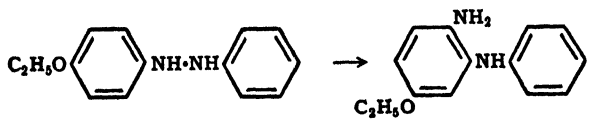
$$NH_4 \cdot O \cdot CN \longrightarrow NH_2 \cdot CO \cdot NH_2,$$

is in fact reversible and incomplete.

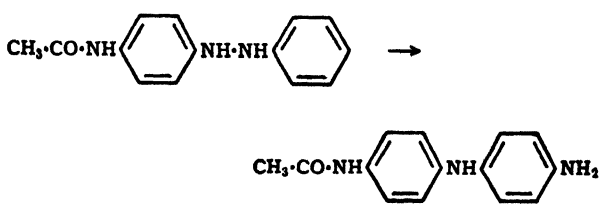
It is also difficult to decide in many cases whether the transformation is merely a rearrangement of the atoms of *a* molecule (*intra*molecular), or whether it is the final result of several intermediate stages in which two or more different molecules take part (*inter*molecular).

Some further important types of isomeric change and the methods by which these problems are investigated may now be considered; many of them are associated with the names of those by whom they were first described or investigated.

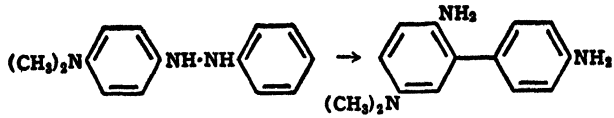
The **benzidine transformation** occurs in the case of various hydrazo-compounds in which both *p*-positions are free (p. 464 and footnote, p. 678); if, however, *one* of these is occupied, the change proceeds in one of three ways: (1) The group in the *p*-position is displaced and the normal change occurs, as in the case of 4-*carboxyhydrazobenzene*, $C_6H_5 \cdot NH \cdot NH \cdot C_6H_4 \cdot COOH$, which yields benzidine. (2) An ortho-*semidine*,



or (3) a para-*semidine* transformation occurs,



In some cases, however, both *ortho*- and *para*-semidine changes take place together, and in others a 2:4′-diamino-derivative of a substituted diphenyl may be formed:



If *both* *p*-positions are occupied, either the *ortho*-semidine change takes place or fission occurs, so that when a pp'-*azo*-derivative is reduced with tin and concentrated hydrochloric acid, the hydrazo-compound which is first formed does not undergo any of the above changes, but is converted into a mixture of two amines,

$$CH_3 \cdot C_6H_4 \cdot N{:}N \cdot C_6H_4 \cdot O \cdot Bz + 4H = CH_3 \cdot C_6H_4 \cdot NH_2 + H_2N \cdot C_6H_4 \cdot O \cdot Bz.$$

That the benzidine transformation is *intra-* and not *inter*-molecular has been shown by Ingold and Kidd (*J.* 1933, 984), who found that 2:2'-*dimethoxy-* and 2:2'-*diethoxy-hydrazobenzene* underwent the change when mixed together but not a trace of an unsymmetrical benzidine could be detected in the product.

The benzidine change has also been carried out with many unsymmetrical hydrazo-compounds, $XC_6H_4 \cdot NH \cdot NH \cdot C_6H_4Y$, in which X and Y are not *p*- to the nitrogen atoms, but no symmetrical benzidine,

$$NH_2 \cdot C_6H_3X \cdot C_6H_3X \cdot NH_2 \text{ or } NH_2 \cdot C_6H_3Y \cdot C_6H_3Y \cdot NH_2,$$

has been isolated from such reactions.

In the structure of hydrazo-compounds as usually written the distance between the two *p*-positions at which union occurs appears to be very large, but in fact the molecule is not linear and it is probable that during the change the two nuclei are in parallel planes. In this event the intramolecular nature of the change can be readily understood and the *o*-semidine and *p*-semidine transformations would require only a rotation of the nuclei relative to one another.

The **diazoamino-aminoazo** transformation (p. 462) is intermolecular and takes place in two stages ; the evidence for this seems conclusive. Firstly, if the change is carried out in the presence of an amino-compound different from that to which the ArN_2-group is attached, a mixture of two aminoazo-derivatives is often formed ; this is easily accounted for by the suggested mechanism,

$$Ph \cdot N_2 \cdot NH \cdot Ph + HCl = Ph \cdot N_2Cl + PhNH_2,$$
$$Ph \cdot N_2Cl + C_6H_4X \cdot NH_2 = Ph \cdot N_2 \cdot C_6H_3X \cdot NH_2 + HCl.$$

Secondly, the formation of phenyldiazonium chloride during such a reaction has been proved by Kidd, who, by the addition of a solution of diazoaminobenzene in hydrochloric acid to an alkaline solution of β-naphthol, obtained a high yield of benzeneazo-β-naphthol.

Lastly, it has been shown that phenyldiazonium chloride and aniline condense to give diazoaminobenzene, aminoazobenzene or mixtures of the two compounds under different conditions of acidity of the solution..

The **Hofmann-Martius** conversion of methylaniline into *o*- and *p*-toluidine (p. 450), and of methylpyridinium iodide into α- and γ-methylpyridines (p. 570), may also occur in two stages and Hickinbottom has suggested that an alkyl radical separates as a positive ion, which may then react with the base to give a nuclear substituted amine or be converted into an olefine :

$$[C_6H_5\cdot NH_2\cdot C_nH_{2n+1}]^+ \longrightarrow \begin{matrix} C_6H_5\cdot NH_2 \\ + \\ C_nH_{2n+1}^+ \end{matrix} \longrightarrow \begin{matrix} [C_nH_{2n+1}\cdot C_6H_4\cdot NH_3]^+ \\ \text{or} \\ [C_6H_5\cdot NH_3]^+ + C_nH_{2n} \end{matrix}$$

In the comparable isomeric change of *N*-alkylpyrroles into *C*-alkyl derivatives (pp. 588, 600), by passing the former through a strongly heated tube, it would seem, however, that the irreversible isomeric change involves a simple transposition of an alkyl group and a hydrogen atom.

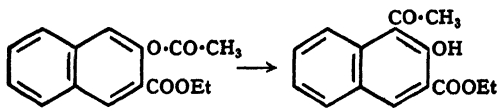
The formation of *p*-chloroacetanilide from the chloroamide, $C_6H_5\cdot NCl\cdot CO\cdot CH_3$ (p. 1016), of anilinesulphonic acid (sulphanilic acid) from sulphamic acid $C_6H_5\cdot NH\cdot SO_3H$ (p. 1015), and of *p*-aminophenol by treating phenylhydroxylamine (p. 465) with sulphuric acid, *seem* to be simple transpositions, but in the first case, at least in aqueous solution, this is not so ; the chloroamide undergoes isomeric change owing to the intermediate formation of chlorine (Orton and Bradfield, *J.* 1927, 986) which then reacts with the acetanilide :

$$C_6H_5\cdot NCl\cdot CO\cdot CH_3+HCl = C_6H_5\cdot NH\cdot CO\cdot CH_3+Cl_2,$$
$$C_6H_5\cdot NH\cdot CO\cdot CH_3+Cl_2 = C_6H_4Cl\cdot NH\cdot CO\cdot CH_3+HCl.$$

This view is confirmed by the fact that chloroamides in the presence of hydrochloric acid, chlorinate amines, phenols, etc.

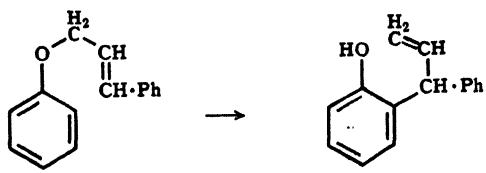
The conversion of phenylmethylnitrosoamine, $C_6H_5 \cdot NMe \cdot NO$, into *p*-nitrosomethylaniline by alcoholic hydrogen chloride, is also probably due to reactions between different molecules.

Many cases are known in which isomeric change occurs owing to the migration of an acetyl, benzoyl, or other acyl radical (**Fries reaction**); in some of these there is direct evidence that the change takes place in stages between different molecules, whereas in others the mechanism is doubtful. *Ethyl 2-acetoxy-3-naphthalenecarboxylate*, for example, treated with aluminium chloride in nitrobenzene solution, is transformed (after the addition of water) into *ethyl 1-acetyl-2-hydroxynaphthalene-3-carboxylate*,



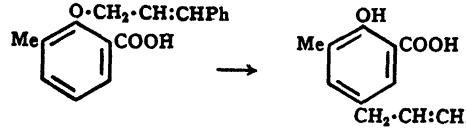
Apparently this is the result of a simple migration of the acetyl group; but since acetyl-α-naphthol, $C_{10}H_7 \cdot OAc$, under similar conditions, gives not only *1-hydroxy-2-acetylnaphthalene*, by 'isomeric change,' but also *1-hydroxy-2:4-diacetylnaphthalene*, it must be concluded that the acetyl group is eliminated as acetyl chloride, which then reacts with the aromatic nucleus of the same or of a different molecule, giving 2- and 2:4-diacetyl derivatives.

When phenylallyl ether is heated at about 200°, *o*-allylphenol is formed (**Claisen**) and in similar cases the product is always the *o*-compound. That this transformation is intramolecular is shown by the fact that when a mixture of phenylcinnamyl ether and β-naphthylallyl ether is heated, the two compounds undergo isomeric change independently of one another. The product from phenylcinnamyl ether is *o*-α-phenylallylphenol,



in which the carbon atom originally combined with oxygen is not attached to the nucleus in the product. In cases where both *o*-positions are occupied the hydrocarbon group migrates to the

p-position, but the carbon atom of this group, which was combined with oxygen, now becomes directly united to the nucleus,



If both *o*- and *p*-positions are occupied decomposition into a phenol and a mixture of unsaturated hydrocarbons occurs.

When the benzoyl derivative of *o*-nitrophenol is reduced with tin and hydrochloric acid, it gives o-*benzoylaminophenol*,

$$NO_2 \cdot C_6H_4 \cdot O \cdot CO \cdot C_6H_5 \longrightarrow C_6H_5 \cdot CO \cdot NH \cdot C_6H_4 \cdot OH ;$$

but although apparently the benzoyl radical in the initial reduction product, $NH_2 \cdot C_6H_4 \cdot O \cdot CO \cdot C_6H_5$, passes directly from oxygen to nitrogen, it is more probable that, after reduction, ring-closure occurs, and subsequently ring-fission, by hydrolysis.

On the other hand the conversion of *triphenylacetaldehyde* into *phenyldesoxybenzoin* (*diphenylacetophenone*),

$$(C_6H_5)_3C \cdot CHO \longrightarrow (C_6H_5)_2CH \cdot CO \cdot C_6H_5,$$

which is brought about by acids, appears to be the result of a simple transposition of a hydrogen atom and a phenyl radical.

In certain aliphatic compounds the displacement of an amino- by a hydroxyl group, with the aid of nitrous acid, is often accompanied by an apparent isomeric change ; propylamine, for example, gives both propyl and *iso*propyl alcohols, and in Demjanov's reaction (p. 784) changes in ring-structure take place.

The **Beckmann transformation** is intramolecular, as is shown by the formation of optically active acetyl-γ-heptylamine from active methyl-γ-heptyl ketoxime (Kenyon and Young, *J.* 1941, 264),

$$C_4H_9 \cdot CH(Et) \cdot \underset{\underset{NOH}{\|}}{C} \cdot Me \longrightarrow \overset{\overset{NH \cdot CH(Et) \cdot C_4H_9}{|}}{OC} \cdot Me$$

since it is clear that the heptyl group is never free during the change, otherwise racemisation would have occurred.

The **Hofmann** and **Curtius** reactions, summarised in the following equations, have already been briefly mentioned,

$$R\cdot CO\cdot NH_2+Br_2+4KOH = R\cdot NH_2+K_2CO_3+2KBr+2H_2O,$$
$$R\cdot COOH+N_3H = R\cdot NH_2+CO_2+N_2.$$

Another change of a similar type, known as the **Lossen** rearrangement, occurs when hydroxamic acids or their salts or esters are heated, or treated with reagents such as thionyl chloride,

$$R\cdot CO\cdot NH\cdot OH \longrightarrow R\cdot NCO+H_2O \longrightarrow R\cdot NH_2+CO_2.$$

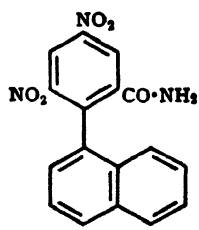
In all these reactions a radical migrates from carbon to nitrogen at some stage and an *iso*cyanate is produced,

$$R\cdot CO\cdot NHBr \longrightarrow R\cdot NCO+HBr,$$
$$R\cdot CON_3 \longrightarrow R\cdot NCO+N_2.$$

Wallis and his co-workers (*J. Am. Chem. Soc.* 1926, 169; 1931, 2787; 1933, 1701) found that if the reactions are performed on an amide, azide and hydroxamic acid in which the α-carbon-group is asymmetric, optical activity is retained and the rotation of the amine so produced is the same in all three cases,

$$\begin{matrix}C_6H_5\cdot CH_2\\CH_3\end{matrix}\!\!>\!CH\cdot CO\cdot X \longrightarrow \begin{matrix}C_6H_5\cdot CH_2\\CH_3\end{matrix}\!\!>\!CH\cdot NH_2.$$

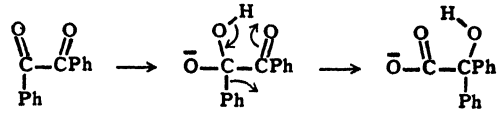
Furthermore when the amide of optically active 2-α-naphthyl-3:5-dinitrobenzoic acid, in which the activity is due to restricted rotation (for which the presence of groups in the phenyl radical in both positions *ortho* to the union with the naphthyl radical is essential), is submitted to the Hofmann reaction, an active amine is formed without any racemisation,



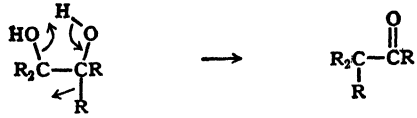
These facts prove that at no time is the migrating radical detached from the molecule and the change therefore is entirely intramolecular.

The **benzil-benzilic acid** transformation occurs when benzil,

heated with concentrated aqueous alkali, is converted into a salt of benzilic acid, and is undergone by certain other 1:2-diketones. The ketone combines with a hydroxyl ion, and the product then undergoes isomeric change :



The **pinacol-pinacolone** transformation (p. 155) is an important general reaction in which isomeric change takes place, together with the elimination of the elements of water. The mechanism may be represented as similar to that of the benzil-benzilic acid change :



Bartlett and his co-workers have found that the *cis*-form of 1:2-dimethyl*cyclo*pentan-1:2-diol gives an 87% yield of 2:2-dimethyl-*cyclo*pentanone with dilute sulphuric acid, whereas the *trans*-isomeride gives tars only ; in other words, the change can only occur when the methyl group can expel a hydroxyl radical from the *trans*-position.

Glycols, $CR_2(OH)\cdot CHR\cdot OH$, like pinacols, $CR_2(OH)\cdot CR_2\cdot OH$, also undergo interesting changes, some of which resemble the pinacol-pinacolone transformation, but proceed in various ways according to the nature of the glycol, and the experimental conditions. These changes are :

I $CRPh(OH)\cdot CHPh\cdot OH \longrightarrow CRPh_2\cdot CHO+H_2O$,
II $CRPh(OH)\cdot CHPh\cdot OH \longrightarrow CHRPh\cdot CO\cdot Ph+H_2O$,
III $CRPh(OH)\cdot CHPh\cdot OH \longrightarrow R\cdot CO\cdot CHPh_2+H_2O$.

In (I) and in (III) the results may be brought about by a pinacol-pinacolone change of the usual kind, but in (II) there is no transference of a phenyl group, and the formation of the ketone may be due to the direct elimination of the elements of water, followed by an enol-keto-change.

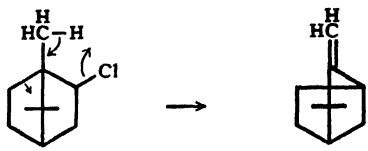
Some very interesting results with related compounds have been obtained by McKenzie and his co-workers (*J.* 1923, 79 ; 1924, 844),

who have shown that when the amino-alcohol, (IV), is treated with nitrous acid, it does not give the glycol, $CPh_2(OH)\cdot CHPh\cdot OH$, as might have been expected, but is converted into the ketone, (V). Similarly, when the amino-alcohol, (VI), is treated with nitrous acid, it gives the ketone, (VII), and the optically active amino-alcohol, (VIII), is transformed into the *optically active* ketone, (IX):

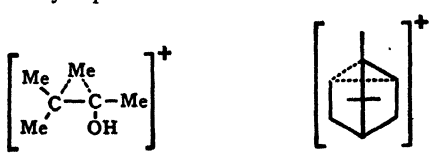
IV	$Ph_2C(OH)\cdot CHPh\cdot NH_2$	⟶	$PhCO\cdot CHPh_2$	V
VI	$PhCMe(OH)\cdot CHPh\cdot NH_2$	⟶	$MeCO\cdot CHPh_2$	VII
VIII	$Ph_2C(OH)\cdot CHMe\cdot NH_2$	⟶	$PhCO\cdot CHMePh$	IX

All these results may be accounted for by assuming that the amino-group is displaced by hydroxyl in a normal manner, and that the glycol then undergoes change by a mechanism corresponding with that suggested for the ordinary pinacol-pinacolone transformation, and the reactions (I) and (III) shown on p. 848. When, however, the glycol, $PhCMe(OH)\cdot CHPh\cdot OH$, corresponding with the amino-alcohol, (VI), is actually prepared (by another method) and submitted to dehydration, it does *not* give the ketone, (VII), as might have been expected, but is converted into an isomeric ketone, (IX).

The **Wagner-Meerwein** rearrangement (p. 933) is of the same type as the pinacol-pinacolone change and may be represented similarly,[1]



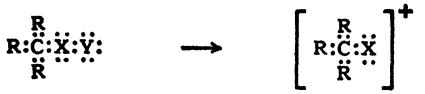
It is possible that an organic ion with a mesomeric structure is first formed, which, in the case of pinacol and camphene hydrochloride, may be respectively represented as below:



Whitmore (*J. Am. Chem. Soc.* 1932, 54, 3274) has put forward a general theory correlating many intramolecular rearrangements and

[1] These formulae are explained on p. 912.

other abnormal reactions. The first stage in all such changes is the rupture of a non-ionic link between a carbon or a nitrogen atom, X, and an electronegative atom or group, Y, which is split off with its complete shell of electrons, thus leaving the carbon (or nitrogen) atom deficient,

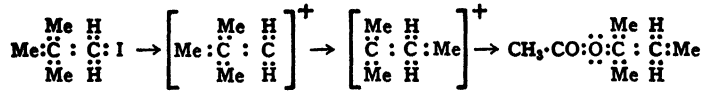


If a negative ion $:\ddot{Z}:^-$ is then taken up directly, obviously no rearrangement occurs, but if X has a greater attraction for electrons than C, then isomeric change occurs leaving C with the incomplete shell:



finally a negative ion is recombined from the reaction mixture or a proton is lost.

The production of $\alpha\alpha$-dimethylpropyl acetate from $\beta\beta$-dimethylpropyl iodide with sodium acetate is thus represented as follows:



The Hofmann reaction may be shown in a similar way:



From most of the examples given above it is obvious that there are many difficulties to be overcome in attempting to formulate the stages of what seem to be comparatively simple transformations. Isomeric change, reversible or irreversible, and in many cases preceded, or followed by other reactions, is, however, such a common phenomenon of organic chemistry, that it is met with in nearly all types of compounds; other interesting examples, not given in this chapter, will be found on pp. 715, 934, and 1024.

CHAPTER 52

THE CONFIGURATIONS, SYNTHESIS, AND GLYCOSIDIC STRUCTURES OF THE MONOSACCHARIDES [1]

The Configurations of the Monosaccharides

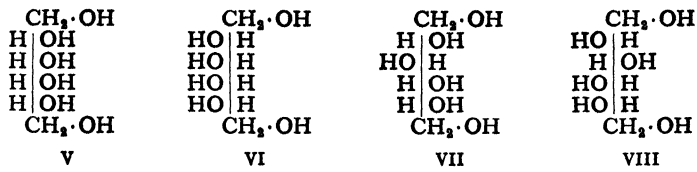
THE molecule of an aldohexose, like that of the *mono*carboxylic acid derived from it, contains four structurally different asymmetric carbon-groups, and theoretically, therefore (p. 307), there will be sixteen optically isomeric aldohexoses of the constitution $CH_2(OH)\cdot[CH(OH)]_4\cdot CHO$, and sixteen optically active monocarboxylic acids corresponding with them. These sixteen optically isomeric forms may be classed in eight pairs of enantiomorphously (antimerically) related compounds.

The molecules of a hexahydric alcohol (hexitol) of the constitution, $CH_2(OH)\cdot[CH(OH)]_4\cdot CH_2\cdot OH$, and those of the corresponding *di*carboxylic acids also contain four asymmetric groups, but in the case of these compounds only ten optical isomerides are theoretically possible. The reason for this is, that whereas all the four asymmetric carbon-groups in the molecule of an aldohexose or monocarboxylic acid are *structurally* different, in the molecule of a hexitol or of a dicarboxylic acid this is not so ; *two* optically isomeric aldohexoses *may* correspond with, and be converted into, *one* hexitol or *one* dicarboxylic acid only. This difference can be made clear with the aid of the usual projection formulae.[2] Thus, the configurations (I) and (II), and (III) and (IV), represent the *d*- and *l*-forms respectively of two hexoses, configurations (V)–(VIII) those of the corresponding hexitols :

I	II	III	IV
CHO	CHO	CHO	CHO
H | OH	HO | H	H | OH	HO | H
H | OH	HO | H	HO | H	H | OH
H | OH	HO | H	H | OH	HO | H
H | OH	HO | H	H | OH	HO | H
$CH_2\cdot OH$	$CH_2\cdot OH$	$CH_2\cdot OH$	$CH_2\cdot OH$

[1] This and the following chapter should be read as a continuation of Chapter 19, p. 310.

[2] Some of the C symbols are for clarity omitted in such projection formulae.



V VI VII VIII

An examination of these shows, however, that when the two ends of the chain in (I) and in (II) have been made the same (in the hexitols), configurations (V) and (VI), which result, are identical; for, after rotating either through 180° in the plane of the paper it can be superposed on the other, whereas this is not the case with (I) and (II), (III) and (IV), or (VII) and (VIII).

It should be clearly understood in using these projection formulae that whilst they may, for comparison, be rotated in the plane of the paper without changing their significance, rotation in other ways is inadmissible; thus by turning (III) through 180° about its long axis, it gives a configuration *apparently*, but not actually, identical with (IV); similarly for (I) and (II), or (VII) and (VIII). That these pairs are not, in fact, identical, will be understood when it is remembered that the molecule does not actually lie wholly in one plane; such a rotation will not, therefore, produce coincidence.

The configuration (V or VI) corresponds with that of *meso*-tartaric acid, and the molecule has a plane of symmetry which is lacking in (I) and (II).

The molecule of an aldopentose, such as *l*-arabinose, and that of the corresponding *mono*carboxylic acid, contain *three* structurally different asymmetric carbon-groups, and eight optical isomerides of both of these types are possible; in each case these eight isomerides constitute four pairs of enantiomorphously related compounds.

The molecule of a pentitol,

$$CH_2(OH)\cdot CH(OH)\cdot CH(OH)\cdot CH(OH)\cdot CH_2\cdot OH,$$

and that of an $\alpha\beta\gamma$-trihydroxyglutaric acid,

$$COOH\cdot CH(OH)\cdot CH(OH)\cdot CH(OH)\cdot COOH,$$

derived from an aldopentose, contain, however, two asymmetric carbon-groups only, because in these compounds the central carbon atom is combined with two structurally *identical* groups—namely, either [—$CH(OH)\cdot CH_2\cdot OH$] or [—$CH(OH)\cdot COOH$], and has

lost its asymmetry. When the two outer —CH(OH)— groups have the same configurations, *d*- and *d*-, or *l*- and *l*-, the compound is optically active, just as in the case of the tartaric acids; when, however, these two asymmetric groups have different configurations (one being *d*- and the other *l*-), although optical inactivity results, the presence of the central >CH(OH) group renders possible the existence of *two* stereoisomeric (inactive) forms. There are, therefore, only *four* stereoisomeric pentitols, of which two, (IX) and (X), are enantiomorphously related and optically active, and two, (XI) and (XII), are inactive *meso*-compounds, each possessing a plane of symmetry.[1] The four stereoisomeric $\alpha\beta\gamma$-trihydroxyglutaric acids correspond with the pentitols, only two of them being optically active.

IX	X	XI	XII	XIII	XIV
HO|H	H|OH	HO|H	HO|H	HO|H	H|OH
H|OH	HO|H	HO|H	H|OH	HO|H	H|OH
H|OH	HO|H	HO|H	HO|H	H|OH	HO|H

It should be noted that formulae (XIII) and (XIV), which might appear at first sight to represent two more pentitols, are identical with (IX) and (X) respectively, and can be superposed on the latter after their rotation in the plane of the paper.

Now it has been found possible to establish not only the structural relationships of the various aldoses and those of their immediate derivatives, but also to determine the manner in which these compounds are related in *configuration*, and to assign to each a definite configurational formula.

There are various ways in which this can be done, but whatever method is used, it is necessary to bear in mind certain facts which have been established experimentally; with these as a basis the configurations may then be deduced in a relatively simple manner.

The basic facts required for the method employed below are as follows:—(1) There are four stereoisomeric pentitols (IX, X, XI, XII, above); of these, two (*d*- and *l*-arabitol) are optically active, whereas the other two (xylitol and adonitol) are inactive.

(2) *l*-Arabinose combines with hydrogen cyanide, and the cyanohydrin thus obtained is converted on hydrolysis into optically isomeric, epimeric acids (p. 749), namely, *l*-gluconic acid and *l*-mannonic acid, formed respectively by the oxidation of *l*-glucose

[1] The carbon symbols and the —CH_2·OH (or —COOH) groups are conveniently omitted in these configurations.

and *l*-mannose. The formation of *two* optically isomeric acids in this way is explained as follows : By the combination of the aldehyde with hydrogen cyanide, a new asymmetric group is synthesised, and consequently *both* the theoretically possible forms of this new group may be produced, just as in the synthesis of lactic acid from acetaldehyde. There are, therefore, two optically isomeric products, both of which contain the three asymmetric groups of the original aldopentose, but which differ in configuration as regards the new asymmetric group. If, for example, the original aldopentose had the configuration (XV), the epimeric products would be (XVI) and (XVII) :

CHO	COOH	COOH
H | OH	H | OH	HO | H
HO | H	HO | H	H | OH
HO | H	HO | H	HO | H
$CH_2 \cdot OH$	$CH_2 \cdot OH$	$CH_2 \cdot OH$
XV	XVI	XVII

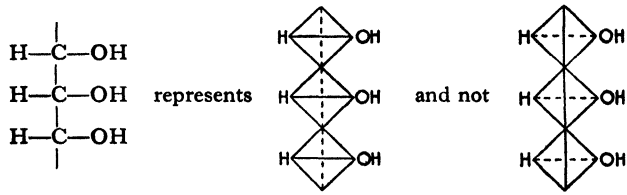
(3) Glucose and gulose are related to one another in the manner shown on p. 860. Both these aldohexoses give on oxidation one and the same optically active dicarboxylic acid (saccharic acid), and on reduction one and the same active hexitol (sorbitol). It is clear, therefore, that any configuration which would lead to the production of an optically inactive (*meso*)dicarboxylic acid or hexitol cannot represent either of these aldohexoses. With these facts in mind, the configurations of the more important members of the monosaccharides may now be considered.

Since the molecules of the two optically inactive pentitols (xylitol and adonitol) must have a plane of symmetry, they must be represented by configurations A and B, whereas *d*- and *l*-arabitol must be represented by C and D, which are antimeric.

HO | H	HO | H	H | OH	HO | H
HO | H	H | OH	HO | H	H | OH
HO | H	HO | H	HO | H	H | OH
A	B	C	D

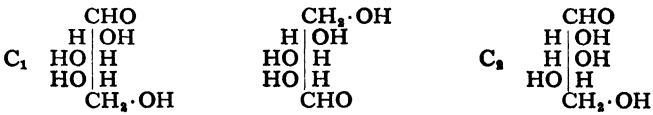
Now, let C represent *l*-arabitol, and D, *d*-arabitol ; this is, of course, an arbitrary choice (p. 859), but according to a convention all members of the *d*-series are represented as having the hydroxyl radical of the bottom H—Ċ—OH group on the right-hand side, and as derived from *d*-glyceraldehyde (p. 874) by extending the

molecule *upwards* from the CHO-group. In such projection formulae, moreover, the main carbon chain is considered to lie in the plane of the paper so that the hydrogen atoms and hydroxyl groups are above this plane, as indicated below. This becomes important when the ring structures of the sugars are considered (p. 872).



Each of the four pentitols gives rise to *two* aldopentoses, because when either the upper or the lower —$CH_2 \cdot OH$ group (not shown) is changed into —CHO, the configuration of the aldopentose which results will depend on which of the two —$CH_2 \cdot OH$ groups has been transformed.

The two aldopentoses derived from *l*-arabitol are therefore C_1 and C_2,[1] according as the upper or the lower —$CH_2 \cdot OH$ group is transformed into —CHO:



Since *l*-arabinose is formed by the oxidation of *l*-arabitol, and is converted into the latter on reduction, the configuration of *l*-arabinose must be expressed by C_1 or C_2.

l-Arabinose can be converted into a mixture of *l*-gluconic and *l*-mannonic acids, from which *l*-glucose and *l*-mannose respectively are obtained (p. 853); since *l*-arabinose has the configuration C_1 or C_2, the configurations of *l*-glucose and of *l*-mannose must be

[1] The central formula is given to show how C_2 is arrived at, namely, by changing the *lower* —$CH_2 \cdot OH$ group into —CHO, and then turning the configuration through 180° in the plane of the paper in order to bring the —CHO groups in C_1 and C_2 into corresponding positions for purposes of comparison.

among the following, all of which are obtained by changing the —CHO group in C_1 or C_2 into —CH(OH)·CHO :

I	II	III	IV
CHO	CHO	CHO	CHO
HO | H	H | OH	HO | H	H | OH
H | OH	H | OH	H | OH	H | OH
HO | H	HO | H	H | OH	H | OH
HO | H	HO | H	HO | H	HO | H
$CH_2 \cdot OH$	$CH_2 \cdot OH$	$CH_2 \cdot OH$	$CH_2 \cdot OH$
Derived from C_1		Derived from C_2	

Now, *l*-glucose on reduction gives *l*-sorbitol, and on oxidation, first *l*-gluconic acid and then *l*-saccharic acid. *l*-Mannose similarly gives *l*-mannitol, *l*-mannonic acid, and *l*-mannosaccharic acid. All these compounds are optically active, whereas an aldohexose having the configuration (III) would give an optically inactive (*meso*)hexitol and an optically inactive (*meso*)dicarboxylic acid, because when the terminal groups are made the same, the molecule has a plane of symmetry ; therefore the configuration (III) cannot represent either *l*-glucose or *l*-mannose, and since these two aldohexoses are derived from a single aldopentose (C_1 *or* C_2), the configuration (IV) is also excluded.

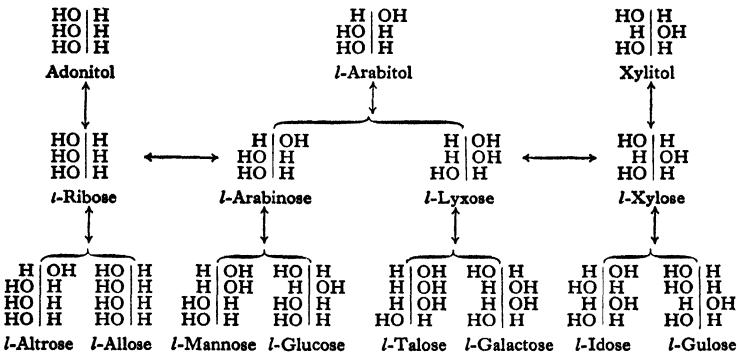
l-Glucose and *l*-mannose, therefore, are represented by the configurations derived from C_1 ; C_1, therefore, and *not* C_2 (p. 855), represents *l*-arabinose.

Now, the aldohexose, gulose, is formed from glucose by transposing the groups —$CH_2 \cdot OH$ and —CHO (p. 860). If *l*-glucose had the configuration (II), such a transposition could not result in the formation of a new aldohexose (gulose) ; an aldohexose identical with *l*-glucose would be formed, as can be seen by transposing the groups and then rotating the configuration in the plane of the paper. Hence l-*glucose* must have the configuration (I), and l-*mannose* the configuration (II).

The configuration of l-*fructose* is also established from its relation to *l*-glucose and *l*-mannose (p. 317), and because, on reduction, it gives a mixture of *l*-sorbitol and *l*-mannitol. The production of *two* optically isomeric hexitols in this reaction is due to the synthesis of *both* forms of a *new* asymmetric group, $>CH \cdot OH$, from the $>CO$ group ; these two epimerides, however, are not necessarily formed even in approximately equal proportions, since the molecule of the ketone is asymmetric (compare p. 747).

The configurations of *l*-glucose, *l*-mannose, and *l*-arabinose, and those of the corresponding hexitols and mono- and di-carboxylic acids, having been settled, those of the other aldohexoses and aldopentoses can be deduced, and are given in the table below. The C symbols and also those of the —CHO and —$CH_2 \cdot OH$ groups are omitted to save space, but it must be remembered that the —CHO group is *at the top of the configuration in all cases*.

Configurations of Members of the l-*Family of Aldohexoses*



The experimental facts and arguments used in these further deductions are briefly as follows : *l*-Arabinose gives on very careful oxidation l-*arabonic acid*, $CH_2(OH) \cdot [CH(OH)]_3 \cdot COOH$, which undergoes epimeric change, giving ribonic acid ; the lactone of ribonic acid, on reduction, gives an aldopentose, l-*ribose*, which, therefore, must have the given configuration, and which on further reduction gives (optically inactive) *adonitol*.

From *l*-ribose two aldohexoses—namely, *l*-allose and *l*-altrose —can be derived, just as *l*-arabinose gives *l*-glucose and *l*-mannose. Since l-*allose* on oxidation gives an optically inactive *di*carboxylic acid (l-*altrose* would give an active one), the configurations of these two aldohexoses must be respectively as shown.

The aldopentose, l-*lyxose*, gives *l*-arabitol on reduction ; its configuration is therefore represented as above.[1] On oxidation, *l*-lyxose gives l-*lyxonic acid*, and the latter undergoes epimeric change, giving l-*xylonic acid*, which is identical with the oxidation product of *l*-xylose ; the configuration of l-*xylose*, and that of its

[1] It will be seen that this configuration is C_2 (p. 855).

reduction product, optically inactive *xylitol*, are thus determined. From *l*-xylose, just as from *l*-arabinose (p. 853), two aldohexoses—namely, *l*-gulose and l-*idose*—can be prepared. Since l-*gulose* on oxidation gives *d*-saccharic acid, and is obtained from *d*-glucose [1] in the manner described (p. 859), its configuration, and consequently that of *l*-idose, is established.

Of the remaining two aldohexoses, l-*galactose*, on oxidation, gives first l-*galactonic acid* and then optically inactive mucic acid (p. 313); as, moreover, it can be transformed into *l*-lyxose by the method already described (p. 321), its configuration and that of l-*talose* must be as above; further, *l*-galactonic acid can be converted into l-*talonic acid* by epimeric change, and *l*-talonolactone can be reduced to *l*-talose.

The four optically isomeric aldotetroses are d- and l-*erythrose* and d- and l-*threose*, which on reduction give three *tetritols* (*d*-, *l*-, and *meso*-) and three dihydroxydicarboxylic acids (*d*-, *l*-, and *meso*-tartaric acids). *l*-Erythrose can be obtained from *l*-arabonic acid by either of the methods for the descent of the aldose series (p. 320), and on oxidation it gives *meso*tartaric acid. *l*-Threose can be obtained from *l*-xylose in a similar manner. The configurations of the tetroses are thus established:

HO|H	H|OH
HO|H	HO|H
l-Erythrose	*l*-Threose

The d- *and* l-*Families*

The configuration of *d*-glucose and that of any member of the *d*-family, is, of course, enantiomorphously related to that of the *l*-isomeride. The configurations of the *ten* optically isomeric hexitols (or dicarboxylic acids) correspond with those of the aldohexoses from which they are derived. *l*-Glucose and *d*-gulose give *l*-sorbitol (*d*-glucose and *l*-gulose give *d*-sorbitol), *d*- and *l*-galactose give (inactive) dulcitol, and *d*- and *l*-allose also would give one hexitol only; *d*-talose and *d*-altrose would give the same hexitol (*d*-talitol), whereas *l*-talose and *l*-altrose would give *l*-talitol.

In the above discussion it has been assumed that every chemical

[1] If the gulose derived from *d*-glucose (i.e. from *d*-saccharic acid) be classed as *d*-gulose, then either the xylose from which this *d*-gulose is obtained must be called *l*-xylose, or the lyxose derived from this (*d*-)xylose by epimeric change must be classed as *l*-lyxose, because it is enantiomorphous with the *d*-lyxose corresponding with *d*-arabitol. It is better, therefore, to call it *l*-gulose, according to the given convention (p. 854).

or epimeric change which has actually been carried out with a member of either the *l*- or the *d*-family is also possible in the case of the enantiomorphously related isomeride.

It may also be noted that an arbitrary choice was made in selecting one of two enantiomorphously related configurations to represent the pentitol, *l*-arabitol. If D (compare p. 854) had been chosen for *l*-arabitol instead of C, the only difference would have been that *l*-arabinose, *l*-glucose, *l*-mannose, and all the other compounds of the *l*-family would have been represented by configurations enantiomorphously related to those actually used. The choice between two enantiomorphously related configurations once made, however, must be adhered to throughout.

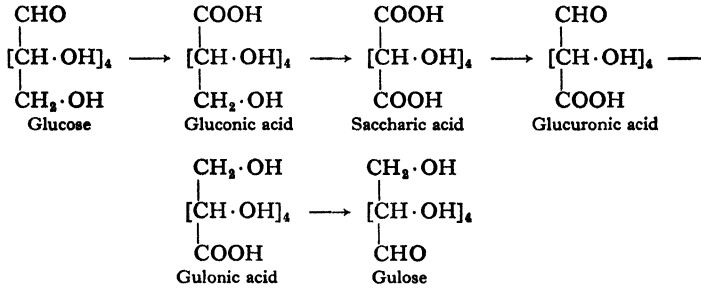
In some examples already given, as in that of ordinary fructose, and in that of arabinose (p. 335), the laevorotatory form is distinguished by *d*, and the dextrorotatory by *l*. This is because ordinary (laevorotatory) fructose is directly related to *d*-glucose in configuration, and the dextrorotatory form of arabinose is directly related to *l*-glucose. As suggested by Fischer, the choice between the letters, *d* and *l*, is based on the configurational relationships of the compound rather than on the direction in which the substance rotates the plane of polarised light. It is therefore customary, where necessary, to employ positive and negative symbols to indicate the sign of the rotation, as in *l*(+)-arabinose, *d*(−)-fructose, etc., the letter showing the group or family relationship.

In studying the above table, and the sugar group in general, it should be remembered that the names of many of the aldohexoses and aldopentoses are based on the epimeric relations (p. 749) of the compounds. The name talose, for example, is taken from that of galactose, ribose from arabinose, lyxose from xylose, the names of any pair of epimerides having many letters in common. This is also so in the case of glucose and gulose because the latter was first obtained from the former, but the two sugars in this case are not epimeric. On the other hand, glucose and mannose, which are epimeric, have unrelated names. The alcohols, except adonitol, sorbitol, and dulcitol, and the monocarboxylic acids have names derived from those of the aldoses from which they may be obtained.

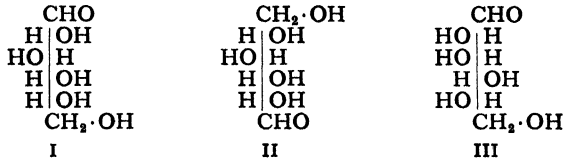
The Relationship between Glucose and Gulose

When saccharic acid, an oxidation product of glucose, is reduced, in the form of its lactone, $C_6H_8O_7$, it is partly converted first into

glucuronic acid [1] and then into gulonic acid, an optical isomeride of gluconic acid ; on reduction, in the form of its lactone, gulonic acid yields gulose, an optical isomeride of glucose. The constitutional relationship between these compounds is therefore as follows :



Gulose, (II or III), is thus formed from *d*-glucose, (I), by a transposition of the groups $—CH_2·OH$ and —CHO. In order to compare their configurations, that of gulose, (II), may be rotated through 180° in the plane of the paper, giving (III), and it will then be seen that this configuration is that of *l*-gulose (footnote, p. 858).

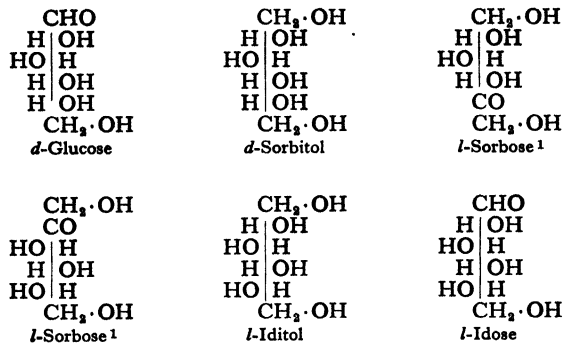


Ketoses

Although *d*(−)-fructose (p. 313) is the only ketose of much importance, others are known, and have been obtained, as already stated (p. 335), with the aid of the sorbose bacterium (*Bacterium xylinum*), which was identified by Bertrand. This organism ferments certain polyhydric alcohols, in which process one of the —CH(OH)— groups is oxidised to —CO— ; *d*-mannitol is thus converted into *d*-fructose, whereas *d*-sorbitol (p. 258), obtained from the juice of the mountain ash, gives l-*sorbose*, and on reduction this ketose gives a mixture of *d*-sorbitol and *l*-iditol, the hexahydric alcohol obtained from *l*-idose.

[1] This acid is sometimes called glycuronic acid ; it occurs in a combined form in nature.

The structural and configurational relationships of *d*-glucose, *d*-sorbitol, *l*-sorbose, *l*-iditol, and *l*-idose are shown below :



The Synthesis of Sugars and their Derivatives

The complete synthesis of the naturally-occurring sugars, glucose, mannose, and fructose, and of many related compounds, including aldohexoses, which were not known to occur in nature, was one of the brilliant triumphs of organic chemistry, and was accomplished by Fischer ; the more important results of this work may be very briefly summarised.

As already stated (p. 318), various sugar-like mixtures can be obtained by treating aqueous solutions of formaldehyde with milk of lime ; from one of these mixtures (formose), Fischer isolated an osazone, which was isomeric with glucosazone and proved to be identical with α-acrosazone (see below). In the meantime he had been investigating other methods of synthesis, and, in conjunction with Tafel, had found that *acraldehyde dibromide*, with ice-cold barium hydroxide solution, gave a mixture of sugars from which two osazones, named *acrosazones* (α- and β-) could be isolated ; from α-acrosazone, by the method already described (p. 318), he obtained a sugar, $C_6H_{12}O_6$, which he named *α-acrose*. The experimental difficulties in preparing α-acrose from the dibromide were, however, very formidable, and since it seemed that this sugar might have been formed by an aldol condensation of *glyceraldehyde*, $CH_2(OH)\cdot CH(OH)\cdot CHO$, attempts were made to obtain it from glycerol.

[1] These two projections are identical.

Glycerol, carefully oxidised with dilute nitric acid or bromine water, gave a product, *glycerose* (a mixture of a little glyceraldehyde with dihydroxyacetone), which was treated with alkalis in the cold ; from the mixture of condensation products so obtained, α-acrosazone was isolated, and converted into α-acrose. This sugar fermented with yeast, and on reduction was converted into a hexahydric alcohol, $C_6H_{14}O_6$, which was found to be very similar in properties to naturally occurring *d*-mannitol (p. 258) ; but, whereas *d*-mannitol was optically active, α-acritol was of course optically inactive.

The possibility suggested itself that α-acritol might be *dl*-mannitol ; but as *dl*-mannitol was then unknown, and as only about 0·2 gram of α-acritol was obtained from 1 kilo of glycerol, even if the identity of α-acritol and *dl*-mannitol were established, the preparation of considerable quantities of this synthetical product for further investigation would be a very laborious task.

Now, *d*-mannitol, on oxidation, gave first the corresponding aldohexose, *d*-mannose (which was afterwards obtained more easily from vegetable-ivory nuts), and then the corresponding monocarboxylic acid, *d*-mannonic acid. The enantiomorphously related *l*-mannonic acid was obtained (together with *l*-gluconic acid) from *l*-arabinose, with the aid of hydrogen cyanide (p. 853).

A mixture of equal quantities of *d*- and *l*-mannonic acids when reduced (in the form of their lactones) gave first an aldohexose, *dl*-mannose, and on further reduction a hexitol, *dl*-mannitol ; the *dl*-mannitol thus prepared was proved to be *identical* with α-acritol. It was thus possible to obtain α-acritol, which had already been synthesised, by *comparatively* easy methods, and to investigate it further.

dl-Mannonic acid, which *could* be prepared from α-acritol, just as *d*-mannonic acid is prepared from *d*-mannitol (but which was actually obtained by mixing the *d*- and *l*-acids), was resolved into its enantiomorphously related components with the aid of its strychnine or morphine salt, and the *d*-mannonic acid (in the form of its lactone) was then reduced, first to *d*-mannose, and then to *d*-mannitol.

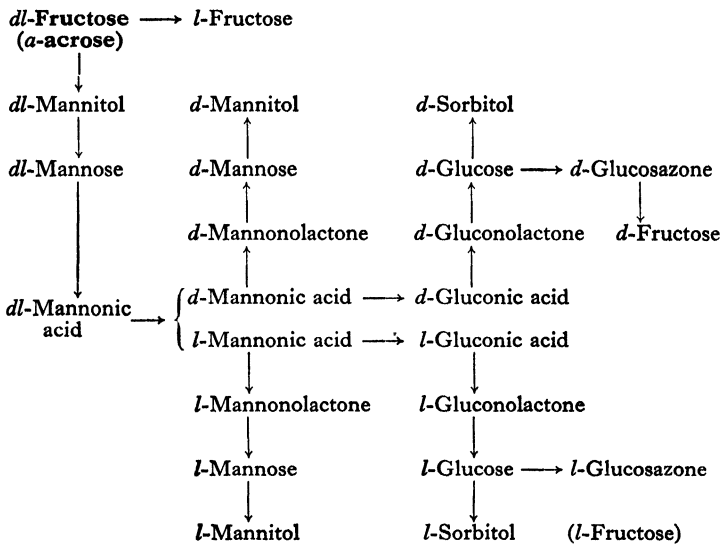
In a similar manner *l*-mannose and *l*-mannitol were obtained from *l*-mannonic acid.

d-Mannonic acid was heated with quinoline, and was partly transformed into *d*-gluconic acid (epimeric change) ; the lactone of the latter was then reduced to *d*-glucose and *d*-sorbitol. In a

similar manner *l*-gluconic acid was obtained from *l*-mannonic acid, and reduced to *l*-glucose and *l*-sorbitol.

d-Fructose was obtained from *d*-glucose with the aid of the osazone in the manner already described (p. 318), and *l*-fructose was prepared from α-acrose, as stated below.

These brilliant results are summarised below ; the starting-point is α-acrose, and the arrows indicate the directions in which the transformations occur :



In addition to these compounds, Fischer also synthesised manno-heptose, manno-octose, and mannononose (p. 320).

The fact that α-acritol is identical with *dl*-mannitol proved conclusively that α-acrose was *dl*-fructose, since the sugar had been obtained from α-acrosazone.

The original product from glycerose, however, might have been *dl*-glucose, *dl*-mannose, or *dl*-fructose, since the osazones of all these hexoses give fructose when the sugar is regenerated (p. 318). In order to settle the nature of the original condensation product, the solution of some of the latter was treated with yeast ; fermentation occurred and the solution became *dextrorotatory*. Now, had the original product been *dl*-glucose or *dl*-mannose, the ordinary

d(+)-form would have fermented, the *l*(−)-form being unchanged, whereas *dl*-fructose, as was proved by separate experiments, would give a dextrorotatory solution, because only *laevorotatory d*-fructose (*d*(−)-fructose) is fermentable (p. 902). The original product from glycerose, therefore, is *dl*-fructose, which is probably formed by an aldol condensation of glyceraldehyde and dihydroxyacetone, or from dihydroxyacetone alone, which is known to give α- and β-acrose when it is treated with dilute alkali.

From the above brief description of work which occupied many chemists during many years, it will be seen that although the synthesis of the sugars was accomplished mainly with the aid of glycerose, it was also proved that the same compounds could have been obtained from formose, and therefore from formaldehyde. Baeyer's view that natural sugars are produced by an aldol condensation of formaldehyde, a transient reduction product of carbon dioxide, was thus supported, but the actual conversion of carbon dioxide into a sugar, independently of plant life, had still to be accomplished.

Experiments with this object in view were made by Moore and Webster (1913–18), who proved that carbonic acid is reduced to formaldehyde by exposing it to ultra-violet light in the presence of certain inorganic catalysts, and that, on exposure to ultra-violet light of longer wave-length, an aqueous solution of formaldehyde gives reducing 'sugars'; such reactions are *photosyntheses*. Baly, Heilbron, and Barker (*J.* 1921, 1025) then stated that these two stages could be combined in one vessel, and carried out in the absence of any inorganic catalysts, but although more recent investigations seem to support these conclusions, they do not afford convincing evidence that the changes are due solely to the action of light or that the products are sugars.

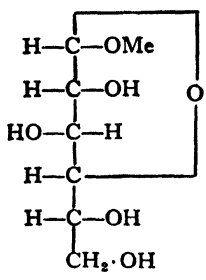
The Glycosidic Structures of the Monosaccharides

It has already been mentioned (p. 316) that the view that monosaccharides are polyhydric aldehydes does not account for all their properties and some of the facts bearing on this question have been stated; these facts are recapitulated here for the sake of clarity.

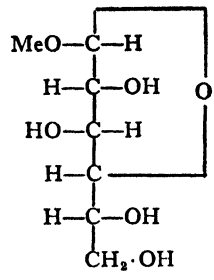
When *d*-glucose is warmed with methyl alcohol in the presence of a little hydrogen chloride, a mixture of two, α- and *β-methyl-glucosides*, $C_6H_{11}O_6 \cdot CH_3$, is produced; these glucosides lack the

reducing action of glucose on Fehling's solution, do not show mutarotation, do not react with phenylhydrazine, and do not ferment with yeast; although fairly stable towards dilute alkalis, they are hydrolysed by dilute acids, regenerating *d*-glucose.

It was suggested by Fischer that these glucosides were ring structures, (I) and (II), and that their isomerism was due to the production from the —CHO group of the *d*- and *l*-forms of a new asymmetric complex, shown in (III) and (IV):

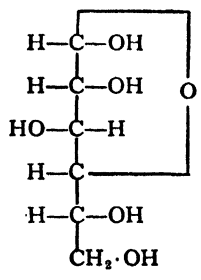


I

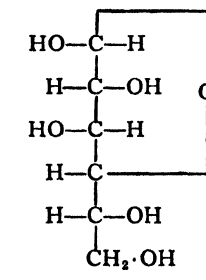


II

Suggested structures, now discarded, for α- and β-methylglucosides



III



IV

Suggested structures, now discarded, for α- and β-glucoses

The glucosidic or oxide ring was assumed to contain five atoms merely from analogy with the lactones (pp. 287, 319), of which the commonest and most easily formed were γ-lactones; such a structure, containing a closed chain of five atoms, was termed a γ- or *butylene oxide* ring.

It was afterwards found that *d*-glucose itself exists in two forms,

both of which may be obtained by crystallisation under different conditions. When it separates slowly from water below 30–35° the sugar is deposited in hydrated crystals, $C_6H_{12}O_6,H_2O$, but from cold alcohol in anhydrous crystals; both these products show an initial rotation of about $[\alpha]_D+110°$, but this value falls slowly (very rapidly if traces of alkali are added) and becomes constant at $[\alpha]_D+52{\cdot}6°$. When, however, a solution of glucose is rapidly evaporated at 100°, and the residue is dissolved in ice-cold water, the addition of ice-cold alcohol precipitates anhydrous crystals, which have an initial and final specific rotation, $[\alpha]_D+52{\cdot}6°$, no change in rotation taking place. Lastly, when an aqueous solution of glucose is crystallised slowly above 98°, or when the sugar is crystallised from hot pyridine, the product shows an initial rotation, $[\alpha]_D+17{\cdot}5°$, which rises to and becomes constant at $+52{\cdot}6°$.

The form produced at ordinary temperatures is called α-glucose, the other is β-glucose, and the product of the rapid evaporation of solutions at 100° is the equilibrium mixture of the two (purified by solution and reprecipitation in the cold); it will be seen from the values for $[\alpha]_D$ that the equilibrium mixture (once believed to be a distinct substance), which is produced when either is dissolved, consists, *roughly*, of equal quantities of the two forms.

A substance like glucose, which gave different initial and final values for its specific rotation, was said to show ' bi-rotation,' and a great many other sugars (having a ' free carbonyl ' group, p. 886) showed this phenomenon, now known as *mutarotation.*

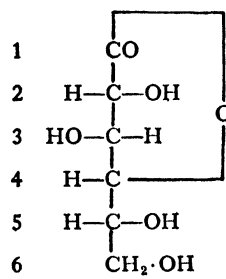
It was suggested by Tollens, long before the two forms of glucose had been isolated, that mutarotation was due to the formation or fission of an oxide ring structure (III and IV, p. 865), but this view could not be established experimentally.

The discovery of the two methylglucosides, however, seemed to show that α- and β-glucose corresponded with the α- and β-methylglucosides, but that in solution the oxide ring structures of both the sugars underwent fission, giving an equilibrium mixture of the two forms and, in consequence, causing mutarotation; the ring structures of the methylglucosides were more stable in solution, so that these compounds did not show mutarotation. This view was confirmed by E. F. Armstrong (*J.* 1903, 1305), who showed that when the glucosides were carefully hydrolysed by the action of enzymes, the changes in rotatory power which occurred could be explained on the assumption that the α-glucoside gave α-glucose,

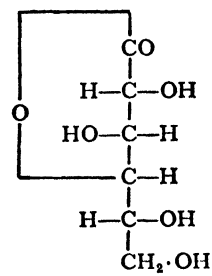
and the β-glucoside, β-glucose. Similar α- and β-methyl isomerides are also formed from the other aldohexoses, and from aldopentoses and ketohexoses; ethyl, propyl, etc., glycosides (p. 316) can also be prepared.

It should be noted that in spite of their glycosidic structure, in which the aldehyde group —CHO is no longer present, the α- and β-sugars retain most of the reactions of aldehydes and behave in solution as if their molecules contained a ' free aldehyde ' or ' free carbonyl ' group.

Now, if a γ-glycosidic ring of the type shown on p. 865 is formed either in a sugar or in a γ-lactone of a sugar acid, it would seem that all the asymmetric groups will retain their configurations, and when that of the product is expressed in the usual way, the glycosidic or lactone ring will be shown on the right- or on the left-hand side of the carbon chain of the projection formula, according to the position of the γ-hydroxyl group on atom 4.[1] In the case of *d*-gluconic acid, for example, the lactone ring would be on the right, whilst in the lactone of *d*-galactonic acid it will be on the left, because of the position of the 4- or γ-hydroxyl group :



d-Gluconolactone
$[\alpha]_D + 68°$



d-Galactonolactone
$[\alpha]_D - 78°$

From an examination of the lactones of twenty-four monobasic acids, obtained by the oxidation of the aldehyde group of sugars, Hudson (*J. Am. Chem. Soc.* 1910, 338) found that on the assumption that they were all γ-lactones, those in which the lactone ring appeared on the one side of the chain of the projection formula were all dextrorotatory, the others, laevorotatory (Hudson's lactone rule).

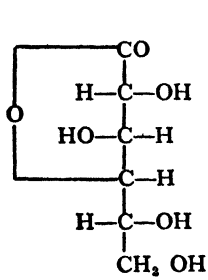
[1] The numbering of the carbon atoms always starts from the aldehyde or carboxyl group, as shown here.

Evidence in support of this assumption was afforded by a study of the rates of hydrolysis of lactones and methylated lactones derived from sugars. In the case of the latter, whose structures are established by oxidation experiments (see later), the γ-, are hydrolysed much more slowly than the δ-lactones ; as the lactones of the sugar acids are only hydrolysed slowly, it may be assumed that they are also the γ-compounds. Hudson also pointed out that ring compounds, such as the lactones and the oxide forms of sugars, had very much higher specific rotations than open chain molecules such as the hexitols and sugar acids ; that is to say, the ring structure had the predominating optical effect.

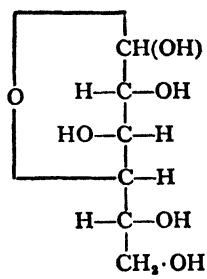
It could be argued, therefore, that the aldoses in their oxide forms should follow the lactone rule, provided that they also were γ-ring compounds of the structures, (III) and (IV), already shown (p. 865). For, if it be assumed that the total effect on the rotatory power is the algebraic sum of the separate effects of each of the asymmetric groups in the molecule (compare optical superposition, p. 745), and that the same hydroxyl group takes part in the formation of the ring both in the sugar and in the lactone of the acid, then this total effect would be due to the asymmetric groups, 1, 2, 3, 4, 5 in the case of the glycosidic sugar, and to the groups 2, 3, 4, 5 in the case of the lactone ; the difference between them would thus be caused by the configuration of group 1. Now if the algebraic mean of the rotations of the α- and β-forms of a sugar is taken it can be assumed that the effects (*d*- or *l*-) of the configuration of group 1 has been eliminated (this value may not be the same as the equilibrium value of the rotation, as the proportions of the two forms at equilibrium are not usually identical, p. 866). It may be inferred, therefore, that the sign, at least, of the rotation due to the groups 2, 3, 4, 5 will be the same in the two cases, and will depend on the right- or left-handedness of the ring structure as shown in the configurational formulae.

When, however, these assumptions were tested, it was found that they were not in accordance with the experimental evidence, if the sugars were represented as γ- or butylene oxides, as in (III) and (IV) (p. 865). It was then pointed out by Drew and Haworth (*J.* 1926, 2303) that if the glycosidic ring of the sugars is composed of six atoms instead of five, that is to say if a δ- or *amylene oxide* ring is formed, then Hudson's rule would hold good with the sugars just as with the γ-lactones. Thus, if *d*-galactose were a γ-oxide, as

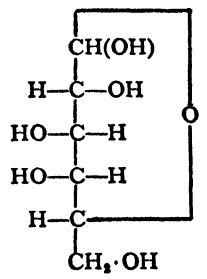
represented in (II),[1] the ring would be on the left-hand side, because of the position of the γ- or 4-hydroxyl group, and according to the rule the sugar should have the same sign of rotation as γ-*d*-galactonolactone, (I):



I



II



III

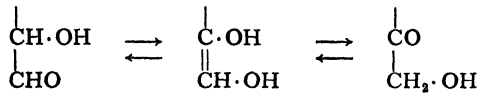
if, on the other hand, *d*-galactose is a δ-oxide, as shown in (III), the ring would be on the right and its rotation should be, as it is, of opposite sign to that of the lactone; the actual values are *d*-galactose $[\alpha]_D+98°$, and *d*-galactonolactone $[\alpha]_D-78°$. Other cases in which a sugar and the γ-lactone of its monocarboxylic acid had specific rotations of different signs were found to conform to Hudson's rule, provided that the sugar was represented by the δ-oxide structure, but clearly further evidence on this point was required; such evidence was obtained from a study of the methylated sugars.

In 1903 Purdie and Irvine made the very important discovery that glucose could be converted into a crystalline tetramethyl derivative by treating α-methylglucoside with methyl iodide and silver oxide, and hydrolysing the tetramethyl-methylglucoside with dilute acid; later, similar compounds were obtained, not only from other mono-, but also from di-saccharides. Denham and Woodhouse then found that cellulose could be methylated with dimethyl sulphate and alkali, a method which, applied to the simpler saccharides by Haworth, has given compounds of the greatest use in the investigation of the carbohydrates in general.

In the preparation of these compounds great care must be taken

[1] When, as in this case, the configuration of the 1-group is not shown, the configuration represents either the α- or the β-form.

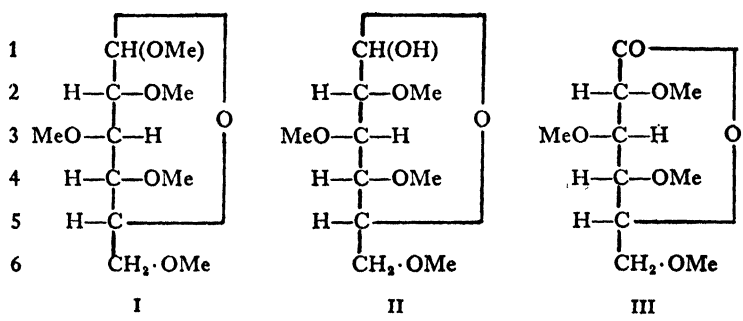
to avoid the presence of much free acid or alkali; acids may bring about the hydrolysis of disaccharides, and alkalis may cause isomeric and other changes, especially with monosaccharides. It has been shown, for example, that glucose, mannose, and fructose all give the same equilibrium mixture in the presence of dilute alkalis (Lobry de Bruyn), probably as a result of keto-enolic changes:



and concentrated alkalis produce a series of complex changes, as has been shown by Nef.

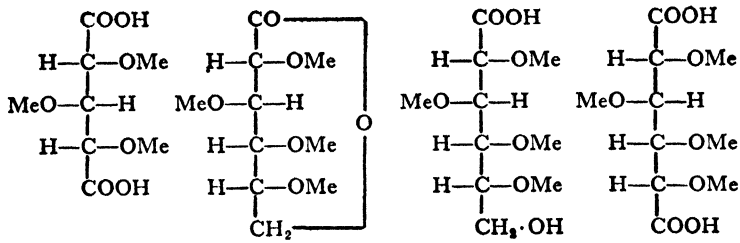
The polymethyl derivatives of the saccharides are more easily dealt with than the parent hydroxy-compounds, since they are soluble in various organic solvents, with which they may be extracted from their aqueous solutions; they usually crystallise well and have definite melting-points, and some of them may even be distilled under greatly reduced pressure.

Now when α- or β-methylglucoside is treated with dimethyl sulphate and dilute alkali, *all* the hydroxyl groups are methylated and a *tetramethyl-methylglucoside*, (I), is formed. This product is hydrolysed by very dilute acid, giving *tetramethylglucose*, (II), the glucosidic methyl group alone being displaced, with the formation of a 'free carbonyl' group (p. 867); these compounds, as will now be shown, are represented by the following structural formulae:[1]



I II III

[1] In studying the *structures* of the glycosidic sugars, it is usually unnecessary for the student to trouble about configurational formulae, although the latter are used in this chapter.



IV V (unknown) VI VII

Tetramethylglucose, (II), on careful oxidation, yields first, *tetramethylgluconolactone*, (III), and afterwards *xylotrimethoxyglutaric acid*,[1] (IV), which may also be obtained directly from xylose ; the formation of this acid, of which one carboxyl group must be that combined in the lactone ring of the tetramethylgluconolactone, shows that three of the methoxy-groups in the lactone and also in the tetramethylglucose must be in the 2, 3 and 4 positions ; otherwise this acid could not have been produced. The lactone ring could not have been in the 4- or γ-, but must have been either in the 5- (as shown) or the 6-position, (V) ; in the latter case the 6-group must have been lost, and the 5-group oxidised to —COOH.

That the lactone ring is *not* 1:6 is shown by many facts, perhaps the simplest being that 2:3:4:5-tetramethylgluconic acid, (VI), which has been prepared from other sources (p. 891), gives tetramethylsaccharic acid, (VII), on oxidation, and cannot be converted into the lactone, (III), mentioned above.

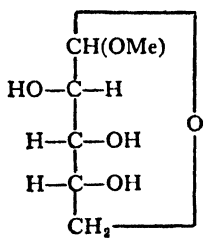
The closed chain in tetramethylgluconolactone, (III), and in tetramethylglucose, (II), and tetramethyl-methylglucoside, (I), is therefore a 1:5-ring, and assuming that its structure is unchanged during the methylation of the glucoside, the α- and β-glucosides and glucoses are also of the 1:5 or *amylene oxide* type, as shown in (I) and (II), and *not* of the butylene oxide type as represented on p. 865.

Evidence that no change occurs during methylation has been provided by (Miss) Isbell, who has shown, mainly by polarimetric methods, that when a sugar, which from other evidence is believed

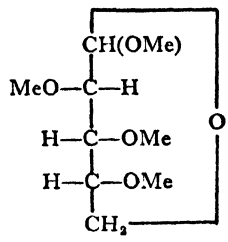
[1] The stereoisomeric [illegible] acids and their methyl derivatives are distinguished as xylo-, ribo-, or arabo- in order to show to which of the pentoses they are related in configuration.

to be of the amylene oxide type, is oxidised with bromine water the δ-lactone of the sugar acid is formed rapidly and almost quantitatively.

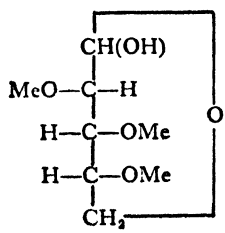
By similar methods it has been proved that the methylglycosides of other hexoses, such as galactose and mannose, and of the pentoses (arabinose, lyxose, and xylose), all contain 6-atom-, δ-, or amylene oxide ring structures ; *methylarabinoside*, (VIII), for example, gives *trimethyl-methylarabinoside*, (IX), which, with dilute acids, yields *trimethylarabinose*, (X) ; on oxidation this compound is then converted into *arabotrimethoxyglutaric acid*, (XI) :



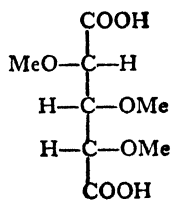
VIII



IX



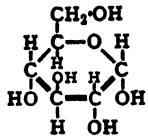
X



XI

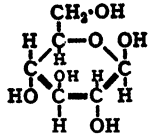
The amylene oxide sugars and their derivatives may therefore be represented by configurations such as (XII, α-glucose) and (XIII, β-glucose), in which there is a nearly planar ring of 5 carbon atoms and one oxygen atom. These configurations, (XII) and (XIII), give, of course, a much more accurate representation of the actual spatial distribution of the atoms than those hitherto used.[1]

[1] The models (p. 855) must be bent *backwards* in order to convert them into the ring structures : the hydrogen atoms in positions 4 and 5 are then *trans* to one another, as shown.



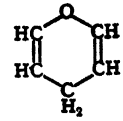
α-*d*-Glucopyranose

XII



β-*d*-Glucopyranose

XIII



Pyran

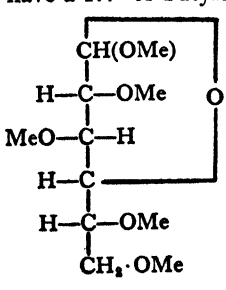
XIV

In the molecule of α-glucose, the hydroxyl groups, 1 and 2 (p. 870), are in the *cis*-position to one another, and *trans*- in β-glucose. This is known from the effect of boric acid on the specific rotation (p. 745) and electrical conductivity of their solutions (Böeseken), and also from the results of X-ray analysis.

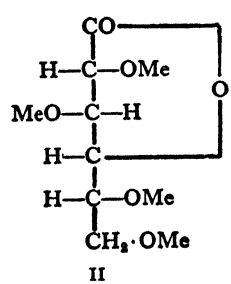
The pentoses and hexoses of the amylene oxide type may therefore be regarded as derivatives of *pyran*, (XIV), and are called *pyranose* (or normal) sugars (Haworth). Further examples of the use of the pyranose configurations will be given later, but in dealing with many points the conventional projection formulae are perhaps easier to follow and will be retained.

Butylene Oxide or Furanose Structures

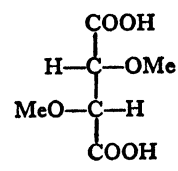
In 1914 Fischer (*Ber.* 1914, 1980) isolated a liquid, γ-methylglucoside,[1] from the products of the interaction of glucose and methyl alcohol; two crystalline *pentabenzoyl-γ-glucoses* have since been prepared (*Ber.* 1927, 1487). This γ-methylglucoside gives a *tetramethyl-methylglucoside*, (I), which is hydrolysed to a liquid tetramethylglucose; on oxidation this liquid product is converted first into *tetramethyl-gluconolactone*, (II), and then into a dimethyltartaric acid, (III). These facts seem to show that the γ-compounds have a 1:4- or butylene oxide structure.



I



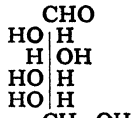
II

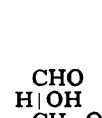


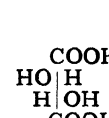
III

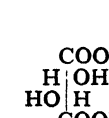
[1] The letter γ here signifies merely a difference from the α- and β-forms.

The dimethyltartaric acid referred to above is dextrorotatory, but is related to *l*-glucose if both substances are regarded as configurationally derived from glyceraldehyde ; it should therefore be called *l*(+)-dimethyltartaric acid.

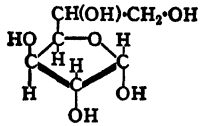

l-Glucose

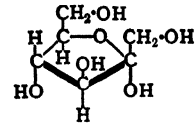

d-Glyceraldehyde


d(−)-Tartaric acid


l(+)-Tartaric acid

These butylene oxide sugars may be regarded as derived from furan (p. 585), just as the *normal* sugars are derived from pyran and are classed as *furanoses* (Haworth) ; [1] their configurations may be represented as shown below :


d-Glucofuranose


d-Fructofuranose

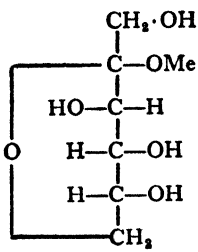
Similar derivatives of other γ-sugars are known, and Haworth and Porter have prepared crystalline α- and β-*ethylglucosides* (p. 879) which are derived from the butylene oxide structure, but the γ-sugars themselves do not appear to exist.

Ketoses and Methylpentoses

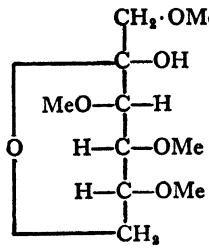
d-Fructose, treated with methyl alcohol and hydrogen chloride, yields d-*methylfructoside*, (I), which exists in α- and β-forms just as do the methylglucosides. The *tetramethyl-methylfructosides*, prepared in the usual way, are hydrolysed to 1:3:4:5-*tetramethylfructose*, (II), which is then oxidised in stages to d-3:4:5-*trimethylfructuronic acid*, (III), d-2:3:4-*trimethylarabolactone*, (IV), and finally to d-*arabotrimethoxyglutaric acid*, (V). These results show that the

[1] There are, theroetically, α- and β-forms of both these furanose sugars. The names pyran and furan suggest saturated structures, but as the latter is used for the unsaturated compound (footnote, p. 585), the furanose sugars are derivatives of *tetrahydrofuran* (p. 834); similarly, if the name pyran is given to the unsaturated ring shown above (p. 873), as seems to be advisable from its relation to the pyrones (p. 983), the pyranose sugars are derived from *tetrahydropyran*.

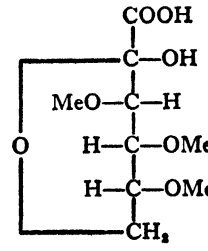
molecule of the fructoside, and presumably that of fructose, contains a 6-atom amylene oxide or pyranose ring, corresponding with that of the normal aldohexoses :



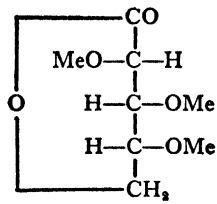
I



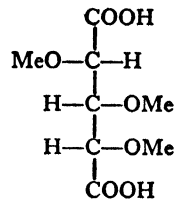
II



III

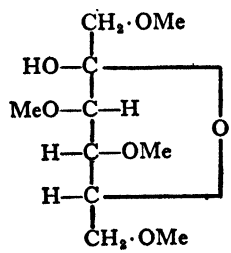


IV

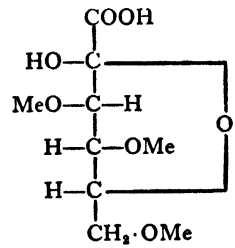


V

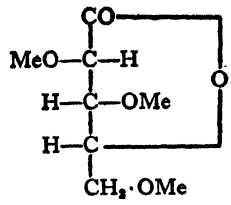
A 1:3:4:6-tetramethyl-γ-fructose, (VI), structurally isomeric with the compound (II), has been obtained from methylated sucrose (p. 893) ; on oxidation, this compound is converted into (VII), then into (VIII), and finally into *d*(−)-dimethyltartaric acid, (IX) ; it has, therefore, a butylene oxide or furanose structure, and is derived from a γ-fructose or fructofuranose (p. 874), of which a crystalline γ-methylfructoside has been isolated.



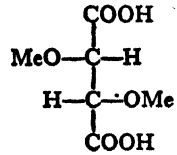
VI



VII



VIII



IX

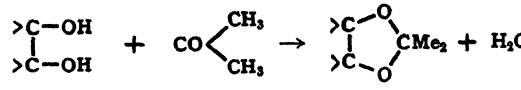
In addition to the aldoses and ketoses of the types already described (in which every carbon atom in the molecule is directly combined with an oxygen atom), various sugars of a somewhat different character are known. Thus, several *methylpentoses*, such as l-*rhamnose*, $CH_3 \cdot [CH \cdot OH]_4 \cdot CHO$, occur in nature in the form of glycosides. These compounds resemble the aldopentoses very closely in their chemical behaviour; they may be reduced to the corresponding alcohols, oxidised to the corresponding monocarboxylic acids, etc., and when heated with mineral acids they give *α-methylfurfuraldehyde*. *l*-Rhamnose has been shown to be a pyranose sugar like the normal hexoses.

Other important sugars are mentioned later (pp. 1076, 1110).

Acetone and Other Derivatives of the Monosaccharides

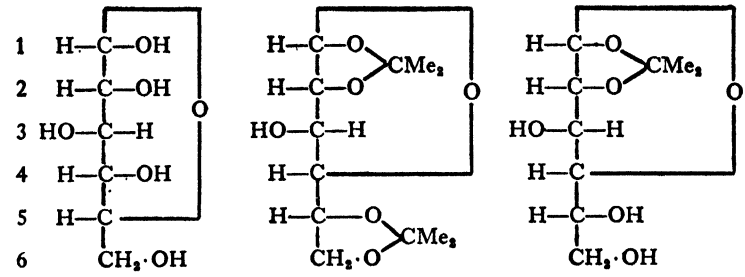
When hexoses are shaken with acetone in the presence of a catalyst, such as hydrogen chloride or zinc chloride, condensation readily occurs (Fischer), giving products, many of which are crystalline and relatively stable towards alkalis, but are more easily hydrolysed by acids than the methyl derivatives.

The structures of such mono- and di-acetone compounds have been determined by methods analogous to those employed in the case of the sugars themselves; methylation is followed by the removal of the acetone groups by acid hydrolysis, and the resulting methylated sugars are identified. It has thus been found that condensation usually occurs with adjacent hydroxyl groups, which are in the *cis*-position,



but the original oxide ring in the sugar may be broken, with the formation of a new one, having, of course, a different structure. α-Glucose, (I), for example, gives a diacetone derivative, (II), in which

the acetone residues are present at positions 1,2 and 5,6, the oxide ring having changed from position 5 (normal glucose) to 4 (γ-glucose).

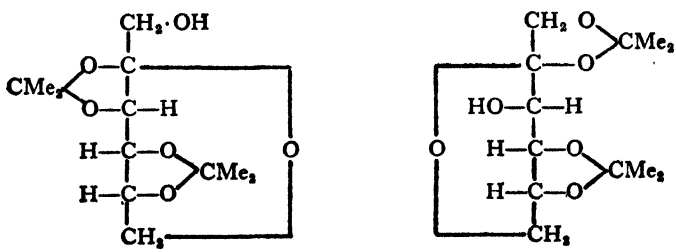


I II III

It appears probable, therefore, that the acetone residue cannot bridge the *trans*-position, so that condensation cannot occur in the 2,3 or 3,4 position ; in solution, however, the oxide ring undergoes fission, 5,6 condensation then occurs, and afterwards the oxide ring is re-formed at atom 4, giving a derivative of γ-glucose. When cautiously hydrolysed with acids, the diacetone derivative gives glucose monoacetone, and as this compound does not reduce Fehling's solution, and does not, therefore, contain in its molecule a ' free carbonyl,' it must be the 1,2-derivative, (III).

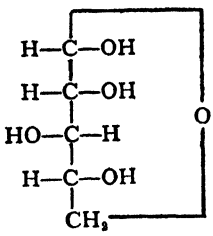
1,2:5,6-Di-*iso*propylideneglucofuranose (glucose diacetone) on methylation and hydrolysis gives 3-methylglucose and 1,2-*iso*-propylideneglucofuranose (glucose monoacetone) similarly yields 3:5:6-trimethylglucose.

In the case of fructose, a diacetone compound can be formed from either the α- or the β-sugar without the fission of the oxide ring, and the structurally different diacetone compounds are both derived from normal fructose.

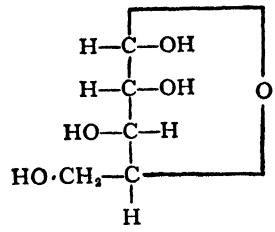


Diacetone derivatives of normal fructose

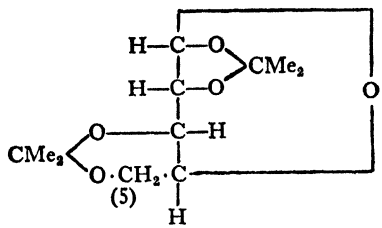
In the molecule of normal *d*-xylose there is only one pair of hydroxyl groups suitably placed for condensation with acetone :



Normal xylose



γ-Xylose



γ-Xylose diacetone derivative

In a γ-xylose the hydroxyl groups at 1,2 are suitable and also those at 3,5, since the latter are separated from one another by about the same distance as the former; with acetone, therefore, xylose gives a diacetone γ-xylose, the oxide ring undergoing fission and re-formation after condensation has occurred, as with glucose.

Benzaldehyde condenses with sugars in a similar manner to acetone, but it often reacts with alternate hydroxyl groups ; with glucose, for example, 4,6-benzylideneglucopyranose is produced and this compound, on methylation and hydrolysis, gives 2:3-dimethylglucose.

Sugar carbonates are formed by the condensation of sugars with phosgene in pyridine solution : they are usually crystalline and in contradistinction to the acetone derivatives are stable towards dilute acids, but are hydrolysed by alkalis, a fact of some importance, as is illustrated by the preparation of glucofuranosides. Thus, 1,2-*iso*propylideneglucofuranose (p. 877) yields 1,2-*iso*propylidene-glucofuranose 5,6-carbonate, and when this is heated with alcohol

and hydrogen chloride the acetone residue is removed and a mixture of α- and β-ethylglucofuranoside 5,6-carbonates is formed by the usual glycoside reaction. After separation the two carbonates can be hydrolysed with dilute alkali to α- and β-ethylglucofuranosides.

Ethyl mercaptan does not react with glucose to form thioglucosides, but condensation occurs with the open chain aldehydo-form of the sugar to give a thioacetal :

$$\begin{matrix} CHO \\ | \end{matrix} \longrightarrow \begin{matrix} CH(SEt)_2 \\ | \end{matrix}$$

Methylation of the thioacetal then gives a pentamethyl derivative from which the two —SEt groups can be removed by treatment with aqueous mercuric chloride ; an open chain 2:3:4:5:6-pentamethylglucose is thus produced.

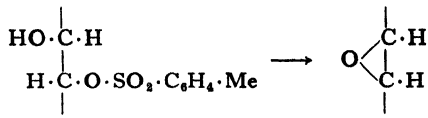
The penta-acetyl and pentabenzoyl derivatives of the hexoses, like the sugars themselves, are oxide structures and exist in α- and β-forms, corresponding with those of the alkyl glycosides ; consequently they do not show aldehyde characteristics.

Acetobromoglucose, $C_6H_7O(OAc)_4Br$, tetra-acetylbromoglucose, is formed by the action of hydrobromic acid on penta-acetylglucose, the glycosidic acetoxy-group being displaced by a bromine atom, so that it is a derivative of the normal or amylene oxide form of glucose. The bromine atom may be easily displaced by other groups, for which reason acetobromoglucose (or *acetochloroglucose*) and corresponding derivatives of other sugars have been used in the syntheses of disaccharides and glycosides (pp. 895, 897).

Interconversion of the Sugars

It has already been seen how inversion of the configuration of the groups on the 2-carbon atom of an aldose may be effected (epimeric change, pp. 749, 857) and a sugar thereby converted into an optical isomeride : the transformation of glucose into gulose has also been mentioned (p. 859). Now there are other ways in which interconversions may be performed and possibly one of the most important uses the *p*-toluenesulphonates (tosyl esters) of the sugars or of suitable derivatives ; such esters are formed by treating the sugar with *p*-toluenesulphonyl chloride in pyridine solution. The esters may then be hydrolysed by mild alkali, but configurational changes often occur during the process. If there is a free hydroxyl radical on the next carbon atom to that directly

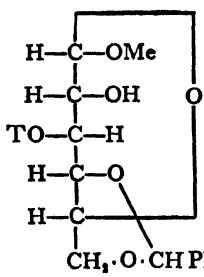
united to the tosyloxy-group and in the *trans*-position, an ethylene oxide ring is first formed on hydrolysis, with an inversion of the groups around the carbon atom to which the tosyloxy-radical was united :



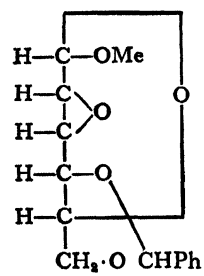
When, for example, a tosyl group at the 3-position in glucose is removed, an anhydro-derivative of allose is produced, with inversion of the configuration around carbon atom-3 ; 3-tosyl-4,6-benzylidine-α-methylglucoside, (I), thus yields 4,6-benzylidene-2,3-anhydro-α-methylalloside, (II).

The oxide ring of an anhydro-sugar may then be opened by the action of alkali, and Walden inversion again takes place at one of the carbon atoms concerned in the oxide ring; (II) therefore gives 4,6-benzylidene-α-methylaltroside (inversion at 2, III) or 4,6-benzylidene-α-methylglucoside (inversion at 3). A mixture containing about 84% of (III) is in fact produced and from (III), α-methylaltroside and altrose may be obtained.

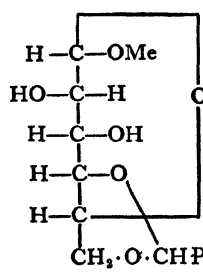
By methods such as this rare sugars may often be prepared from common ones.



I, T=Me·C_6H_4·SO_2



II



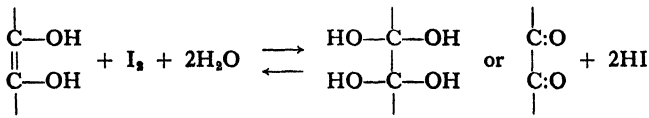
III

Ascorbic Acid

l-Ascorbic acid, $C_6H_8O_6$, was first isolated by Szent-Györgyi in 1928 from the adrenal glands, and later, in considerable quantity, from *paprica* (Hungarian pepper) ; it occurs widely distributed in animals and plants. It has strong antiscorbutic properties (p. 653)

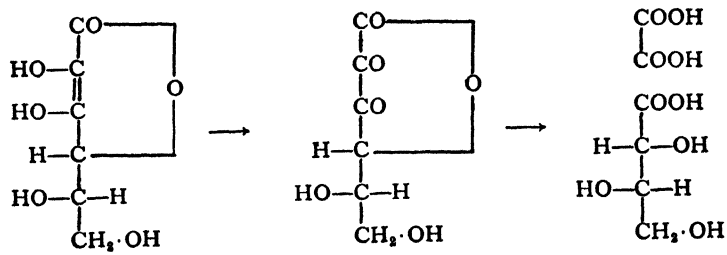
and has been identified as Vitamin C. It melts at 192°, has $[\alpha]_{5780}+24°$ in aqueous solution, and behaves like an unsaturated carboxylic acid.

The constitution of ascorbic acid was elucidated mainly as a result of the work of Haworth and Hirst and their collaborators. The acid is a very powerful reducing agent and is attacked by oxygen in alkaline, but only very slowly in acid solution; with iodine in the presence of acid, a reversible oxidation takes place,



the oxidation product being reduced to ascorbic acid by hydrogen iodide or by hydrogen sulphide.

Ascorbic acid is only a weak monobasic acid and gives a sodium salt, $C_6H_7O_6Na$, whereas the oxidation product just mentioned is neutral and behaves like the lactone of a hydroxycarboxylic acid, thus showing that the acidity of ascorbic acid is due to an enolic hydroxyl group. When the primary oxidation product is further oxidised with sodium hypoiodite, or when ascorbic acid is oxidised with permanganate, oxalic acid and a *trihydroxybutyric acid* are obtained.

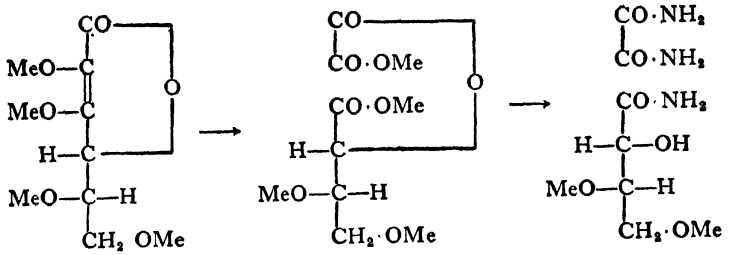


l-Ascorbic acid

The trihydroxybutyric acid can be methylated and the product converted into its crystalline amide; this compound is identical with *trimethyl-l-threonamide*, derived from *l*-threose (p. 858). Its configuration is further confirmed by its oxidation to *l*(+)-tartaric acid, and that of *l*-ascorbic acid is therefore as shown above.

When ascorbic acid is methylated first with diazomethane (p. 469)

and then with methyl iodide and silver oxide, a *tetramethyl* derivative, (I), is obtained which, on ozonolysis, yields a derivative of *threonic acid*, (II); on treatment with alcoholic ammonia this substance is quantitatively converted into oxamide and 3:4-*dimethyl*-l-*threonamide*, (III),



I II III

The structure of the 3:4-dimethyl-*l*-threonamide is proved by the fact that with sodium hypochlorite, sodium cyanate is produced (Weerman), a reaction which has been shown to be characteristic of α-hydroxy-amides,

$$\begin{matrix} & & \\ H-C-OH & + NaClO + NaOH & = CHO + NaNCO + 2H_2O + NaCl. \\ & & \\ CO\cdot NH_2 & & \end{matrix}$$

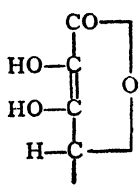
The α-hydroxyl group, therefore, is not methylated.

When (II) is hydrolysed with baryta it gives barium oxalate and *barium dimethylthreonate*, and from the latter the amide, previously prepared from the direct oxidation product of ascorbic acid, may be obtained.

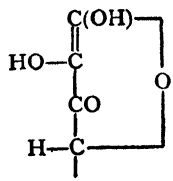
The presence of the unmethylated hydroxyl group in the α-position to the amide radical in the dimethylthreonamide proves that the lactone ring in tetramethylascorbic acid, and by inference that in ascorbic acid itself, is furanose or 1:4, as shown in the above formula. That ascorbic acid is not a carboxylic acid with a 2:4-oxide ring is shown by many considerations, among which may be mentioned the great strain which would be involved in such a ring, and the fact that the first oxidation product of ascorbic acid is a lactone and not an acid.

From the evidence given above it is clear that the structure of tetramethylascorbic acid is as indicated, (I), and that ascorbic acid itself has either the corresponding structure (p. 881), or that in

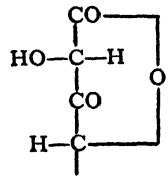
which the group, (IV), has changed into one of the possible tautomeric forms, (V), (VI), or (VII).



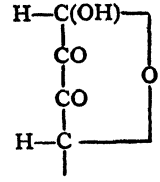
IV



V



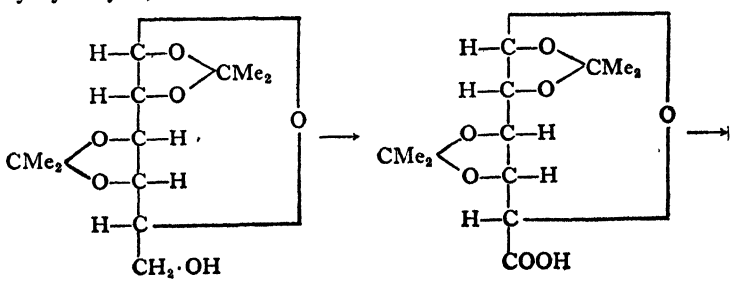
VI



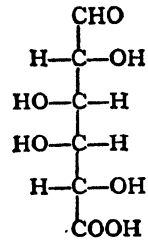
VII

Formulae (VI) and (VII) should give rise to stereoisomerides, which have not been detected in the study of ascorbic acid, and neither configuration represents a flat molecule, such as is revealed by an X-ray examination of the compound (Cox). Further, ascorbic acid gives, with diazomethane, a *dimethyl* derivative which, from its properties, is no doubt derived from (IV), and this dimethyl derivative has an absorption spectrum very similar to that of the acid itself. This is a very good example of the important part played by a study of physical properties in the elucidation of structure.

The above formula (p. 881) was established by the synthesis of *l*-ascorbic acid by Haworth, Hirst, and their collaborators (*J.* 1933, 1419). An examination of the configuration of the acid showed that it might be synthesised from *l*-lyxose or *l*-xylose, but even the preparation of one of these pentoses in sufficient quantity was a task of considerable difficulty. For this purpose, *d*-galactose, which is easily obtained, is converted into its diacetone derivative, (I); this compound is then oxidised to the corresponding derivative of galacturonic acid, from which d-*galacturonic acid*, (II), is obtained by hydrolysis,

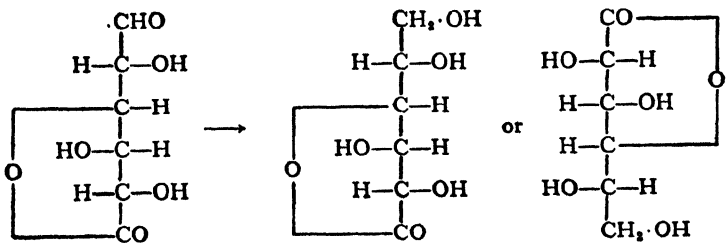


I



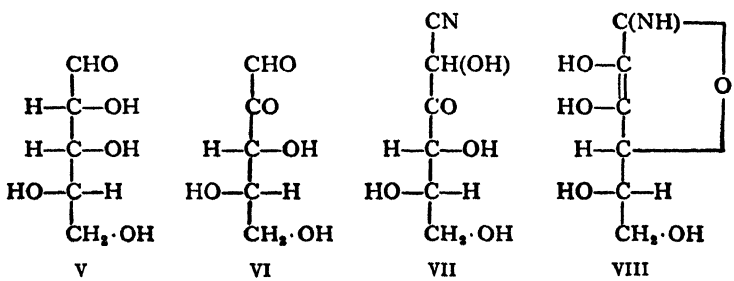
II

The reduction of the γ-lactone of this aldehydic acid, (III), yields l-*galactonolactone*, (IV),



III IV [1]

which is first converted into its amide and then into *l*-lyxose, (V), by the Weerman reaction (p. 882); the osazone of *l*-lyxose gives l-*xylosone* (l-*lyxosone*, VI), on hydrolysis,



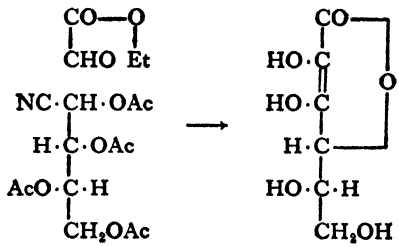
V VI VII VIII

and this osone, with potassium cyanide and calcium chloride in aqueous solution, in the course of twenty minutes, is almost quanti-

[1] The two configurations shown here are identical.

tatively converted into the compound, (VIII), the intermediate nitrile, (VII), undergoing isomeric change. This product is hydrolysed by 8% hydrochloric acid at about 40–50°, and from the resulting solution *l*-ascorbic acid (p. 881), identical in all respects with the natural substance, is obtained.

A much simpler synthesis of *l*-ascorbic acid has been achieved (Helferich and Peters, *Ber.* 1937, 45) by condensing the tetra-acetate of the cyanohydrin of *l*-threose with ethyl glyoxylate in the presence of sodium methoxide ; the ethyl radical and the acetyl groups are removed during the process, which is similar to the benzoin reaction :



Other syntheses of the vitamin, which are now used commercially, have also been devised, and various compounds analogous to ascorbic acid in structure have been prepared, but most of them are either inert or have little antiscorbutic activity.

CHAPTER 53

DISACCHARIDES AND POLYSACCHARIDES

THE disaccharides (pp. 321-325) are hydrolysed by acids and by enzymes, giving two molecules of the same or of different hexoses ; maltose, for example, gives two molecules of glucose, whereas lactose gives glucose and galactose, and sucrose gives glucose and fructose.

Many other disaccharides are known, such as cellobiose, gentiobiose, and melibiose.[1] *Cellobiose* is obtained by treating cellulose with acetic anhydride and sulphuric acid, when *acetolysis* occurs, and octa-acetylcellobiose is formed ; this compound is readily hydrolysed giving cellobiose. *Gentiobiose* is formed, together with *d*-fructose, by the partial hydrolysis with an enzyme of a trisaccharide, *gentianose*, which occurs in the roots of the gentian. *Melibiose* is obtained also, together with *d*-fructose, from a trisaccharide, *raffinose*, which occurs in the molasses from beet-sugar and in Australian manna, from eucalyptus.

Two different types of disaccharides are known :

Type I. Those such as lactose and maltose, which show mutarotation, give osazones, and may be oxidised with bromine and water to monocarboxylic acids of the molecular formula, $C_{12}H_{22}O_{12}$. Lactose, for example, gives *lactobionic acid*, and maltose, *maltobionic acid*, so that the molecule of each of these sugars must contain a so-called ' free carbonyl ' group, that is to say a modified aldehyde group corresponding with that in α- and β-glucose, etc. Hence, when lactose and maltose are produced by the condensation of two aldohexose molecules, the aldehyde group of *one* of the aldohexoses is not directly concerned in the process. Lactobionic acid and maltobionic acid, like the disaccharides from which they are derived, are readily hydrolysed ; lactobionic acid is thus transformed into *d*-galactose and *d*-gluconic acid, whereas maltobionic acid is converted into *d*-glucose and *d*-gluconic acid. From these facts, and from a consideration of the formulae of the alkylglycosides, it would seem that lactose is a glycoside derived from *d*-galactose, and maltose a glycoside derived from *d*-glucose.

Type II. Sucrose, unlike lactose and maltose, does not show

[1] The suffix ' biose ' is often used to denote a disaccharide. The term ' biose link ' is employed below to denote the group C—O—C by which the two hexose residues are united in the disaccharide.

mutarotation, does not give an osazone, and cannot be oxidised to an acid of the molecular formula, $C_{12}H_{22}O_{12}$; consequently, its molecule does not contain a 'free carbonyl' group and must differ considerably in type from that of lactose or of maltose; the modified aldehyde group of glucose as well as the ketonic group of fructose have both been changed as a result of the combination of the two hexoses. *Trehalose*, which occurs in various plants, is also a disaccharide of Type II.; on hydrolysis it gives *d*-glucose only.

The two types of disaccharides may therefore be classified as follows:

I. Glucose-glycoside type (with a 'free carbonyl' group). (*a*) Maltose, Lactose, Cellobiose. (*b*) Gentiobiose, Melibiose.

II. Glycosido-glycoside type (with no 'free carbonyl'). Sucrose, Trehalose.

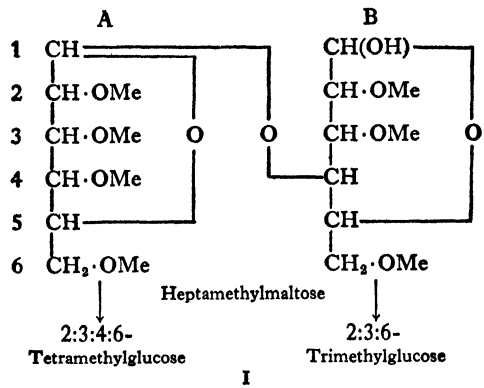
Theoretically there are many different ways in which members of Type I. might be formed, since the elimination of a molecule of water from two molecules of the glycosidic forms of the same or of different aldohexoses might involve any one of the four hydroxyl groups of one of the compounds; the first step, therefore, is to ascertain which of these hydroxyl groups takes part in the production of the biose link of the disaccharide.

This can be done by first submitting the disaccharide to complete methylation, and then hydrolysing the product carefully so that two methylated hexoses are obtained; these compounds are tri- and tetra-methyl derivatives, the structures of which can be (and have been) determined by studying their products of oxidation, and in other ways. The results of such experiments show which of the four hydroxyl groups of each aldohexose were not concerned in the disaccharide formation because hydroxyl groups which are methylated in the fission products must have been present as such in the disaccharides. This method of investigation is illustrated by the examples given below.

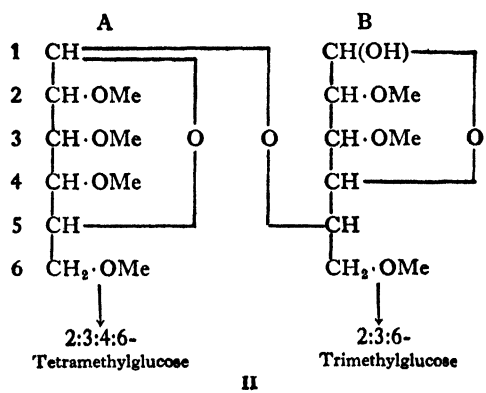
Maltose, exhaustively treated with dimethyl sulphate and alkali, is converted into *methyl-heptamethylmaltoside*, a compound which lacks the reducing power of the parent sugar because the 'free carbonyl' group has been methylated. The hydrolysis of methyl-heptamethylmaltoside gives *heptamethylmaltose*, the glycosidic methyl group being displaced by hydrogen, and on further hydrolysis the disaccharide derivative gives 2:3:4:6-tetramethylglucose and 2:3:6-trimethylglucose.

The production of 2:3:4:6-tetramethylglucose shows that the linkage of the hexose molecules occurs through carbon atom 1 in the case of the A-part of the molecule (see below), because carbon atom 5 is a part of the oxide-ring structure; the formation of 2:3:6-trimethylglucose shows that B is linked to A through the oxygen of carbon atom 4 or 5, as the 4 and 5 hydroxyl groups of the B-part of the disaccharide are not methylated.

Now if it be assumed that the glucose residue B is of the normal amylene oxide type, the formula of maltose must correspond with (I); but this might not be so, since the molecule of maltose might contain a labile γ-glucose residue (p. 873) as shown in (II), which structure would give the same products of fission as (I).



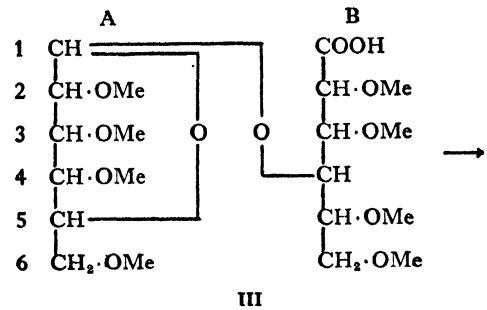
I



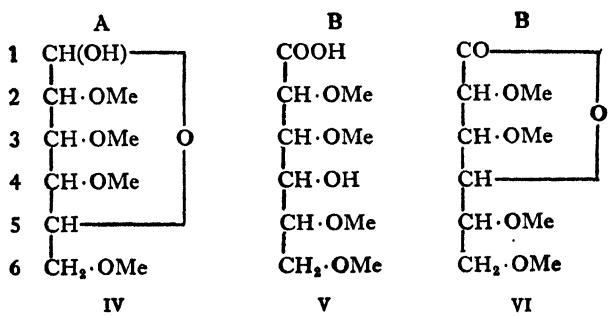
II

That (I) represents heptamethylmaltose is proved as follows :

When maltobionic acid, obtained by oxidising maltose, is methylated, it yields the methyl ester of octamethylmaltobionic acid, (III), which on hydrolysis gives the same 2:3:4:6-tetramethylglucose, (IV), as before (from A), together with a 2:3:5:6-tetramethylgluconic acid, (V, from B), instead of a 2:3:6-trimethylglucose ; the carbon atom 5 which escaped methylation in the disaccharide is methylated in maltobionic acid because the 5 oxide-ring underwent fission in the formation of the latter. The 2:3:5:6-tetramethylgluconic acid, (V), forms a γ-lactone, (VI), identical with tetramethyl-γ-gluconolactone (p. 873). Clearly, then, the γ- or 4-hydroxyl group of the B molecule takes part in the formation of the biose link, as shown in (I) and (III).



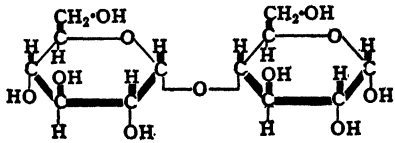
III



IV V VI

Maltose, therefore, is a glucose-glucoside, but it remains to be decided whether the glucoside structure of A is α- or β-, that is to say whether the configuration of A corresponds with that of α-

methyl- or β-methyl-glucoside. Now maltose is hydrolysed by maltase (p. 332), an enzyme which has been found to attack α- but not β-glucosides; it is therefore glucose-α-glucoside, as shown below.



The *structures* of lactose and cellobiose (p. 886) have been elucidated in a similar manner and are identical with that of maltose. The heptamethyl derivatives of these sugars, obtained from the *methyl-heptamethyldisaccharides*, are hydrolysed, giving the following products:

Heptamethyllactose { 2:3:4:6-tetramethylgalactose. / 2:3:6-trimethylglucose.

Heptamethylcellobiose { 2:3:4:6-tetramethylglucose. / 2:3:6-trimethylglucose.

These results show that in both disaccharides, just as in the case of maltose, the two aldohexose residues (A and B) are linked together through the 4 or 5 carbon atom of B; the position of the biose link is proved to be the same as that in maltose by a study of the fission products of *octamethyllactobionic* and *octamethylcellobionic acids* respectively; the former gives 2:3:4:6-tetramethylgalactose and 2:3:5:6-tetramethylgluconic acid, and the latter gives 2:3:4:6-tetramethylglucose and 2:3:5:6-tetramethylgluconic acid.

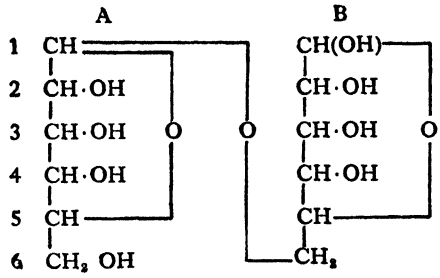
Though structurally identical with maltose, lactose and cellobiose differ from maltose in configuration. Lactose is hydrolysed by *lactase*, and is a β-galactoside; cellobiose is hydrolysed by emulsin (p. 499), not by maltase, and is therefore a β-glucoside (compare p. 903).

The structure of melibiose has been established by the same methods as those used for maltose, lactose, and cellobiose. The disaccharide is completely methylated, and the octamethyl derivative is then converted into *heptamethylmelibiose* by graded hydrolysis; this compound undergoes fission, giving 2:3:4:6-tetramethylgalactose and 2:3:4-trimethylglucose.

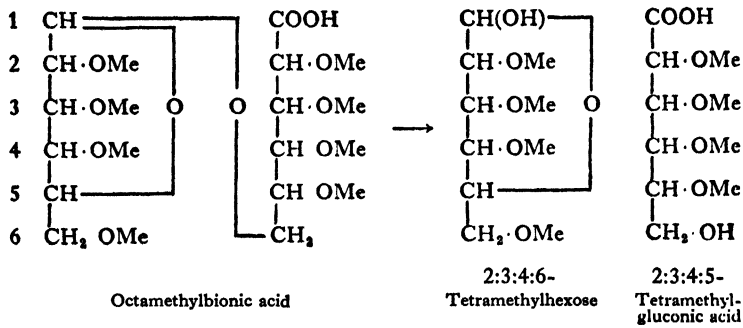
The two hexose molecules are therefore linked together through carbon atoms 5 or 6 of the glucose residue B, probably 6, if the glucose residue is the normal pyranose form.

Now *methyl octamethylmelibionate*, on hydrolysis, affords 2:3:4:6-tetramethylgalactose and 2:3:4:5-tetramethylgluconic acid which can be oxidised to tetramethylsaccharic acid.

These facts prove that the biose linkage must be from atom 1 in the galactose residue, A, to atom 6 in the glucose residue, B.



Melibiose and Gentiobiose



Octamethylbionic acid

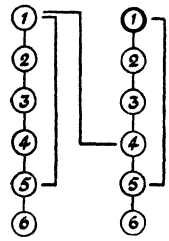
2:3:4:6-Tetramethylhexose

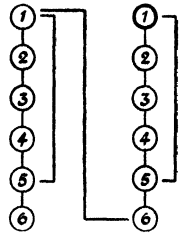
2:3:4:5-Tetramethyl-gluconic acid

In a similar manner gentiobiose has been shown to be structurally identical with melibiose, but its molecule contains a glucose, in place of the galactose residue, A; this structure has been confirmed by synthesis (p. 895), and from its behaviour towards emulsin, the biose link of A is that of a β-glucoside.

It will be seen that the disaccharides of Type I. may be classed

in two groups (p. 887), and the results of their investigation may be summarised as follows :





Maltose	α-Glucose—Glucose		Melibiose	α-Galactose—Glucose
Lactose	β-Galactose—Glucose		Gentiobiose	β-Glucose—Glucose
Cellobiose	β-Glucose—Glucose			
Methylated bioses give :	Methylhexoses 2, 3, 4, 6	2, 3, 6	Methylhexoses 2, 3, 4, 6	2, 3, 4
Methylated bionic acids give :	Methyl-hexose 2, 3, 4, 6	Methylhexonic acid 2, 3, 5, 6	Methyl-hexose 2, 3, 4, 6	Methylhexonic acid 2, 3, 4, 5

The 1 carbon atom of the ' free carbonyl ' group is indicated by the dark circle. The hydroxyl group of this carbon atom is methylated in the octamethyl derivative of the disaccharide, but *not* in its first product of hydrolysis (heptamethyl derivative) ; it is this ' free carbonyl ' which gives the carboxyl group of the bionic acid.

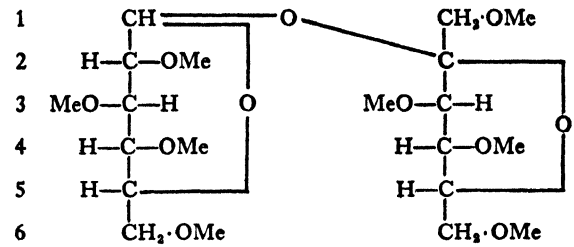
With the aid of this summary most of the experimental data given in this chapter are easily reproduced, since the above symbols are based on the facts there recorded. It is easily seen, for example, that methylated lactose will give 2:3:4:6-tetramethylgalactose and 2:3:6-trimethylglucose ; that lactobionic acid will give 2:3:4:6-tetramethylgalactose and 2:3:5:6-tetramethylgluconic acid, the 5-hydroxyl group which is ' blocked ' in the disaccharide, owing to the oxide ring, being methylated in lactobionic acid, in which this ring is no longer present.

Disaccharides of Type II., the molecules of which do not contain a ' free carbonyl,' must have been formed by the elimination of water from the reducing groups of both monosaccharides, so that it is only necessary to determine the structure of the oxide rings in the two hexoses.

This is accomplished by methods corresponding very closely with those used in the case of the disaccharides of Type I.; that is to say the compounds are completely methylated, under conditions which do not bring about any change in structure, and the products of fission of the methylated compounds are then identified.

Sucrose, with dimethyl sulphate and alkali, yields *octamethylsucrose*, which is hydrolysed by very dilute (0·4%) hydrochloric acid, giving a 2:3:4:6-tetramethylglucose and a 1:3:4:6-tetramethyl-γ-fructose; the former compound is identical with normal 2:3:4:6-tetramethylglucose (p. 870), and the constitution of the latter was proved in the manner already described (p. 875).

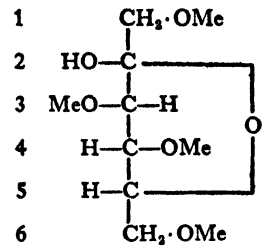
Octamethylsucrose, therefore, consists of normal tetramethylglucose condensed with γ-tetramethylfructose, and these two molecules must be linked by the elimination of water from the 1-hydroxyl group of tetramethylglucose and the 2-hydroxyl group of γ-tetramethylfructose, as will be seen from the following formula:



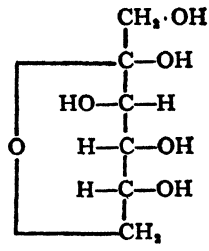
Octamethylsucrose

Sucrose itself is represented by a formula corresponding with that of its octamethyl derivative.

Octamethylsucrose, $[\alpha]_D+67°$, is hydrolysed to a mixture of methylated hexoses, which has $[\alpha]_D+57°$, so that no *inversion* occurs as with the unmethylated sugar (p. 323). This fact is readily explained by the above structural and *configurational* formula, since both the methylated hexoses produced are dextrorotatory (Hudson's rule); when, however, the unmethylated sugar is hydrolysed, the dextrorotatory γ-fructose which is first formed immediately passes into normal *d*(−)-fructose with a change of the oxide-ring structure, and as *d*(−)-fructose has a larger laevo-specific rotation than dextrorotatory *d*-glucose, inversion occurs.



Tetramethylfructofuranose



Normal fructopyranose

The above constitutional formula represents sucrose as a fructosido-glucoside, or glucosido-fructoside, both the hexoses being united through their glycosidic groups ; as, therefore, the molecule contains no ' free carbonyl,' sucrose does not show those reactions of disaccharides of Type I. which are due to such a group. Since a glycoside (or fructoside) may exist in α- and β-forms, the configuration of sucrose is not settled until it has been determined whether this linkage is α- or β- in the glucose residue and α- or β- in the fructose residue—clearly four possibilities ; conclusive evidence on this point, however, is still lacking, but sucrose is probably a β-fructosido-α-glucoside.

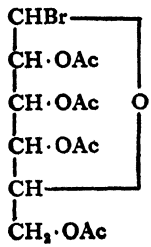
The Synthesis of Disaccharides

Several methods for the synthesis of disaccharides have been investigated. Thus the hydrolysis of a disaccharide by an enzyme is a reversible process, and if a mixture of the constituent monosaccharides is submitted to the action of the enzyme some of the disaccharide is produced ; maltose is thus obtained from *d*-glucose.

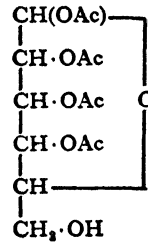
Pictet and his collaborators synthesised a sugar, which they believed to be maltose, by heating a mixture of α- and β-glucose at 160° in a vacuum, and, similarly, a product, thought to be lactose, from a mixture of β-glucose and β-galactose. By the condensation of tetra-acetyl-γ-fructose and tetra-acetylglucose, they obtained a sugar, now known as *iso*sucrose, which differs from sucrose only as regards the biose link.

Syntheses such as the above do not give much information as to the structure of the disaccharide, and as an illustration of a more definite synthesis that of gentiobiose (Helferich and Klein, *Ann.* **450**, 219) may be given.

2:3:4:6-Tetra-acetyl-1-bromoglucose, (I), and 1:2:3:4-tetra-acetyl-β-glucose, (II), compounds of proved constitution, react in the presence of silver oxide, and when the product is very cautiously hydrolysed in order to displace the acetyl groups, it gives a glucose-β-glucoside [1] which was proved to be identical with gentiobiose (p. 892).



I



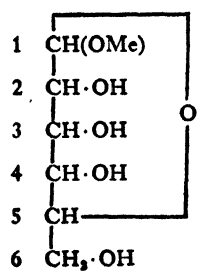
II

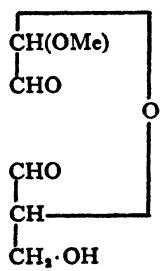
The Oxidation of Sugars with Periodic Acid

Very interesting results have been obtained by the oxidation of sugars or their derivatives, with periodic acid ; one or more groups —CH(OH)—CH(OH)— undergo fission with the formation of dialdehydes, and the reactions are quantitative.

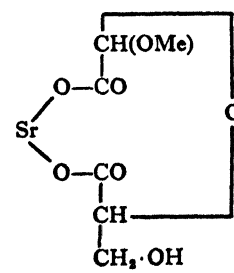
Thus, with a methylhexosepyranoside fission occurs between carbon atoms 2 and 3 and also between 3 and 4 with the elimination of the CH(OH) group at 3 as formic acid and the formation of (I) :

$$C_7H_{14}O_6+2HIO_4 = C_6H_{10}O_5+H\cdot COOH+2HIO_3+H_2O,$$





I

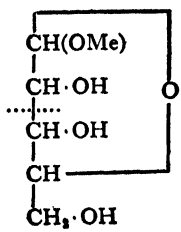


II

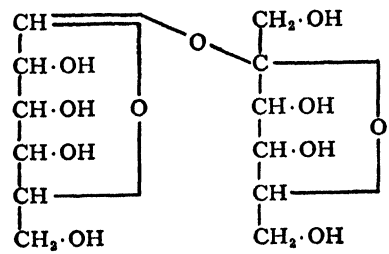
[1] 2:3:4:6-Tetra-acetylbromoglucose gives glucosides derived from β-glucose.

When the dialdehyde, (I), is then oxidised with bromine water in the presence of strontium carbonate, the crystalline strontium salt, (II), is obtained.

Both α- and β-methylglycosides give such oxidation products and, in either the *d*- or the *l*-series, the corresponding derivatives are distinguished merely by the different configurations of their 1-group ; as all α-methylglycosides of the *d*-series (so far examined) give the same strontium salt, (II), it follows that they all have the same configuration at carbon atom-1. Methylpentosefuranosides, (III), give the same oxidation products, with a fission of the molecule as indicated, but without, of course, any production of formic acid,

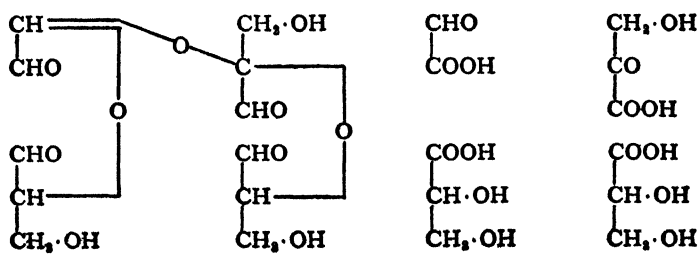


III



IV

The application of this method has fully confirmed the structure of sucrose, (IV) : with three molecules of periodic acid the sugar gives (V) together with one molecule of formic acid. On further oxidation with bromine water, followed by hydrolysis, glyoxylic, glyceric, and hydroxypyruvic acids are formed (Fleury and Courtois, *Compt. Rend.* 1942, 214, 366) :



V

Vegetable Glycosides

Several naturally-occurring glycosides, such as amygdalin (p. 354), salicin (p. 535), arbutin (p. 491), ruberythric acid (p. 562), and indican (p. 681), have already been mentioned, and their products of hydrolysis have been given ; such compounds are derived from sugars by the condensation of the glycosidic hydroxyl group with a hydroxyl group of the non-sugar part of the molecule or *aglycone*, just as the disaccharides are derived from two monosaccharides. The structures of many glycosides have been determined by isolating the products of hydrolysis obtained with enzymes or acids, and also applying the methods used in investigating the structures of the saccharides. In the case of arbutin, for example, hydrolysis yields glucose and quinol, and as hydrolysis is effected by emulsin, arbutin is a β-glucoside ; arbutin gives a pentamethyl derivative, which is hydrolysed with methyl alcohol and hydrogen chloride to α- and β-2:3:4:6-tetramethyl-methylglucosides. Arbutin, therefore, is a quinol-β-glucoside, $C_6H_{11}O_5 \cdot O \cdot C_6H_4 \cdot OH$, derived from normal glucopyranose, and during its hydrolysis, in the presence of methyl alcohol, both the α- and β-glucosides are produced. Michael has synthesised methylarbutin from quinol monomethyl ether and [illegible] (p. 879), and Macbeth and Mackay have obtained pentamethylarbutin by condensing tetramethylglucose and quinol monomethyl ether, thus confirming the above structure.

Amygdalin has been proved to be a gentiobioside (p. 892) of *l*-mandelonitrile, $C_6H_5 \cdot CH(CN) \cdot O \cdot C_{12}H_{21}O_{10}$, and has been synthesised by Campbell and Haworth (*J.* 1924, 1337).

Various other types of glycosides, such as the tannins (p. 998), anthocyanins (p. 989) and cardiac poisons (p. 1110), occur in nature.

Polysaccharides

The polysaccharides, such as starch (p. 325) and cellulose (p. 328), are hydrolysed by acids and by enzymes, and their molecules are finally resolved into monosaccharides ; during this process many intermediate products are formed, and from starch, for example, various soluble, comparatively simple substances, composed of only eight or fewer monosaccharide molecules closely related to maltose have been isolated. From this and much other evidence it has been inferred that the polysaccharides are highly complex

condensation products of the oxide forms of the monosaccharides (generally glucose), the molecules of which are linked together by the elimination of the elements of water, as indicated below :

$$HO\cdot C_6H_{10}O_5\cdot \overset{\frown}{H\ HO}\cdot C_6H_{10}O_5\cdot \overset{\frown}{H\ HO}\cdot C_6H_{10}O_5\cdot \overset{\frown}{H\ HO}\cdot C_6H_{10}O_5\cdot \overset{\frown}{H}\ \text{etc.}$$

If, then, as seems very probable, the polysaccharides are open chain compounds, their empirical formulae will approach the more nearly to $C_6H_{10}O_5$, the larger the number of monosaccharide residues in their molecules ; if, as is conceivable, they are closed chain compounds, the elimination of the elements of water from the ends of the chain will give a product, $(C_6H_{10}O_5)_n$, whatever the number of monosaccharide residues in the molecule. It is not to be inferred, however, that all the links indicated above by $\frown$ are of the same nature ; they may be formed by either the α- or the β-configuration and may vary alternately or otherwise, so that hydrolysis may bring about the fission of the less stable links only, giving products which are still polysaccharides.

The determination of the structures of such complex molecules is obviously a task of the greatest difficulty, but a good deal of information has been gained by employing methods similar to those used in the study of the disaccharides.

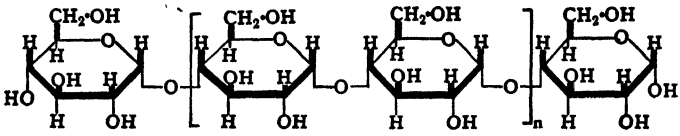
Starch. By the hydrolysis of starch under suitable conditions an 80% yield of maltose is obtained, a fact which would appear to show that the polysaccharide consists wholly of linked maltose molecules ; on methylation, starch yields nearly 90% of trimethyl-starch, $(C_6H_7O_5Me_3)_n$, which, on hydrolysis, is converted mainly into 2:3:6-trimethylglucose.

When starch is heated at 120° with butyl alcohol, *amylose* (20–25%) separates ; *amylopectin* passes into solution and can be precipitated by ethyl alcohol. These two components differ in many respects ; although amylose may be dissolved from starch with warm water (p. 326), when it has been thoroughly dried it is more sparingly soluble than is amylopectin ; the former gives an intense blue with iodine and is completely converted into maltose by β-amylase ; [1] the latter gives a red-brown colour with iodine and yields only 50% of maltose with β-amylase, together with a residue of dextrin-A.

Now Haworth and his collaborators have shown that when fully methylated amylose is hydrolysed, in addition to 2:3:6-*tri*methyl-

[1] Diastase is a mixture of enzymes of which one is β-amylase.

glucose, which is the main product, a small proportion of 2:3:4:6-*tetramethylglucose* is obtained; the latter, apparently, must have been formed from the commencing group [1] of an *open chain* structure, such as that shown below, and by determining its proportion, the number of hexose units in the chain may be estimated. It was found by this method (*end-group* assay) that the amylose molecule contains about 100 or more hexose units, and molecular weight determinations by osmotic pressure measurements agree with this value. The structure of amylose may therefore be expressed as below, the maltose units being united by α-glucose linkages:

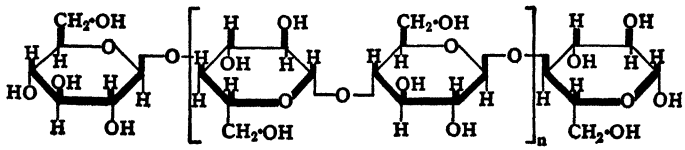


Amylose

Amylose has been obtained crystalline and the results of its X-ray examination suggest a helical arrangement of the chain.

In amylopectin, end-group assay gives a chain length of about 20 glucose units, whereas osmotic pressure measurements show a very much higher molecular weight; this and other evidence indicate that the relatively short chains are bound to one another by 1:6-α-linkages, thus giving a sort of tree-like structure.

Cellulose. Evidence of a like nature points to the conclusion that the structure of cellulose is similar to that of amylose, but that the linked hexose molecules are those of β-glucose, since cellulose consists of cellobiose units.



Cellulose

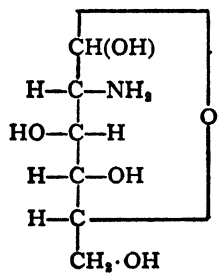
[1] It is to be noted that the other terminal group yields *tri*methylglucose, as the methyl group attached to the glucosidic oxygen atom is displaced on hydrolysis.

Molecular weight determinations of cellulose by various methods give values from about 300,000–500,000, and the molecules have a long thread-like structure.

Some interesting results have been obtained by Hess and Schultze (*Ann.*, **448**, 99 ; compare Pringsheim, *Ann.*, **450**, 255) during their investigations of crystalline cellulose diacetate, a compound obtained by treating cellulose triacetate with sulphuric and acetic acids. Molecular weight determinations in acetic acid solution in the absence of dissolved air give values corresponding with those required for $C_6H_8O_5Ac_2$, but in the course of a few days the molecular weight gradually increases and becomes infinitely large ; the compound then recovered from the solution is identical with the original one, and gives the same small molecular weight as before. Cellulose triacetate shows a similar behaviour.

Inulin (p. 327), like starch and cellulose, yields on methylation a trimethyl-derivative, which on hydrolysis gives 3:4:6-trimethyl-γ-fructose (over 90% yield) ; inulin, therefore, is represented as a condensation product of α- or β-fructofuranose. In addition to fructose, on hydrolysis inulin gives a very small proportion of glucose ; it is not yet known how this is combined in the molecule.

Chitin, a polysaccharide which is contained in the shells of crustaceans, yields *glucosamine* and acetic acid on hydrolysis ; it is probably composed of units of *N*-acetylglucosamine joined in the same way as the glucose units of cellulose. As will be seen from the formula, glucosamine is theoretically formed by displacing the hydroxyl group on carbon atom 2 of glucose by the amino-group.



Glucosamine

Alginic Acid, $(C_6H_8O_6)_n$, occurs both in the free state and as the calcium salt in many seaweeds. The sodium salt gives a very

viscous solution in water even at a concentration of only 2% and is used in the dyeing, textile and explosives industries and in making ice-cream, etc. On hydrolysis alginic acid gives *d*-mannuronic acid, $C_6H_{10}O_7$, and its molecule consists of units of this acid combined in the same way as the glucose units of cellulose.

Pectin is widely distributed in plants, especially in fruit juices, and the setting or jellying of jams is due to its presence. It is composed of units of *d*-galacturonic acid, $C_6H_{10}O_7$ (p. 883), and its methyl ester linked in the same way as the mannuronic acid in alginic acid.

Fermentation

The production of intoxicating liquors from various natural sweet substances by the process of fermentation (compare p. 330) has been known from the very earliest times, but it was not until some 150 years ago that Lavoisier showed that, in this process, a sugar is decomposed, roughly quantitatively, into alcohol and carbon dioxide. This result was confirmed by Gay-Lussac some twenty years later, and in 1860 Pasteur proved that small proportions of glycerol, succinic acid, and other substances are also produced ; it is now known that whereas the alcohol, carbon dioxide, and glycerol are formed from the sugar (p. 332), fusel oil and succinic acid are produced from the amino-acids (leucine, *iso*leucine, glutamic acid, pp. 623-625) contained in the yeast, malt, potatoes, or other material, which is used in this process for manufacturing alcohol.

In order that fermentation may take place, the temperature must be kept within certain limits ; there must also be present certain mineral salts, particularly those of potassium and magnesium, sulphates, and phosphates, and some source of combined nitrogen, which serve as food for the yeast organism.

The sugars in the materials generally used for the production of alcohol are sucrose, glucose, and maltose, the last two of which are formed from starch ; it was believed at one time that the disaccharides, sucrose and maltose, must first be hydrolysed to monosaccharides (by invertase and maltase respectively) before they could ferment, but from the results of investigations by Willstätter and his co-workers it would seem this is not so, and that such disaccharides may be directly fermented by particular enzymes.

In addition to the sugars just mentioned, *d*-mannose is fermented by yeast ; *d*-galactose ferments only very slowly at first, but as the

yeast becomes accustomed to this sugar the rate of change increases and ultimately may surpass that of *d*-glucose.

When Fischer prepared new aldoses, which were not known in nature, he investigated their behaviour towards yeast and found that glycerose (p. 862) fermented slowly but that tetroses and pentoses were not attacked ; the new aldohexoses, *l*-glucose, *l*-mannose, and *l*-fructose (p. 864), did not ferment, but *d*-mannononose (p. 320) gave alcohol and carbon dioxide ; mannoheptose and manno-octose, however, were unfermentable. It was thus shown (*a*) that only those sugars containing 3 or a multiple of 3 carbon atoms are acted on by yeast, and (*b*) that, of two enantiomorphously related compounds, only the *one* form ferments. These facts led Fischer to suggest that the sugar, and the enzyme which attacks it, might be compared with a lock and key, since a very slight alteration in the configuration of the one prevents the proper working of the other.

Little progress was made in the investigation of this subject until Buchner showed in 1897–98 that the alcoholic fermentation of certain sugars can take place in the absence of any living yeast cells. By grinding yeast with quartz sand and kieselguhr and submitting the mixture to great pressure, he obtained a yeast extract which was passed through a kieselguhr filter ; although this extract did not contain any living cell, it was capable of bringing about the decomposition of certain sugars into alcohol and carbon dioxide. This important discovery proved that, contrary to Pasteur's views, the presence of a living organism is not essential to fermentation ; although the living cell produces the active agent, the latter works independently. This active agent or *zymase*, a mixture of enzymes, although inanimate, has, as stated above, a highly selective action ; it can only attack a very few of the sixteen optically isomeric aldohexoses. Its action is restricted and specific, and this is true of the numerous other enzymes which are known. These nitrogenous ' organic catalysts ' are usually named after the substance on which they act (the *substrate*), or to which they give rise ; invert*ase* or sacchar*ase* produces invert sugar by the hydrolysis of sucrose ; amyl*ase* hydrolyses starch (amylose), and so on. Further examples of the specific action of enzymes are afforded by the sorbose bacterium (p. 335), which can oxidise to a *ketose*, *l*-arabitol, and *d*-sorbitol, but not xylitol or dulcitol ; by malt*ase* (p. 332), which hydrolyses maltose and α-, but not β-methylglucoside, and α- but not β-biose links of the disaccharides (p. 890) ; by emulsin (p. 354)

or *synaptase*, which hydrolyses the β- but not the α-forms of glucosides, including disaccharides. Many enzymes have now been obtained crystalline and are proteins.

Buchner's discovery, important though it was, threw no light on the mechanism of alcoholic fermentation, and it was not until 1906 that any substantial advance was made. It was then found by Harden and Young that, in the presence of alkali phosphates, the evolution of carbon dioxide from a fermenting sugar is greatly accelerated, and further investigation has proved that a diphosphoric ester of a hexose is produced in the solution ; this ester is derived from *d*-fructose, whether the original sugar is *d*-glucose, *d*-mannose, or *d*-fructose (which may be converted one into the other), and Robison has shown that it is a 1:6-ester of fructose.

In more recent years, owing mainly to the work of Neuberg, Embden, Meyerhof, and others, much has been learned about the mechanism of alcoholic fermentation. It is now known that zymase contains various enzymes, some of which can act only in the presence of *co-enzymes*, formerly known collectively as *co-zymase*.

These co-enzymes are relatively simple substances and unlike the enzymes themselves are not destroyed by heat. One is a phosphate carrier, adenosine triphosphate,[1] (ATP), which gives up a part of its phosphate content to the sugars undergoing fermentation and is thereby converted into adenosine diphosphate, (ADP) ;[1] this latter is reconverted into ATP at a subsequent stage. Another, co-enzyme I or co-zymase, (Co), adenine-nicotinamide dinucleotide[1] is capable of combining with two atoms of hydrogen per molecule to form Co,2H and giving them up again, thus acting as a hydrogen carrier. Aneurin pyrophosphate, co-carboxylase, is mentioned later (p. 1067).

According to current views, the first step (*a*) in the fermentation of glucose is its phosphorylation by ATP :

$$\text{Glucose} + 2\text{ATP} \xrightarrow{(a)} \text{fructofuranose 1:6-diphosphate} + 2\text{ADP};$$

the liberated ADP becomes rephosphorylated at a later stage (*e* and *g*) and is then available for the phosphorylation of more glucose.

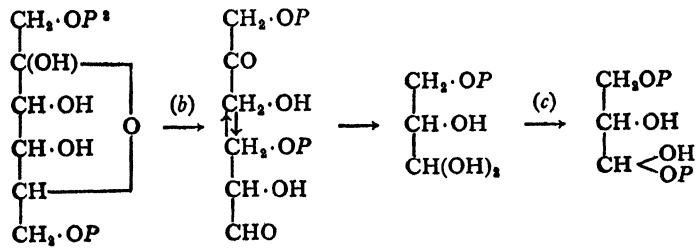
This change, (*a*), actually occurs in three stages :

$$\text{Glucose} \longrightarrow \text{glucopyranose 6-phosphate} \longrightarrow \text{fructofuranose 6-phosphate} \longrightarrow \text{fructofuranose 1:6-diphosphate}.$$

[1] The structures of these compounds are shown in the table, p. 906.

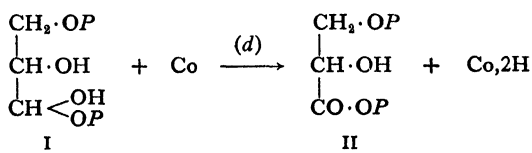
Each stage is brought about by a specific enzyme and the first and last require ATP as co-enzyme.

The next transformation (*b*) is the fission of the fructose diphosphate into (two 3-carbon atom chains of) *triose phosphate*, which consists of an equilibrium mixture of *dihydroxyacetone phosphate* and *glyceraldehyde phosphate*.[1] Both reaction (*b*) and the interconversion of the triose phosphates are catalysed by enzymes.

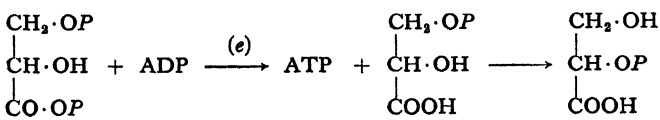


I

In the next stage (*c*), the glyceraldehyde phosphate combines with inorganic phosphate to give a *diphosphate* (I), of the hydrated form, which in the presence of an enzyme and co-zymase, (Co), gives Co,2H and a mixed anhydride of phosphoric acid and glyceric acid phosphate, (II, commonly called 1:3-*diphosphoglyceric acid*):



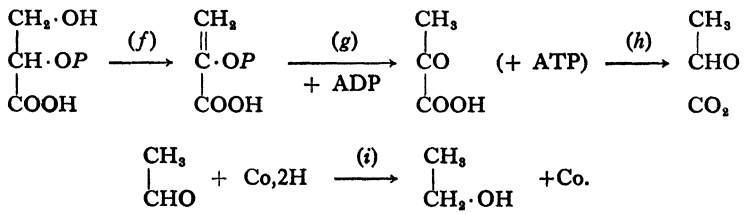
The diphosphoglyceric acid, (II), now loses a phosphate radical to ADP, which is reconverted into ATP and the resulting *glyceric acid β-phosphate* is transformed into the α-ester, both changes being catalysed by enzymes.



[1] These compounds are also called phosphodihydroxyacetone and phosphoglyceraldehyde respectively; the more systematic names are used here and in the following pages.

[2] $P = —OPO(OH)_2$.

The glyceric acid α-phosphate now loses a molecule of water (*f*) and is converted into (*enol*) *pyruvic acid phosphate* : this product then reacts (*g*) with ADP to form pyruvic acid and ATP. Under the influence of an enzyme, *carboxylase*, which requires as co-enzyme aneurin pyrophosphate, the pyruvic acid is converted into acetaldehyde and carbon dioxide (*h*). In the last stage (*i*), reduced co-zymase (Co,2H), produced in reaction (*d*), converts acetaldehyde into alcohol, and the co-zymase returns to (*d*).



These reactions, summarised in the accompanying table, account for about 90% of the products of normal fermentation. The normal yield (2½%) of glycerol (p. 901) can be increased to as much as 37% by the addition of sodium sulphite at the beginning of the process (see table) ; advantage was taken of this fact in Germany during the war of 1914–18, when glycerol was so urgently needed for the manufacture of explosives.

Another variation of the fermentation process can be brought about by the addition of ammonium or potassium carbonate or dipotassium hydrogen phosphate ; acetic acid is then produced, together with glycerol, alcohol and carbon dioxide, as shown in the table (p. 907).

In all these cases glyceraldehyde phosphate may be regarded as the primary and acetaldehyde as the secondary product of fermentation, their fates depending on the conditions.

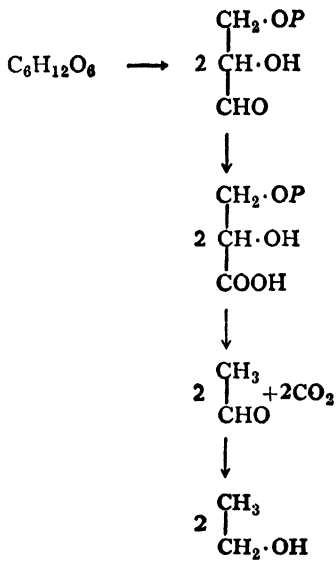
Certain bacteria yield butyric acid and butyl alcohol, and their formation is often accompanied by that of acetone and hydrogen ; a suggested mechanism for these processes is shown in the table.

l-Lactic acid is produced when certain micro-organisms act on glucose, and also by the enzymes of muscle acting on glycogen ; this is an example of asymmetric synthesis (p. 746), common among reactions brought about by enzymes, as the lactic acid is probably formed by the reduction of pyruvic acid by Co,2H.

FERMENTATIONS

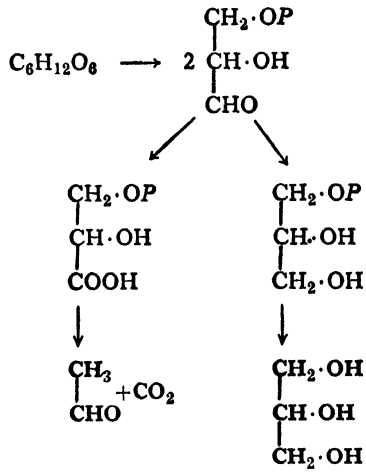
Ethyl Alcohol

$C_6H_{12}O_6 = 2C_2H_5 \cdot OH + 2CO_2$

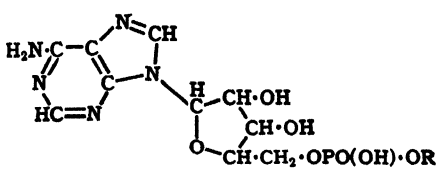


Glycerol

$C_6H_{12}O_6 = C_3H_8O_3 + CO_2 + CH_3 \cdot CHO$



The sodium sulphite, with carbon dioxide, gives bisulphite, which unites with the acetaldehyde; the reaction (*i*) being thus inhibited, the glyceraldehyde phosphate is reduced to glycerol phosphate by Co,2H which itself returns to (*d*); the glycerol phosphate so produced is converted into glycerol by an enzyme.



Adenine Ribose

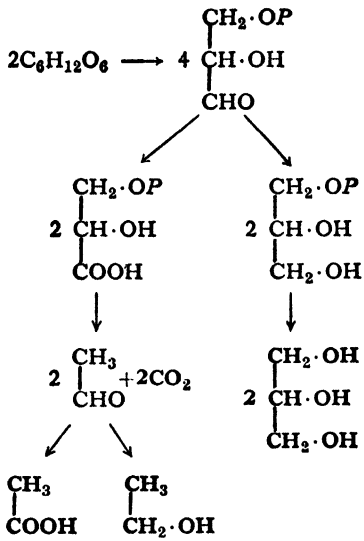
ADP, R = $-PO(OH)_2$

ATP, R = $-PO(OH)\cdot O\cdot PO(OH)_2$

FERMENTATIONS

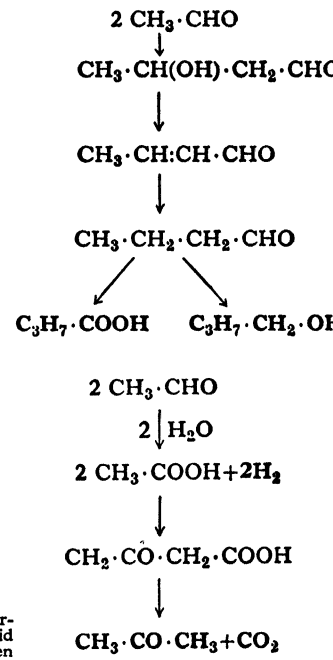
Mixed

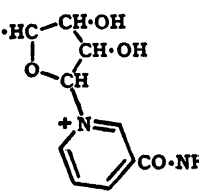
$$2C_6H_{12}O_6+H_2O = 2C_3H_8O_3+2CO_2 +CH_3\cdot COOH+C_2H_5\cdot OH$$



In alkaline solution the acetaldehyde undergoes a Cannizzaro reaction, giving acetic acid and alcohol, and as reaction (*i*) cannot then occur the glyceraldehyde phosphate undergoes the same changes as those shown in the case of the glycerol fermentation.

Butyric Acid, Butyl Alcohol and Acetone



Co-zymase, R = 

At the present time large quantities of sugar are fermented, mainly for the production of yeast, which is required in bread-making; in this operation ammonium sulphate is added to the fermenting liquid, which is vigorously aerated. The result is a very rapid increase in the growth of the yeast, which utilises the ammonium sulphate and the whole of the alcohol, for the formation of protein matter; it is thus possible to manufacture valuable nitrogenous food material from carbohydrates and (synthetic) ammonium salts and at the same time to obtain a supply of carbon dioxide, which is solidified (*dry ice*) and used for refrigerating purposes.

CHAPTER 54

THE MONOCYCLIC TERPENES AND RELATED COMPOUNDS

ALTHOUGH the carbohydrates, the proteins, and the non-volatile fatty glycerides (olive, linseed, palm oil, etc.) form by far the greater part of dry vegetable matter, many plants contain various other types of most interesting compounds; among these are certain volatile, odoriferous liquids, called *essential oils*, most of which occur in the flower, fruit or leaves, possess a pleasant odour or taste, and are used in the preparation of essences and perfumes (p. 949); some of them are also employed in medicine.

A few essential oils have already been mentioned—as, for example, oil of wintergreen (p. 533), oil of mustard (p. 339), oil of bitter almonds (p. 499), and oil of aniseed (p. 503)—and some of their components have been described. Many such oils, however, are complex mixtures of many different types of compounds, the separation and identification of which are tasks of great difficulty; in their investigation, Wallach, Baeyer, Semmler, Perkin jun., Wagner, Ruzicka, and many others have taken part.

A very abundant and well-known, but not a typical, essential oil is the liquid, *turpentine*, which is obtained by making shallow cuts in the bark of pine-trees (coniferae), and collecting the liquid which exudes. Turpentine consists of a solution of various *resins* in liquid *oil of turpentine*; when the crude oil is distilled in steam, 'spirit of turpentine' passes over, leaving a residue of rosin or *colophony* (p. 948).

Spirit of turpentine is a mobile, optically active liquid of sp. gr. about 0·86, boiling from about 155 to 165°; it is, however, a mixture, and shows considerable variations in properties according to the species of pine from which it has been obtained. It has a well-known, rather pungent odour, which is probably not due to its principal component, but to small quantities of substances formed from the latter by oxidation. On exposure to moist air, the oil gradually changes; it darkens in colour, becomes more viscous, and is slowly converted into resinous oxidation products.

Spirit of turpentine is practically insoluble in water, but is

miscible with most organic liquids; it is an excellent solvent for many substances, which are insoluble in water, such as phosphorus, sulphur, and iodine, and it also dissolves resins and caoutchouc; it is used on the large scale in the preparation of varnishes and oil-paints.

The principal component of spirit of turpentine is a hydrocarbon, *pinene*, $C_{10}H_{16}$. This substance occurs not only in all pine-trees, but also in the essential oils of a great many other plants—as, for example, those of eucalyptus, laurel, lemon, parsley, sage, juniper, and thyme. These, and other essential oils, may also contain hydrocarbons, such as *limonene*, *camphene*, etc., which are isomeric with, and more or less closely related to, pinene.

Such hydrocarbons, $C_{10}H_{16}$, obtained from plants, and certain related isomerides, which have been prepared synthetically, are classed together as (true) *terpenes*. Other types of naturally-occurring hydrocarbons, $(C_5H_8)_n$ related to the terpenes, $C_{10}H_{16}$, are classed as *sesquiterpenes*, $C_{15}H_{24}$, or *polyterpenes*, $(C_5H_8)_n$, where $n > 3$; in addition, many derivatives of these hydrocarbons occur in essential oils, and will be considered in due course.

General Properties and Reactions of the Terpenes, $C_{10}H_{16}$

These compounds are mostly highly refractive liquids, readily volatile in steam and having a pleasant odour; their boiling-points range from about 155 to 185°. Most of them are optically active and occur in both *d*- and *l*-forms. They are very reactive, easily oxidised, combine with ozone, and show the general behaviour of unsaturated compounds. Thus, they unite directly with bromine, hydrogen chloride, hydrogen bromide, and nitrosyl chloride, forming additive products, which, as a rule, are crystalline and serve for the isolation and identification of the hydrocarbons. But whereas some of the terpenes combine directly with four atoms of bromine or two molecules of hydrogen bromide, others unite with only two atoms of bromine or one molecule of hydrogen bromide. This behaviour affords strong evidence that the terpenes, $C_{10}H_{16}$, are not *open chain* hydrocarbons; if they were they should unite directly with six atoms of bromine or with three molecules of a halogen acid, because their molecules would contain either three olefinic or one olefinic and one acetylenic binding. They are therefore *cyclic olefines* and are classed in two groups:

I. *Monocyclic di-olefinic* terpenes, which combine with $2Br_2$ or with 2HBr. Limonene, terpinolene, phellandrene, sylvestrene.

II. *Dicyclic mono-olefinic* terpenes, which combine with Br_2 or with HBr. Pinene, camphene, bornylene.

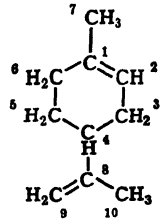
Many other members of each of these types, as well as a few open chain terpenes, $C_{10}H_{16}$ (p. 940), are known.

Important evidence as to the nature of the closed chains in the molecules of the monocyclic terpenes was obtained at a comparatively early stage of their investigation, since it was found that some terpenes and some of their simpler derivatives could be converted into cymene (*p-iso*propylmethylbenzene), $C_{10}H_{14}$; *p*-toluic acid and terephthalic acid could also be obtained from them by oxidation in other ways. It was inferred, therefore, that such terpenes are closely related to cymene—that is to say, that their molecules probably contain the same framework of carbon atoms as that which occurs in cymene. Further investigation, more especially the study of the products of their graded oxidation, served to confirm this view, and, in the course of time, it was proved that some of the terpenes are, in fact, *dihydro*-p-*cymenes*, the structures of which were finally established.

Nomenclature. For the nomenclature of the *monocyclic* terpenes, the fully saturated *cyclo*paraffin, *hexahydrocymene*, $C_{10}H_{20}$, which may be regarded as the parent hydrocarbon, is called p-*menthane*, derived from that of its well-known derivative menthol; the *cyclo*-olefines derived from it are known as p-*menthenes*, $C_{10}H_{18}$, or p-*menthadienes*, $C_{10}H_{16}$, according as their molecules contain one or two ethylenic linkages respectively. Substances of a corresponding type, namely, *o*- or *m*-menthenes, and *o*- or *m*-menthadienes, as the case may be, may also be derived from *o*- and *m*-menthanes.

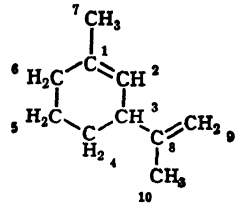
In order to express the structures of the monocyclic terpenes, and those of their derivatives, the carbon atoms of the corresponding parent menthanes are numbered in a conventional manner as shown (p. 912); the presence and positions of the double bonds are then indicated by Δ, with the addition of the numerals of those carbon atoms from which the double binding *starts*, when these atoms are taken in the conventional order (compare pp. 799, 801). Limonene,

for example, is Δ-1:8(9)[1]-*p*-menthadiene, and sylvestrene is Δ-1:8(9)-*m*-menthadiene :



Limonene,
Δ-1:8(9)-*p*-menthadiene

I

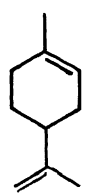


Sylvestrene,
Δ-1:8(9)-*m*-menthadiene

II

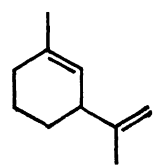
it will be seen that many structurally isomeric *o*-, *m*-, and *p*-menthadienes are theoretically possible.

Formulation. The structures (I) and (II) may also be conveniently represented by, and should be carefully compared with, (III) and (IV) respectively :



Limonene

III



Sylvestrene

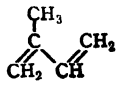
IV

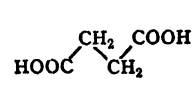
It will then be clear that the C and H symbols, omitted from *both* ends of *every* (single or double) bond in (III) and (IV), can be readily pictured and that the number of hydrogen atoms combined with any carbon atom follows from the quadrivalency of carbon.

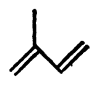
Many other formulae can be conveniently represented in this way ; for open chain compounds a zig-zag framework is used as shown : [2]

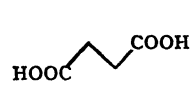
[1] The number in brackets, (9), is to show without ambiguity that the carbon atoms 8 and 9, and not 8 and 4, are united by the olefinic binding.

[2] The angles (about 90°) of the zig-zag are purely arbitrary.







Propane Isoprene Acetone Succinic acid

Here, however, as in all cases, substituents of the parent hydrocarbons are shown (by their symbols with numbers) in the ordinary way; thus although a CH_3— group is shown merely by a line a —CH_2Cl, —$CH_2 \cdot OH$, —COOH, etc., are usually shown in full.

Limonene and its Derivatives

Limonene, $C_{10}H_{16}$ (Δ-1:8(9)-p-*menthadiene*), is a pleasant-smelling, mobile liquid, boiling at 175°.

d-Limonene is found in oil of lemon, orange, caraway, cummin, etc., whereas *l*-limonene occurs in pine-needle oil and in oil of peppermint. *dl*-Limonene occurs in *Oleum cinae* and was named *dipentene* before its relation to the optically active forms was known. Dipentene is formed (as the result of racemisation) when either of the active modifications is heated at 250–300°; it is also produced when pinene (p. 925) is treated in a similar manner, and may be prepared by heating terpineol (p. 917) with potassium hydrogen sulphate.

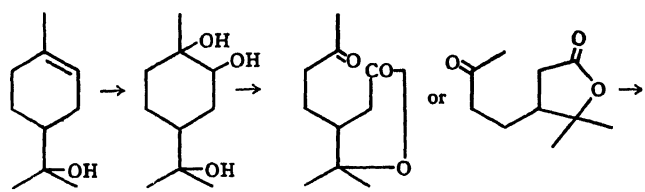
Limonene (*d*- or *l*-) combines with one molecule of hydrogen chloride in the absence of water, giving an optically active *limonene* (*mono*)*hydrochloride* (8-*chloro*-Δ-1-p-*menthene*), $C_{10}H_{17}Cl$,[1] but in the presence of water it unites with two molecules of hydrogen chloride or bromide, and the crystalline products, *limonene dihydrochloride*, $C_{10}H_{18}Cl_2$ and *limonene dihydrobromide*, $C_{10}H_{18}Br_2$, are optically inactive and identical with those obtained from dipentene. Both these compounds exist in *cis*- and *trans*- forms and it is the latter which are produced from limonene; the *cis*-compounds are formed from cineole (p. 918). With bromine the limonenes yield *tetrabromides*, $C_{10}H_{16}Br_4$, which are optically active and melt at

[1] The trivial names of such additive products of the terpenes are generally used, and formulae such as $C_{10}H_{16},HCl$, $C_{10}H_{16},2HCl$, etc., are often employed instead of these given here.

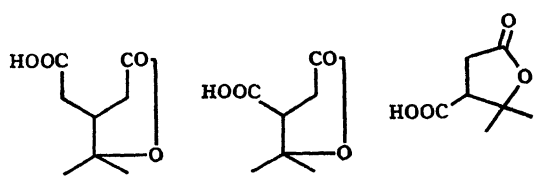
104°, whilst *dipentene tetrabromide* melts at 125° and is, of course, optically inactive.

The limonenes and dipentene also combine directly with nitrosyl chloride, as was first shown by Tilden, giving well-defined crystalline *nitrosochlorides*, $C_{10}H_{16}ONCl$ (p. 923); these compounds may be prepared more easily by treating the terpene with an alkyl nitrite in the presence of hydrochloric acid. Each of the active terpenes gives a mixture of two (α- and β-, or *cis-* and *trans-*) optically active isomeric nitrosochlorides, all of which are bimolecular, and probably contain in their molecules the group $>CH\cdot NO{:}NO\cdot CH<$. In the formation of the mono-hydrochloride, the halogen atom combines with the 8-carbon atom, whereas with nitrosyl chloride the chlorine atom takes up the 1- and the NO-group the 2-position (p. 912).

The structure of limonene is based mainly on the results of the investigation of the oxidation products of *α-terpineol*, $C_{10}H_{18}O$, a compound which is formed, by the addition of the elements of water, when limonene or dipentene is shaken with a 5% aqueous solution of sulphuric acid. With potassium permanganate, terpineol yields *trihydroxyhexahydrocymene*, which, with other oxidising agents, gives *homoterpenylmethyl ketone*, *terpenylic acid* (m.p. 90°), and finally *terebic acid* (m.p. 175°), as shown below:



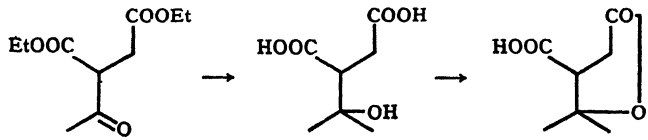
α-Terpineol — Trihydroxy-hexahydrocymene — Homoterpenylmethyl ketone [1]



Terpenylic acid — Terebic acid [1] — Terebic acid [1]

[1] The alternative formulae of homoterpenylmethyl ketone and of terebic acid are merely set out differently.

Terebic acid is the lactone of a hydroxydicarboxylic acid and is formed by the oxidation of *iso*propylsuccinic acid ; its constitution is established by the following synthesis (Simonsen) : Diethyl acetylsuccinate, obtained from ethyl sodioacetoacetate and ethyl chloroacetate, is treated with methyl magnesium iodide (1 mol.) ; the product gives on hydrolysis a hydroxydicarboxylic acid, the lactone of which is terebic acid :



Diethyl acetylsuccinate — Terebic acid

In a similar manner terpenylic acid is formed by the oxidation of β-*iso*propylglutaric acid, and has been synthesised from diethyl β-acetylglutarate [1] with the aid of methyl magnesium iodide.

Now from a general knowledge of the behaviour, on oxidation, of compounds of known constitution (olefines, glycols, ketones, etc.) it is possible, from the structure of terpenylic acid, to deduce that of homoterpenylmethyl ketone and then those of trihydroxyhexahydrocymene, and α-terpineol respectively, as shown above. This is an important example of the use of *graded* oxidation, for the determination of structure.

It is to be noted, however, that the structure of limonene is not completely decided by this series of changes as terpinolene (p. 917) might also give α-terpineol by the addition of water. The optical activity of limonene, however, shows that the double binding which was concerned in the formation of α-terpineol must be 8:9, and not 4:8, in the molecule of the terpene.

The Synthesis of Terpenes

The structures of α-terpineol, and of limonene, having thus been determined with a high degree of probability, were fully established by Perkin, who accomplished *complete syntheses* of these and various other naturally occurring terpenes by the methods given below.

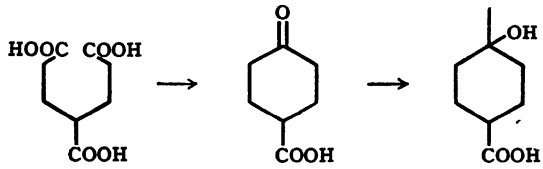
Ethyl cyanoacetate reacts with two molecules of ethyl β-iodo-

[1] β-Acetylglutaric acid is obtained, in the form of a dilactone, when the sodium salt of tricarballylic acid is heated with acetic anhydride.

propionate, in the presence of sodium ethoxide, giving *triethyl 3-cyanopentane-1:3:5-tricarboxylate*,

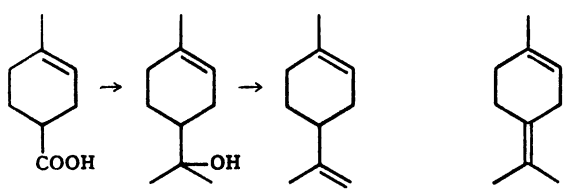
$$CN\cdot CH_2\cdot COOEt + 2CH_2I\cdot CH_2\cdot COOEt + 2NaOEt = CN\cdot C(COOEt)(CH_2\cdot CH_2\cdot COOEt)_2 + 2NaI + 2EtOH;$$

this ester, on hydrolysis with hydrochloric acid, yields *pentane-1:3:5-tricarboxylic acid*, (I), as the group $>C(COOH)_2$, produced by the hydrolysis of the $>C(COOEt)\cdot CN$ complex, decomposes with the loss of carbon dioxide. This acid is converted into *4-keto-hexahydrobenzoic acid*, (II), when it is heated with acetic anhydride, or when its ester is treated with sodium (Dieckmann) and the resulting β-keto-ester is submitted to ketonic hydrolysis. The ethyl ester of (II), treated with methyl magnesium iodide and then with dilute acid, yields the ester of a *hydroxyhexahydro*-p-*toluic acid* (*4-methyl-4-hydroxy*cyclo*hexanecarboxylic acid*, III):



I II III

The last-named hydroxy-compound, (III), gives, with hydrobromic acid, the corresponding bromo-derivative, which, on treatment with pyridine, loses one molecule of hydrogen bromide and is converted into a *tetrahydro*-p-*toluic acid* (*4-methyl-Δ-3-*cyclo*hexenecarboxylic acid*, IV). The *ester* of this acid reacts with methyl magnesium iodide, and when the product is decomposed with dilute acid it gives dl-*α-terpineol*, (V), which is converted into *dipentene* when it is treated with potassium hydrogen sulphate.



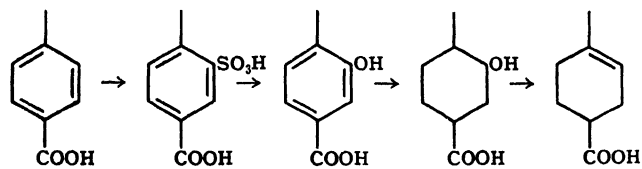
IV V VI VII

α-Terpineol Dipentene Terpinolene

Theoretically, this loss of the elements of water might occur in one of two ways, giving either (VI) or (VII), but as dipentene is a *dl*-mixture it must have a dissymmetric structure and cannot therefore be represented by (VII).

The *dl*-acid, (IV), was resolved with the aid of strychnine or brucine, and the active esters were both prepared; these compounds, treated with methyl magnesium iodide, gave *d*- and *l*-terpineol respectively (Fischer and Perkin, *J.* 1908, 1871).

The preparation of 4-methyl-Δ-3-*cyclo*hexenecarboxylic acid, (IV), as above, was very laborious; later the necessary material for the resolution was obtained by a simpler method: *p*-Toluic acid was sulphonated and the sulphonic acid converted into 3-hydroxy-4-methylbenzoic acid by fusion with potash; this acid was then reduced with sodium and alcohol to the corresponding hexahydro-compound of which the hydroxyl group was displaced by bromine. The product, with pyridine, gave (IV):



The active terpineols melt at 38–40°, boil at 219° and have a very strong smell of hyacinths.

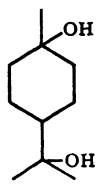
***dl*-α-Terpineol** (Δ-1-p-*menthen*-8-*ol*)[1] melts at 35°; it can be prepared on the large scale by boiling terpin hydrate (p. 918) or dipentene with dilute sulphuric acid and is used in perfumery.

Terpinolene (Δ-1:4(8)-p-*menthadiene*, VII, p. 916), an optically inactive structural isomeride of limonene, is produced when terpineol is dehydrated with alcoholic sulphuric acid or oxalic acid; it occurs in various essential oils, and when treated with acids it undergoes isomeric change, giving 'terpinene,' which is a mixture of various *p*-menthadienes (α or Δ-1:3-, β or Δ-1(7):3-, γ or Δ-1:4-).

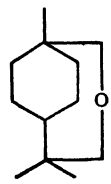
***cis*-Terpin**, $C_{10}H_{20}O_2$ (p-*menthan*-1:8-*diol*), is produced by the addition of the elements of water, when terpineol is shaken with dilute sulphuric acid, and its structure is as shown (p. 918); it may be prepared by treating oil of turpentine (pinene) with dilute sulphuric

[1] β-Terpineol is Δ-8(9)-p-*menthen*-1-*ol* and has not been found in nature.

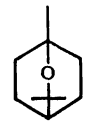
acid and alcohol at ordinary temperatures, as a result of complex changes. It has been synthesised by treating ethyl 4-ketohexahydrobenzoate (cf. II, p. 916), with an excess of methyl magnesium iodide and decomposing the product with water, a method which establishes its constitution. *cis*-Terpin melts at 104°, boils at 258°, and combines readily with water, giving crystalline *terpin hydrate*, $C_{10}H_{20}O_2,H_2O$, which melts at 117°. *trans*-Terpin melts at 158–159° and is formed from *trans*-dipentene dihydrobromide ; it does not unite with water. When *cis*-terpin is dehydrated, terpineol, dipentene, terpinene, terpinolene, and cineole are produced.



Terpin



or



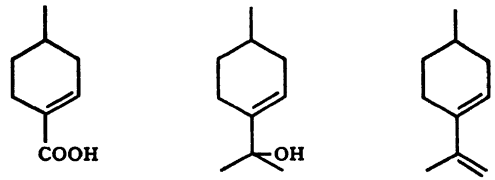
Cineole

Cineole, $C_{10}H_{18}O$, occurs in many oils (eucalyptus, rosemary, etc.) and in *Oleum cinae* ; it boils at 172° and has a camphor-like odour. With phosphorus pentoxide it yields cymene, and with an acetic acid solution of hydrogen bromide it gives *cis*-dipentene dihydrobromide.

Two other *p*-menthadienes may be mentioned. *α-Phellandrene* occurs in both *d*- and *l*-forms in many essential oils ; it is Δ-1:5-*p*-menthadiene, and is very unstable.

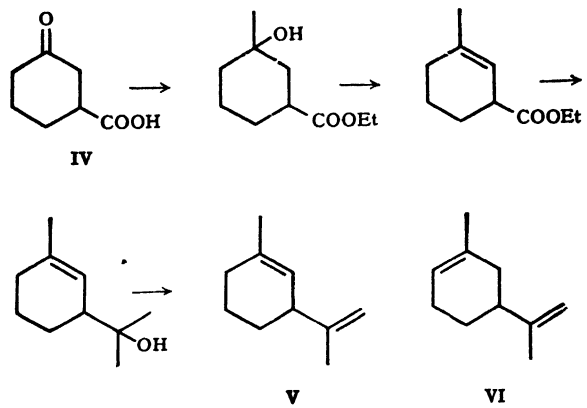
β-Phellandrene is Δ-1(7):2-*p*-menthadiene, and occurs in water-fennel oil.

Terpenes which are not known to occur in nature can also be prepared from the toluic acids (Perkin) : *p*-Toluic acid, for example, is first reduced to *hexahydrotoluic acid*, which is then brominated in the α-position ; the product, treated with quinoline, yields a *tetrahydro*-p-*toluic* acid (4-*methyl*-Δ-1-cyclo*hexenecarboxylic acid*, I), the ester of which, with methyl magnesium iodide, yields Δ-3-p-*menthen*-8-*ol*, (II). This isomeride of terpineol, on dehydration, gives Δ-3:8-p-*menthadiene*, (III), an isomeride of limonene, which has not been discovered in plants. In a similar manner *o*-toluic acid yields an o-*menthenol* and an o-*menthadiene*. A



I II III

m-*menthadiene* has also been synthesised (Perkin) as follows: *m*-Hydroxybenzoic acid is reduced to the hexahydrohydroxy-acid, which is then oxidised to the corresponding keto acid, (IV). The ester of this acid is treated with methyl magnesium iodide in the usual way and is finally converted into a *m*-menthadiene, *carvestrene*, or dl-*sylvestrene*, (V).[1]



IV V VI

Various menthadienes have also been synthesised by Henderson and his co-workers (*J.* 1920, 144).

d-**Sylvestrene** was first obtained from Swedish pine-needle oil prepared from the wood of *Pinus sylvestris*; the oil, treated with hydrogen chloride, gave a crystalline optically active dihydrochloride, from which, with aniline, there was formed a dextrorotatory terpene,

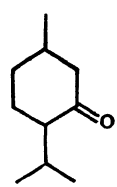
[1] Both sylvestrene and carvestrene probably consist of mixtures of (V) and (VI).

named *sylvestrene* from its origin. It was afterwards shown by Simonsen that *d*-sylvestrene does not actually occur in the essential oil obtained from Swedish turpentine, but that it is formed from a dicyclic terpene, carene (p. 924); when the oil is treated with hydrogen chloride the *cyclo*propane ring undergoes fission, and the dihydrochloride thus obtained gives *d*-sylvestrene, together with dipentene, when it is decomposed with aniline.

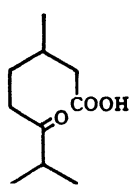
Ketones and Alcohols derived from p-*Menthane*

***l*-Menthone,** $C_{10}H_{18}O$ (p-*menthan*-3-*one*), is one of the numerous components of oil of peppermint, the essential oil of *Mentha piperita*, which also contains menthol, pinene, cadinene (p. 944), and many other compounds It boils at 208°, and its chemical behaviour shows that it is a ketone ; on reduction with sodium and alcohol, it is converted into the secondary alcohol, *menthol*, and on oxidation with permanganate it gives *ketomenthylic acid*, (I), and d-*β-methyladipic acid*, (II).

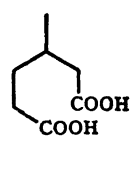
The structures of these products having been determined, that of menthone may be deduced, and is shown below.



Menthone



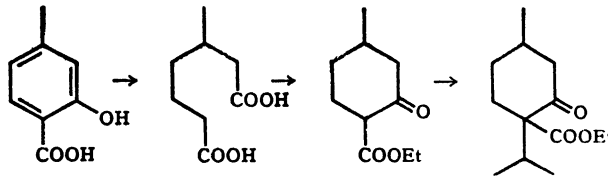
I



II

An optically inactive menthone has been synthesised as follows : 2-*Hydroxy*-4-*methylbenzoic acid*, (III),[1] is reduced with sodium and amyl alcohol to *β-methylpimelic acid*, (IV) :[2] the ester of this acid with sodium ethoxide undergoes the Dieckmann condensation, yielding the *β*-ketonic ester, (V), which on treatment with sodium ethoxide and *iso*propyl iodide gives (VI) ; the ketonic hydrolysis of this ester yields optically inactive menthone, a mixture of *cis*- and *trans-dl*-forms :

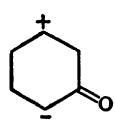
[1] Prepared by treating the sodium derivative of *m*-cresol with carbon dioxide ; compare salicylic acid (pp. 531, 533).
[2] Compare p. 534.



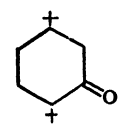
III IV V VI

***l*-Menthol**, $C_{10}H_{19}\cdot OH$ (p-*menthan*-3-*ol*), occurs in oil of peppermint both in the free state and as menthyl acetate, and it is principally to the presence of these compounds that oil of peppermint owes its very powerful odour. Menthol melts at 44° ; on reduction with hydriodic acid, it is converted into hexahydrocymene. On oxidation with chromic acid it yields a mixture of *two* active menthones, because the $>CH—CO—$ group of the latter undergoes keto-enolic change, giving both *cis*- and *trans*-forms of the cyclic ketone. On oxidation with permanganate, however, it gives *keto-menthylic acid* and *β-methyladipic acid*. With some dehydrating agents menthol affords a mixture of isomeric *menthenes*, and with hydrogen chloride it forms *menthyl chloride*. It is used in pharmacy.

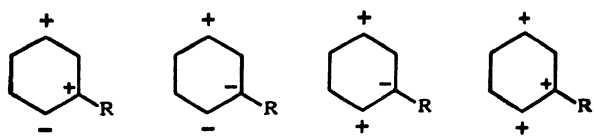
The menthones, menthols and menthylamines furnish interesting examples of stereochemical relationships ; thus, from each of the two (*cis*- and *trans*-) *dl*-menthones, two *dl*-menthols (or *dl*-menthylamines) are derived, as shown below (R=OH or NH_2) for the members of the *d*- *or* the *l*-series : [1]



Menthone (*trans*-)



*Iso*menthone (*cis*-)



Menthol *Neo*menthol *Iso*menthol *Neoiso*menthol

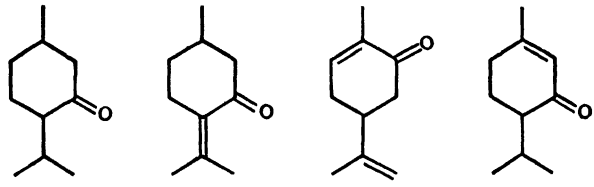
[1] The meaning of the + and − signs in these formulae is explained on p. 718.

***l*-Menthylamine**, $C_{10}H_{19}\cdot NH_2$, is formed, together with three optical isomerides, by heating *l*-menthone with ammonium formate or by the reduction of *l*-menthoxime with sodium and alcohol. It is a strongly basic liquid, and has been much used for the resolution of *dl*-acids.

The four *dl*-menthylamines were first prepared by Kipping and Tutin in 1904 and have since been studied, together with the menthols, by Read. The configurations (p. 921) have been assigned to them from a comparison of their physical and chemical properties with those of similar compounds of known configurations.

It is interesting to note that when *neo*menthol is treated with phosphorus pentachloride or formic acid, a good yield of Δ-3-*p*-menthene is obtained, whereas the stereoisomeric menthol, under the same conditions, gives menthyl chloride or menthyl formate; it is therefore from the compound in which the hydrogen and hydroxyl groups are believed to be in the *trans*-position that water is readily eliminated. Similarly, menthylamine gives menthol with nitrous acid, whereas *neo*menthylamine gives Δ-3-*p*-menthene.

Three other ketones derived from *p*-menthane, namely *pulegone*, *carvone* and *piperitone*, may be mentioned; their structures and their relationship to menthone are shown below:

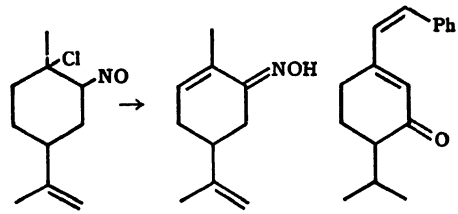


Menthone Pulegone Carvone Piperitone

***d*-Pulegone**, $C_{10}H_{16}O$ (Δ-4(8)-p-*menthen*-3-*one*), occurs in oil of *Mentha Pulegium* (pennyroyal), and boils at 221°. On reduction it yields menthone or menthol, and on oxidation β-methyladipic acid and acetone, reactions which prove its constitution.

***l*-Carvone**, $C_{10}H_{14}O$ (Δ-6:8-p-*menthadien*-2-*one*) occurs in caraway oil, spearmint oil, etc., and boils at 230°. With phosphorus pentoxide it is readily converted into carvacrol (hydroxycymene) by isomeric change, a fact which shows that the carbonyl is in the *o*-position to the methyl group.

When limonene nitrosochloride (p. 914) is treated with alcoholic potash it is converted into *carvoxime*, with the elimination of hydrogen chloride and the conversion of the group $>CH\cdot NO$ into the oximino-group $>C{=}NOH$:



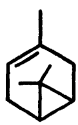
Limonene nitrosochloride — Carvoxime — Benzylidene-piperitone

***l*-Piperitone** occurs in eucalyptus oils. It gives thymol on oxidation with ferric chloride and menthone or menthol on reduction. It condenses with benzaldehyde to give the benzylidene derivative (above), a very interesting example of the activation of a methyl group which is united to a carbon atom conjugated with a carbonyl radical. It is also to be noted that pulegone, carvone and piperitone are all $\alpha\beta$-unsaturated ketones and behave as such towards, for example, hydroxylamine (p. 825).

CHAPTER 55

DICYCLIC TERPENES AND RELATED COMPOUNDS

THE dicyclic terpenes, $C_{10}H_{16}$, as already stated (p. 911), combine with one molecule of bromine or hydrogen bromide only and are bridged ring structures (p. 819) which contain one olefinic binding. One of the closed chains always consists of six carbon atoms but the other may contain three, four or five atoms only. Those which form the *cyclo*propane or *cyclo*butane rings (carene, pinene) are in a condition of strain (p. 789) and consequently may readily undergo fission.



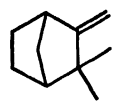
Carene



α-Pinene



Bornylene



Camphene

The dicyclic terpenes and their derivatives are usually known by their trivial names, as those based on the system applied to bridged rings in general (p. 819) are too cumbersome.[1]

The chemistry of the dicyclic terpenes and their derivatives is much more difficult than that of the monocyclic compounds, as will be seen from the account given later of the behaviour of some of the more important members of this group ; some of the changes which these compounds undergo are very remarkable, one of the rings undergoing fission, giving products, which sometimes pass again into bridged ring structures of a different kind. Owing to such transformations, at one time quite novel and unexpected, the determination of the constitutions of the dicyclic terpenes was a task of great difficulty and was only accomplished by the work of many chemists, not only on the terpenes themselves, but on many related compounds, particularly camphor.

[1] α-Pinene, for example, is 1:3-endo*dimethylmethylene*-4-*methyl*-Δ-4-cyclo*hexene* or 2:6:6-*trimethyl*-1,1,3-dicyclo-Δ-2-*heptene*, and camphor is 1:4-endo*dimethylmethylene*-1-*methyl*cyclo*hexan*-2-*one* or 1:7:7-*trimethyl*-1,2,2-dicyclo*heptan*-2-*one*.

Pinene

α-Pinene, $C_{10}H_{16}$, is the most abundant and important dicyclic terpene, and its separation from turpentine, in a crude form, has been described. The oils from some varieties of pine are dextrorotatory, others laevorotatory, and the isolation of optically pure *d*- or *l*-pinene is a task of great difficulty.

dl-Pinene is obtained from the nitrosochloride (below) by treatment with aniline and is a mobile liquid of sp. gr. 0·858 at 20°, having an odour of ' turpentine.' It boils at 155–156°, and is readily volatile in steam.

Pinene combines directly with two atoms of bromine, giving a crystalline *dibromide*, $C_{10}H_{16}Br_2$, which when heated alone, at a moderately high temperature, is converted into cymene and hydrogen bromide. Cymene is also produced, together with various other hydrocarbons, when pinene is heated with iodine. In light petroleum solution at −70°, pinene forms, with dry hydrogen chloride, a crystalline *pinene hydrochloride*,[1] $C_{10}H_{17}Cl$; this compound gives pinene on treatment with alcohol at a very low temperature, but at −10° it passes into an isomeric hydrochloride, *bornyl chloride*, which is formed directly from pinene and dry hydrogen chloride at ordinary temperatures (p. 934). With moist hydrogen chloride, *dipentene dihydrochloride* is formed, the *cyclo*butane ring undergoing fission.

Pinene also combines directly with nitrosyl chloride, giving a crystalline dl-*pinene nitrosochloride*, $C_{10}H_{16}ONCl$, which is probably bimolecular in the solid state (compare limonene nitrosochloride, p. 914). The active nitrosochlorides are very much more soluble than the *dl*-form and so the latter separates first when a mixture containing both *d*- and *l*-pinene is treated with nitrosyl chloride; it serves for the preparation of the pure *dl*-compound.

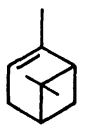
When pinene is heated at 250–270° it yields dipentene; with sulphuric acid in alcoholic solution at ordinary temperatures, it gives α-terpineol, and with dilute nitric and sulphuric acids, terpin hydrate. When heated with organic acids it yields esters of borneol and *iso*borneol (p. 932), from which camphor can be obtained.

Pinene readily undergoes oxidation, yielding various compounds, the simpler of which are *p*-toluic, terephthalic, terpenylic, and terebic acids (p. 914). In moist air in sunlight it gives *sobrerol* or

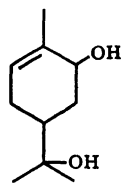
[1] Compare pp. 930, 933.

pinol hydrate, $C_{10}H_{16}(OH)_2$, which, treated with dilute mineral acids, is converted into *pinol*, $C_{10}H_{16}O$.

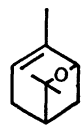
The formation from pinene of cymene and of various other compounds obtainable from limonene, including the two aliphatic acids named above, seemed to show that pinene and limonene were closely related in structure, and various formulae were suggested for the former in accordance with this view. Finally, from a study of the first oxidation products of pinene, sobrerol and pinol, Wagner, in 1894, concluded that the terpene must be represented by the structure already given, and is related to sobrerol and pinol as shown below:



Pinene

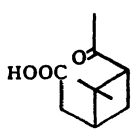


Sobrerol

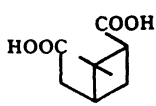


Pinol

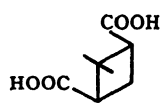
This conclusion was confirmed by Baeyer: Pinene, on careful oxidation with potassium permanganate, is converted into *α-pinonic acid*, which, on treatment with an alkali hypobromite, gives *pinic acid*; this product, on further oxidation by indirect methods, is converted into cis-nor*pinic acid*[1] (*dimethylcyclobutanedicarboxylic acid*), a very stable compound which resists further oxidation. A synthesis by Kerr (*J. Am. Chem. Soc.* 1929, 614) confirmed Baeyer's formula for *nor*pinic acid.



Pinonic acid



Pinic acid



*Nor*pinic acid

Accompanying α-pinene in most of the turpentine oils, there is found a variable and small proportion of a closely related terpene, l-*β-pinene*; in the molecule of this compound the group, $\geqslant C—CH_3$,

[1] The prefix *nor* generally, but not invariably, indicates the next lower homologue of some fairly well-known compound.

of pinene becomes $>C{=}CH_2$ and the 6-carbon atom ring does not contain any olefinic binding, but the *cyclo*butane structure remains as before.

Of the other dicyclic terpenes, shown on p. 924, bornylene and camphene will be briefly described when the chemistry of camphor has been considered.

Camphor and its Derivatives

***d*-Camphor**, $C_{10}H_{16}O$, is a component of oil of camphor, and is obtained from the wood of the tropical camphor-tree (*Cinnamomum camphora*), by distillation in steam.

It is a soft, crystalline solid, melting at 178–179°, and boiling at 209° ; it is very volatile, sublimes readily even at ordinary temperatures, and has a highly characteristic smell. It is only sparingly soluble in water, but sufficiently so to impart to the solution a distinct taste and smell (*Aqua camphorae*), and it dissolves readily in alcohol and most ordinary organic solvents. It is used in medicine, in the manufacture of xylonite or celluloid, and also in the preparation of a few explosives ; in the laboratory it is employed in the determination of molecular weights.

l-Camphor also occurs in certain essential oils ; a mixture of the *d*- and *l*-forms is manufactured from oil of turpentine (p. 930).

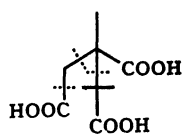
Camphor is a saturated ketone, and its molecule contains the group $—CH_2—CO—$, as is proved by the following reactions : It is reduced by sodium and alcohol, giving two stereoisomeric secondary alcohols, borneol and *iso*borneol (p. 932), from which it is formed by oxidation. It reacts with hydroxylamine, giving *camphoroxime* (m.p. 119°), and, when treated with *iso*amyl nitrite and sodium ethoxide, it affords syn- and anti-iso*nitroso*-derivatives, $—C(:N\cdot OH)—CO—$, which are converted into a diketone, *camphorquinone*, —CO—CO—, by boiling dilute sulphuric acid. With chlorine and with bromine it gives, in the first place, stereoisomeric monohalogen compounds, —CHX—CO—.

Sodiocamphor, $—CH{=}C(ONa)—$, reacts with esters of formic acid, giving an acidic substance, *hydroxymethylenecamphor*, $—C(:CH\cdot OH)\cdot CO—$ or $—C(CHO){:}C(OH)—$,[1] which *condenses* with primary and secondary bases and has been utilised for the

[1] The complete formulae of all these derivatives can be obtained from that of camphor (p. 928), since only the $—CH_2—CO—$ group of this compound undergoes change in the reactions just mentioned.

resolution of *dl*-compounds of such types. Some other camphor derivatives are mentioned later (p. 931).

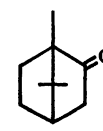
When camphor is heated with iodine, it is converted into carvacrol, and when it is distilled with phosphorus pentoxide, it is transformed into *p*-cymene, reactions which seemed to give important clues to its structure, but as it could also be changed into *m*-cymene, *m*-xylene, *p*-acetyl-*o*-xylene, and other benzene derivatives, such indications had to be accepted with caution. The determination of the constitution of camphor was, in fact, a problem of very great difficulty ; during a period of more than twenty years, many formulae were assigned to it only to be discarded as further experimental data were accumulated. Although few of the derivatives just mentioned had been prepared in those days, it was known that camphor could be oxidised by boiling nitric acid, giving a dicarboxylic acid, d-*camphoric acid*, $C_{10}H_{16}O_4$, which was easily converted into its anhydride ; on further oxidation, this dicarboxylic acid gave a tricarboxylic acid, *camphoronic acid*, $C_9H_{14}O_6$, but for a long time no conclusive evidence as to the structures of these compounds could be obtained. In 1893, however, Bredt found that when camphoronic acid is heated slowly it decomposes into carbon dioxide, water, carbon, *iso*butyric acid, and *trimethylsuccinic acid* ; from this result he deduced for camphoronic acid, camphoric acid, and camphor respectively the structures shown below :



Camphoronic acid [1]



Camphoric acid

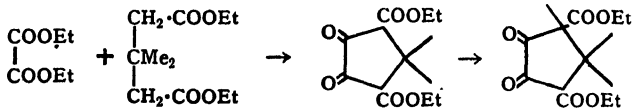


Camphor

The synthesis of camphoric acid by Komppa in 1903 fully established Bredt's formula, and was accomplished as follows : 5:5-Dimethyldihydroresorcinol, prepared by the method already described (p. 800, and therefore obtainable from its elements), is treated with an alkaline solution of sodium hypobromite, whereby it is converted into bromoform and *ββ-dimethylglutaric acid.* The ester of this acid, (I), condenses with diethyl oxalate in the presence of sodium ethoxide, yielding the (di-)β-ketonic ester, (II), which is treated

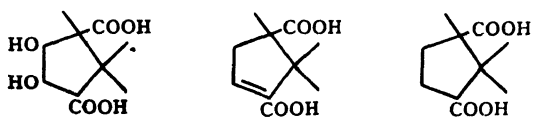
[1] The dotted lines indicate the various points at which the molecule seemed to undergo fission.

with sodium and methyl iodide. The oil thus produced is a mixture of the monomethyl, (III), and dimethyl derivatives, with the unchanged compound; when it is extracted with dilute sodium carbonate solution the inert dimethylated product is left undissolved. The extract contains the sodium derivatives of the enolic forms of (II) and (III); these are separated by making use of the fact that the copper derivative of the methylated product, (III), only is soluble in ether.



I II III

From this soluble copper salt the ester is regenerated and reduced in alkaline solution, when it gives an alkali salt of (IV), the ester having undergone hydrolysis. Hydriodic acid and red phosphorus convert (IV) into (V), which is treated first with hydrobromic acid and then with zinc-dust and acetic acid. The product, (VI), is an oil, which must have the given constitution, whatever the position of the double bond in (V), or that of the bromine atom in the hydro-

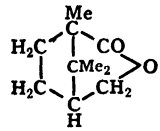


IV V VI

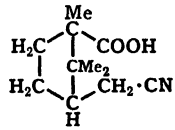
bromide; it is a mixture of *cis-* and *trans-dl*-camphoric acids and is separated into its components by heating it with acetyl chloride, when only the *cis*-form gives an anhydride. On hydrolysis, this anhydride gives *cis-dl*-camphoric acid, which is resolved with the aid of cinchonidine. Another synthesis of *d*-camphoric acid, by a different method, was accomplished by Perkin and Thorpe, almost at the same time as that of Komppa.

Camphor can be obtained from camphoric acid: Camphoric anhydride, treated with sodium amalgam and water, is reduced to *campholide*, (VII), which, when heated with potassium cyanide, gives the cyano-acid, (VIII); from this compound, by hydrolysis,

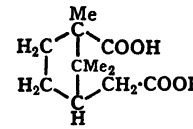
homocamphoric acid, (IX), is obtained, and the destructive distillation of the calcium salt of this acid gives camphor :



VII



VIII



IX

The conversion of camphoric anhydride into campholide might occur in two ways, either as shown above (which is actually the case), or by the reduction of the other carbonyl group. This synthesis, therefore, is not by itself a complete proof of the structures of campholide and the first two substances obtained therefrom ; but as camphor gives carvacrol with iodine, the methyl group must be attached to the carbon atom α to the carbonyl group in camphor, and the above reactions, therefore, take place as shown.

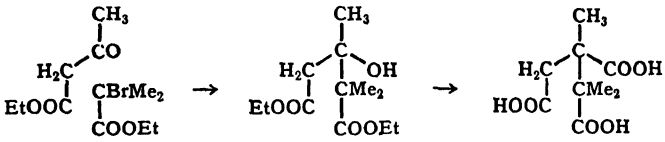
Commercial Preparation of Camphor from Pinene. Pinene, from oil of turpentine, saturated with hydrogen chloride at 0°, yields *bornyl chloride* (p. 933), which, heated with sodium acetate and acetic acid, is converted into iso*bornyl acetate*. *Iso*borneol, prepared by the hydrolysis of the acetate, on oxidation with chromic acid, is transformed into camphor. Pinene also gives camphene when its vapour is passed over a heated catalyst ; camphene can then be converted into bornyl acetate and hence into borneol and camphor.

It was thought at one time, before pinene hydrochloride (p. 925) was known, that in the formation of bornyl chloride a molecule of hydrogen chloride was merely added to that of pinene without the occurrence of any other change, and the product was therefore misnamed ' pinene hydrochloride ' ; it was also called ' artificial camphor ' because it resembled camphor in smell and in other outward properties.

*cis-d-***Camphoric acid**, $C_{10}H_{16}O_4$ (p. 928), crystallises very readily, melts at 187°, and when heated alone, or with acetyl chloride, is converted into its anhydride (m.p. 221°). The formula, (VI, p. 929), shows that four optically active forms (*d-* and *l-cis-*, and *d-* and *l-trans-*camphoric acid), as well as two *dl*-modifications, should be obtainable ; all of these are known.

*d-***Camphoronic acid**, $C_9H_{14}O_6$ (p. 928), melts at 137°, is readily soluble in water and when strongly heated is decomposed into

trimethylsuccinic acid, *iso*butyric acid, carbon dioxide, water, and carbon, as already stated (p. 928). *dl*-Camphoronic acid has been prepared synthetically (Perkin and Thorpe). Ethyl acetoacetate condenses with *ethyl bromoisobutyrate* in the presence of zinc (Reformatsky reaction) to form, after treatment with dilute acid, *diethyl β-hydroxy-αaβ-trimethylglutarate*, (I). The hydroxyl group in this ester is first displaced by chlorine, with the aid of phosphorus pentachloride, and the halogen atom is then displaced by a —CN group with the aid of potassium cyanide ; the product, on hydrolysis, yields *dl*-camphoronic acid, (II) :



I II

As might have been anticipated, these changes proved exceedingly difficult to carry out ; (I) and the corresponding chloro-acid readily lose the elements of water or hydrogen chloride respectively, giving *αaβ*-trimethylglutaconic acid, and the yield of the cyanide, even under special conditions, was very bad.

Camphorsulphonic acids. Various optically active sulphonic acids have been obtained from camphor and from its monohalogen derivatives, and as these compounds are strong acids, the salts of which usually crystallise very readily, they have often been used in the resolution of *dl*-bases (pp. 762, 767, 773).

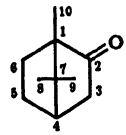
***d*-α-Chloro-** and ***d*-α-bromo-camphor-π-sulphonic acids**, $C_{10}H_{14}OX \cdot SO_3H$, are obtained by the sulphonation of the *a*-halogen derivatives ; they are crystalline and give well-defined *sulphonyl chlorides*, *sulphonyl bromides*, and *sulphonamides*. On reduction, the α-bromo-acid gives *d-camphor-π-sulphonic acid*, whereas the direct sulphonation of *d*-camphor with anhydrosulphuric acid yields the *dl-π*-sulphonic derivative. When gently heated the α-halogen-*π*-sulphonyl halides are decomposed, with the evolution of sulphur dioxide, giving *απ*-dihalogen derivatives of camphor.[1]

[1] The halogen derivatives, $C_{10}H_{14}OX_2$, obtained from the sulphonyl halides, $C_{10}H_{14}OX \cdot SO_2X$, were distinguished by the letter *π* (before their structures were known), because of their *pyrogenic* origin : hence the acids from which they were formed were classed as *π*-acids (Kipping and Pope).

All these compounds contain the group —CHX—CO—, and in the presence of alkalis they give solutions of *cis-* and *trans-*isomerides, as the result of a tautomeric change (p. 835). d-*Camphor-β-sulphonic acid* (Reychler's acid) is easily obtained by treating camphor with sulphuric acid in acetic anhydride solution; in aqueous solution it gives $[M]_D$+51·7°.

It is interesting to note that the sulphonic group of the π-acids has displaced a hydrogen atom of one of the twin or *gem*-dimethyl groups of camphor, whereas, in Reychler's acid, hydrogen from the solitary methyl group is displaced.

Nowadays the positions of substituents in the camphor molecule are often indicated by numerals; it will be seen from the numbered formula that the letters α, β and π correspond respectively with 3, 10 and 8 (or 9):



***d*-Borneol**, $C_{10}H_{17}\cdot OH$, occurs as *bornyl acetate* in many essential oils, as, for example, in those of thyme, valerian, and pine-needle, and, in a free condition, in the oils of spike and rosemary; its principal source, however, is *Dryobalanops aromatica*, a tree growing in Borneo and Sumatra. *l*-Borneol occurs in baldrian oil.

d-Borneol can be obtained, together with *iso*borneol, by reducing *d*-camphor with sodium and alcohol; it is also formed when bornyl magnesium chloride is treated with oxygen, and the product is decomposed with a dilute acid. It is rather like camphor in outward properties, but is more distinctly crystalline, and, although it has an odour recalling that of camphor, it also smells faintly of peppermint. It melts at 208°, boils at 212°, and is readily volatile in steam.

Borneol is a secondary alcohol; when treated with phosphorus pentachloride, it is converted into a mixture of *bornyl* and iso*bornyl chlorides*, and when this product is heated with aniline, it gives *camphene*, with the elimination of the elements of hydrogen chloride (p. 934).

***Iso*borneol**, $C_{10}H_{17}\cdot OH$, is a stereoisomeride of borneol, the secondary alcohol group in conjunction with the rigid ring structure

giving rise to *cis*- and *trans*-forms (compare p. 821). It melts at 217° and resembles borneol in physical and chemical properties, but it has not been found in nature.

Bornyl chloride and *iso*bornyl chloride are related in the same way as the alcohols.

Other Dicyclic Terpenes

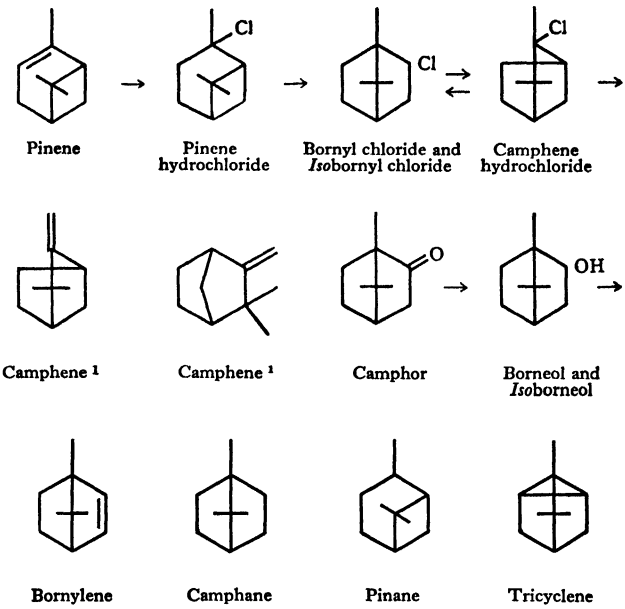
Bornylene, $C_{10}H_{16}$, is a dicyclic terpene (p. 934) closely related to camphor and the stereoisomeric borneols, and is formed by heating bornyl iodide with alcoholic potash. It melts at 133° and on oxidation with nitric acid it gives camphoric acid ; it does not occur in nature.

Camphene, $C_{10}H_{16}$, is a dicyclic terpene (m.p. 51°) which is found in a number of essential oils (ginger, citronella, spike, valerian oil), either in the *d*-, *l*-, or *dl*-form. It is formed when bornyl or *iso*bornyl chloride is warmed with aniline, or heated at 200° with sodium acetate and glacial acetic acid, and it may also be obtained by heating borneol with potassium hydrogen sulphate ; from the formulae on p. 934, it will be seen that these reactions involve changes in the cyclic structures (Wagner-Meerwein rearrangement, p. 849).

Camphene unites directly with one molecule of hydrogen chloride, forming *camphene hydrochloride*, $C_{10}H_{17}Cl$, which is unstable and passes into *iso*bornyl chloride (p. 934). It is much more stable than pinene, and is only oxidised with difficulty, giving many products, among others camphor, the formation of which involves complex changes.

The structural relationships of the more important dicyclic terpenes and a few of their derivatives are shown on p. 934, and it will be seen that the bridged rings in these compounds sometimes undergo unusual changes, which are all the more noteworthy because they take place in solution at ordinary temperatures.

Pinene hydrochloride, prepared at −70° (p. 925), undergoes a remarkable transformation in solution even at −10°, and passes into bornyl chloride, which is therefore easily obtained by treating pinene, dissolved in chloroform, with hydrogen chloride at 0°. Bornyl chloride at 130°, in chlorobenzene solution, gives a small proportion of *iso*bornyl chloride, which, in its turn, is very partially converted into camphene hydrochloride ; on the other hand, the



last-named compound, prepared from camphene (p. 933), passes into *iso*bornyl chloride rapidly and almost completely, when it is merely dissolved in cresol, and a large proportion of the *iso*-compound is then slowly transformed into bornyl chloride. In solution, therefore, there is an equilibrium mixture of the three compounds, bornyl chloride, *iso*bornyl chloride, and camphene hydrochloride, of which, at ordinary temperatures, the bornyl chloride is by far the largest component (Meerwein and Emster, *Ber.* 1922, 2520).

Many of the monocyclic terpenes have been converted into saturated substituted *cyclo*paraffins by reduction under suitable conditions. Limonene (p. 913), for example, has been reduced to hexahydro-*p*-cymene (*p*-menthane) with hydrogen and a nickel catalyst, and phellandrene gives a mixture of *p*-menthane and *p*-menthene with colloidal palladium. Dicyclic terpenes can be similarly reduced to saturated bridged ring structures ; bornylene, for example, with nickel and hydrogen, gives *camphane*, and cam-

[1] These two formulae for camphene represent identical structures which are merely set out differently.

phene gives iso*camphane*, a saturated hydrocarbon which corresponds with camphene in structure. Pinene, in contact with palladium black at 190–200°, in an atmosphere of carbon dioxide, is converted into a mixture of cymene and *pinane*,

$$2C_{10}H_{16} = C_{10}H_{14} + C_{10}H_{18}.$$

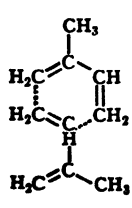
Tricyclene (p. 934) is an interesting example of a saturated tricyclic hydrocarbon ; it does not occur in nature but has been obtained from various terpene derivatives. It has also been prepared by the oxidation of camphor hydrazone with mercuric oxide ; on reduction, using a nickel catalyst, it is converted into *iso*camphane.

The mono- and di-cyclic terpenes and some of their derivatives, which have been described above, are merely the more important representatives of those particular types of naturally-occurring compounds. It is interesting to note that all, or nearly all, these optically active substances occur in nature in both the *d*- and the *l*-form, whereas in the case of the sugars and optically active alkaloids only the one enantiomorph, either *d*- or *l*-, is found in the vegetable kingdom.

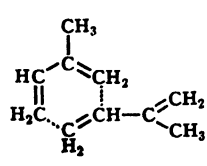
Isoprene Theory

In addition to the foregoing mono- and di-cyclic compounds, $C_{10}H_{16}$, various other classes of terpenes are known, namely open chain terpenes, $C_{10}H_{16}$ (p. 940), and sesquiterpenes, $C_{15}H_{24}$ (p. 943), as well as numerous derivatives of each type. All the parent hydrocarbons have the empirical formula C_5H_8, and, as suggested by Wallach during his long study of the sesquiterpenes, they may all be regarded as derived from isoprene.

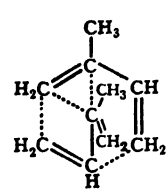
Thus, by some unknown mechanism, two molecules of isoprene might give rise to a *p*-menthadiene, (I), such as limonene, terpinolene, etc. ; to a *m*-menthadiene, (II), such as carvestrene ; or to a dicyclic terpene such as pinene or bornylene, (III).



I

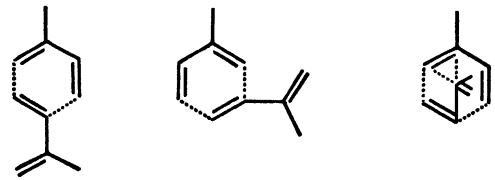


II



III

The dotted lines indicate where combination might occur, followed of course by a redistribution of some of the hydrogen atoms and the olefinic links, and with the simplified formulae (p. 912) these hypothetical syntheses may be expressed as follows :



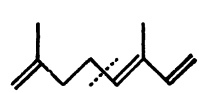
Now it is known that isoprene can be obtained by heating dipentene at about 300° (as also by the destructive distillation of rubber, p. 970), and it has been proved that isoprene, treated with a little sulphuric acid in acetic acid solution, gives cyclic (α-terpineol, cineole) and open chain (geraniol, linalool, p. 941) terpene derivatives. In spite of such facts it seems to be unlikely that this diolefine is really the starting-point in the natural production of terpenes and their derivatives, since isoprene is not known to occur in plants; other views have therefore been advanced (p. 942).

Nevertheless Wallach's hypothesis is of very considerable aid in memorising the formulae of the various types of terpenes and their derivatives, as well as those of related substances such as natural rubber, the carotenoids (p. 972), etc. It has also been employed in deciding between various possible formulae for a natural product (pp. 945, 974). Some of its applications are given below.

From isoprene, by a head-to-tail union [1] of two molecules, the structures of many open chain (*acyclic*) terpenes, such as ocimene and myrcene and related compounds such as citral (p. 940), are easily derived :

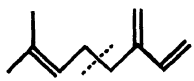


Isoprene

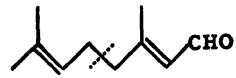


Ocimene

[1] Isoprene is 2-methylbutadiene and the ' head ' is the 1-carbon atom.

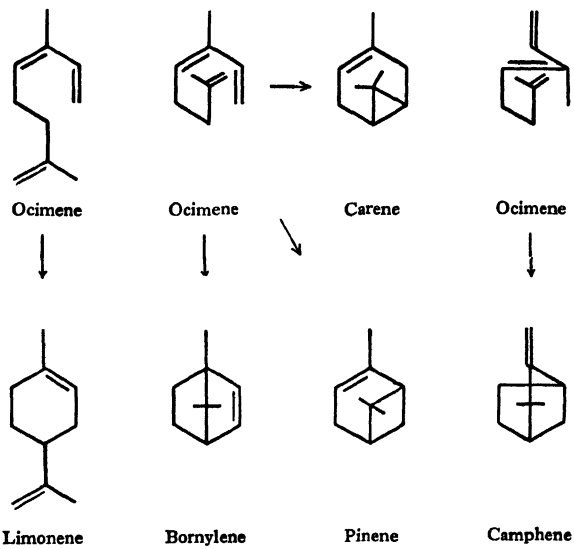


Myrcene

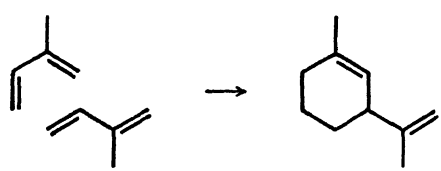


Citral

By curling the formula of, say, ocimene in various ways the carbon skeletons of numerous monocyclic terpenes, such as limonene, and of dicyclic terpenes such as bornylene, pinene, etc., are obtained :



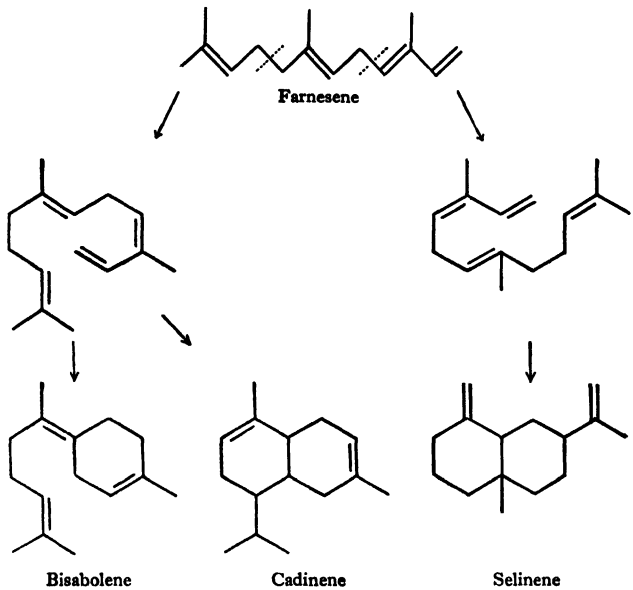
In the case of the *m*-menthadienes the union is tail-to-tail,



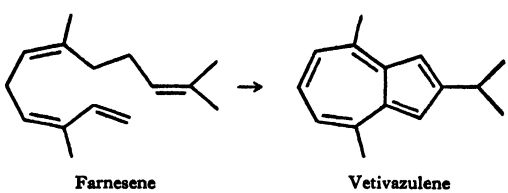
Sylvestrene

The addition of a third isoprene molecule to ocimene, again head-to-tail, gives the structure of an acyclic sesquiterpene such as

farnesene and by curling this in various ways the different groups of mono- and di-cyclic sesquiterpenes (p. 943) are produced :



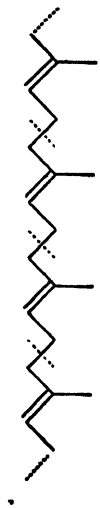
Another arrangement of farnesene gives vetivazulene (p. 954),



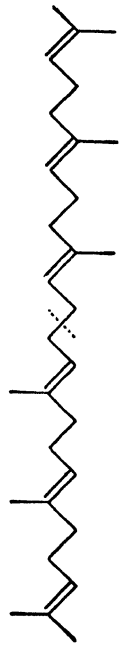
If now a fourth isoprene skeleton is added to farnesene in the same head-to-tail manner, the skeleton of phytol (p. 1083), a reduced diterpene alcohol, is obtained while rubber is represented by an extended isoprene chain. Squalene, a dihydro*tri*terpene (p. 948), is made up of two farnesene skeletons joined tail-to-tail and a similar union of two phytol molecules gives lycopene (p. 972) :



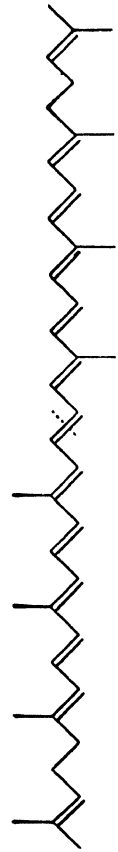
Phytol



Rubber



Squalene



Lycopene

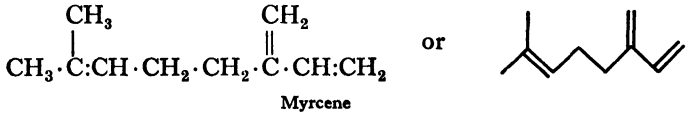
CHAPTER 56

OPEN CHAIN TERPENES AND SESQUITERPENES

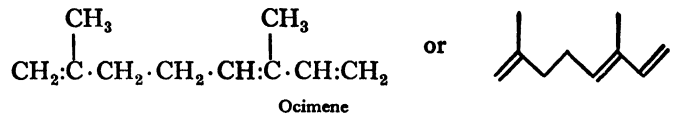
Open Chain Terpenes

COMPARATIVELY few open chain terpenes, $C_{10}H_{16}$, are known, but many of their derivatives occur in essential oils and are of commercial importance in the perfume industry.

Myrcene, $C_{10}H_{16}$ (b.p. 166°), occurs in bay oil and **ocimene**, $C_{10}H_{16}$ (b.p. 177°), in the oil of *Ocimum basilicum*; both are open chain tri-olefinic terpenes and are respectively represented by the following formulae:



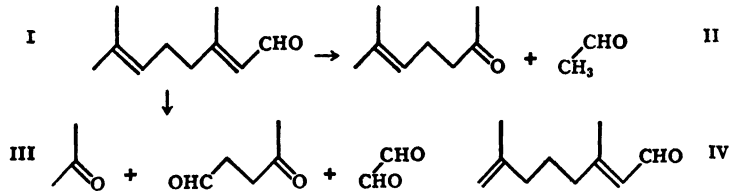
Myrcene



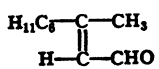
Ocimene

Both hydrocarbons are reduced to dihydro-derivatives by sodium and alcohol by the addition of two hydrogen atoms to the ends of the conjugated system.

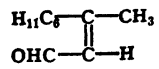
Citral, $C_{10}H_{16}O$, occurs in many essential oils, particularly in lemon-grass oil, of which it forms about 80%. It is a liquid, having a pleasant odour of lemons, and can be distilled under reduced pressure. It combines directly with sodium hydrogen sulphite, and when heated with potassium hydrogen sulphate it yields cymene. When boiled with alkalis it yields *2-methyl-Δ-2-hepten-6-one*, and acetaldehyde, (II), and on oxidation with permanganate, followed by chromic acid, it gives acetone, and oxalic acid; when submitted to ozonolysis it yields acetone, laevulic aldehyde, and probably glyoxal, (III). These, and other results prove that citral has the constitution, (I); later, formaldehyde was also found among the products of ozonolysis and it was therefore inferred that the natural oil contains a structural isomeride, (IV):



Crude citral was therefore regarded as a mixture of (I) and (IV), each of which exists in *cis*- and *trans*-forms ; these four components are *geranial* or *citral a* (*cis*-2:6-dimethyl-Δ-1:6-octadien-8-al) and *neral* or *citral b* (*trans*-2:6-dimethyl-Δ-1:6-octadien-8-al) and the corresponding Δ-2:6-isomerides :



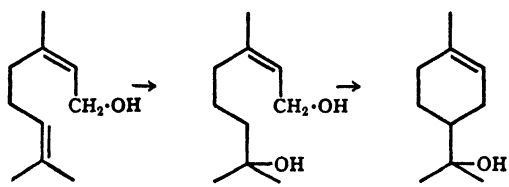
Geranial



Neral

Studies of absorption spectra, however, seem to indicate that there is very little, if any, of form (IV) in either stereoisomeride, and it appears that migration of the double bond from (I) to (IV) may occur to some extent during ozonolysis, to account for the production of formaldehyde.

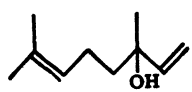
Geraniol and **Nerol**, $C_{10}H_{18}O$, occur in many essential oils, and are the stereoisomeric alcohols corresponding respectively with geranial and neral ; the configurations of these alcohols, and hence of the citrals, are inferred from the fact that nerol gives *a*-terpineol much more easily with dilute sulphuric acid than does geraniol,



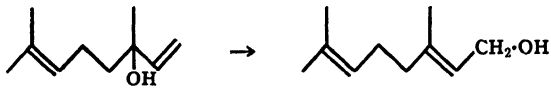
Nerol

α-Terpineol

Linalool, $C_{10}H_{18}O$, is a tertiary alcohol which occurs notably in oils of lavender and bergamot. It is optically active, and both *d*- and *l*-forms occur in various oils. It is represented by the formula:



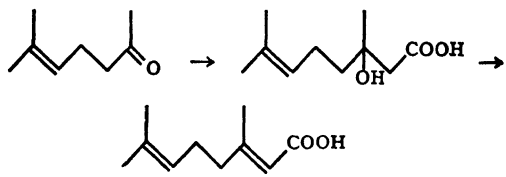
When linalool is treated with acetic anhydride it gives (an ester of) geraniol, by an isomeric change which is commonly shown by all alcohols of the same type as linalool (p. 840),



Geranic acid, $C_{10}H_{16}O_2$, is formed by the oxidation of citral with silver oxide, but is better prepared by the conversion of the aldehyde into the oxime, dehydration to the nitrile and hydrolysis,

$$R\cdot CHO \longrightarrow R\cdot CH{:}NOH \longrightarrow R\cdot CN \longrightarrow R\cdot COOH.$$

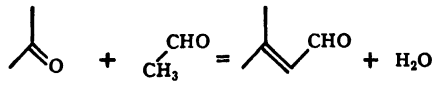
It has been synthesised from 2-methyl-Δ-2-hepten-6-one by the Reformatsky reaction with ethyl iodoacetate and zinc, followed by dehydration of the resulting hydroxy-acid,

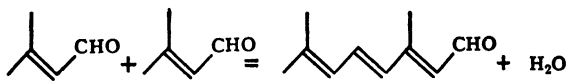


Its calcium salt heated with calcium formate yields citral.

When citral is treated with potassium hydrogen sulphate it is converted into cymene, and from geraniol, with the aid of various dehydrating agents, dipentene (p. 913) and other *p*-menthadienes are obtained ; linalool, under various conditions, gives α-terpineol, terpin hydrate, dipentene, and other menthadienes.

Facts such as these and the lack of experimental evidence in support of the isoprene hypothesis have led to the suggestion that such open chain aldehydes and alcohols are intermediate products in the formation of the cyclic terpenes and their derivatives, and that the former are produced from acetone and aldehyde by reactions such as the following (I and II) :

I 

II 

The aldehyde, $C_{10}H_{14}O$, formed according to (II), might undergo reduction, first to citral, $C_{10}H_{16}O$, and then to nerol, $C_{10}H_{18}O$, and it is known that the latter can be converted into α-terpineol, dipentene, etc.

Against this view there is the fact that the condensation of acetaldehyde and acetone in the laboratory leads to the formation of ethylideneacetone, and not to β-methylcrotonal as represented above, as an aldehyde group is far more reactive than a ketone group in such a mixed condensation. Finally, there is no evidence of the occurrence of acetaldehyde or acetone in the vegetable kingdom.

Sesquiterpenes

The sesquiterpenes, $C_{15}H_{24}$, are of three chief types : open chain, monocyclic and dicyclic. They occur in essential oils, together with innumerable derivatives, and their molecules may be regarded as based on isoprene units as suggested by Wallach (p. 938).

For the determination of their structures in bygone times the first step was usually a study of the physical properties of the compound, more especially its molecular refraction (p. 702), from the value of which the presence of one or more closed chains in the molecule could be inferred ; the results were then confirmed (or otherwise) by an examination of the behaviour of the compound towards hydrogen chloride, hydrogen bromide, and other reagents for olefinic bindings. Further information might then be obtained by submitting the substance to ozonolysis and graded oxidation, but the products were generally either too simple or too complex to give useful information.

It was not until 1921 that rapid progress was made. About that time Ruzicka found that sulphur, first used by Vesterberg, was an invaluable reagent for the dehydrogenation of sesquiterpenes and their derivatives, many of which at moderately high temperatures

were thereby transformed into substituted naphthalenes. Later it was shown that selenium could be used instead of sulphur. The structure of the aromatic oxidation product could then be determined without much difficulty and that of the parent sesquiterpene could be deduced with some assurance.

Farnesene, $C_{15}H_{24}$, is an example of an open chain sesquiterpene; it is formed by the dehydration of **farnesol**, $C_{15}H_{26}O$, an alcohol which occurs in oil of ambrette seeds. These two compounds may be respectively represented as follows, but both are probably mixtures of structural and stereoisomerides :

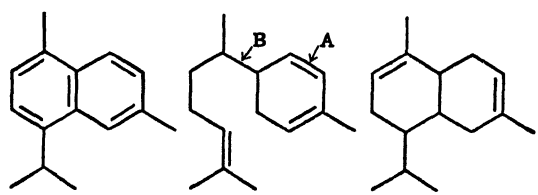


Farnesene



Farnesol

Zingiberene, $C_{15}H_{24}$, is the main component of ginger oil and may be taken as an example of a *monocyclic* tri-olefinic sesquiterpene. It is optically active, and boils at 134° (14 mm.). When it is heated with sulphur, oxidation and ring-closure occur, and it gives a hydrocarbon, *cadalene*, $C_{15}H_{18}$, which has been synthesised and proved to be 1:6-*dimethyl*-4-iso*propylnaphthalene*, (I). From the results of further investigation, involving ozonolysis, etc., it has been proved that zingiberene has the structure, (II).



I II III

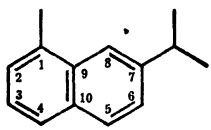
Bisabolene, $C_{15}H_{24}$, occurs in oil of bergamot and myrrh and is very closely related to zingiberene, from which it differs in that the olefinic binding, A (II), in zingiberene is at B in bisabolene.

Cadinene, $C_{15}H_{24}$, occurs in oil of cubebs, etc., and is a representative of the *dicyclic* di-olefinic sesquiterpenes ; when it is heated with sulphur it gives cadalene, and from other results it would

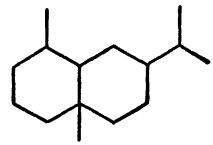
seem that the natural product, purified so far as possible, is mainly (III).

Cadinol, $C_{15}H_{26}O$, is a mixture of structural isomerides, which may be regarded as derived from cadinene by the addition of the elements of water.

Selinene, $C_{15}H_{24}$, which occurs in celery oil, is a representative of a rather different type of dicyclic di-olefinic sesquiterpenes. It combines with two molecules of hydrogen in the presence of platinum and gives with hydrogen chloride a dihydrochloride ; its molecular refraction accords with that of a dicyclic structure containing two ethylenic linkages. When oxidised with sulphur selinene yields *eudalene*, $C_{14}H_{16}$, or 1-methyl-7-*iso*propylnaphthalene, (IV), and in this change one carbon atom is eliminated. From a study of many similar cases it is inferred that this carbon atom is attached to the 1, 7, 9, or 10 position in the *reduced* naphthalene ring of selinene, from any of which it must be displaced in the formation of the naphthalene derivative. An examination of the possibilities shows that 10 is the only position which conforms to the isoprene rule, so that the framework of selinene is very probably represented by (V), in which case the only matter remaining to be decided is the distribution of the two double bonds :

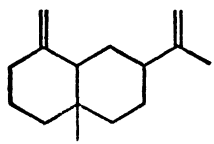


IV

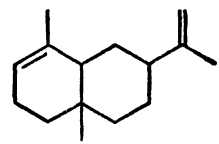


V

But when selinene dihydrochloride is reconverted into selinene the product is different from the original sesquiterpene ; and from a study of their oxidation products, the isomerides have been given the following structures :

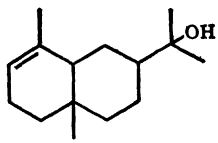


β-Selinene

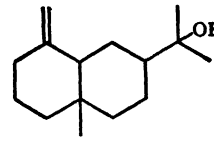


α-Selinene

Eudesmol, $C_{15}H_{26}O$, melts at 82–83° and is very closely related to selinene ; it is a mixture of two alcohols, the proportion of which appears to show considerable variations without any change in the melting-point :

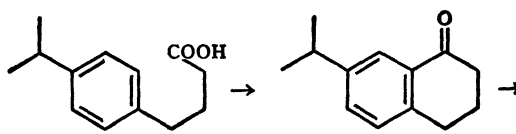


α-Eudesmol

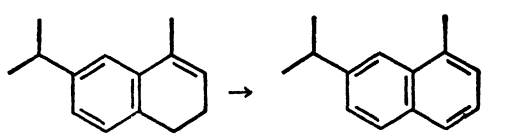


β-Eudesmol

As an example of the way in which the structure of a naphthalene derivative, obtained by the dehydrogenation of a sesquiterpene is established, the synthesis of eudalene is given : Ethyl p-*iso*propyl-cinnamate is reduced to the saturated alcohol, which is converted successively into the bromide, cyanide and acid, (I), the chloride of which undergoes an internal Friedel-Crafts reaction giving an iso*propyltetralone*, (II). The tertiary alcohol formed from (II) after treatment with methyl magnesium iodide is dehydrated and the resulting dihydronaphthalene derivative, (III), dehydrogenated with sulphur, gives eudalene, (IV), which must therefore be 1-methyl-7-*iso*propylnaphthalene :



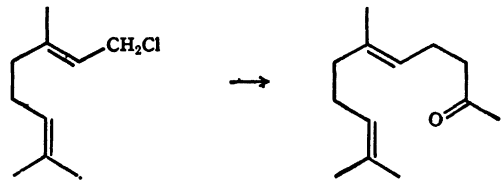
I II



III IV

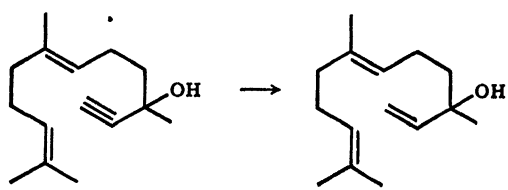
Synthetic Sesquiterpenes

Very interesting syntheses of sesquiterpenes and their derivatives from geraniol have been accomplished. This alcohol, with phosphorus trichloride, gives the chloride, (I),[1] from which, with the aid of ethyl sodioacetoacetate in the usual way, *αβ-dihydro*pseudo-*ionone* (II, cf. p. 952), is obtained :



I II

This ketone is then converted into (III) by treatment with acetylene in the presence of sodamide, a most important method for the preparation of tertiary alcohols of this type ; reduction by sodium and moist ether[1] converts the acetylenic into an olefinic link and the product, (IV), is a sesquiterpene alcohol, dl-*nerolidol*, which occurs notably in neroli oil from bitter oranges :



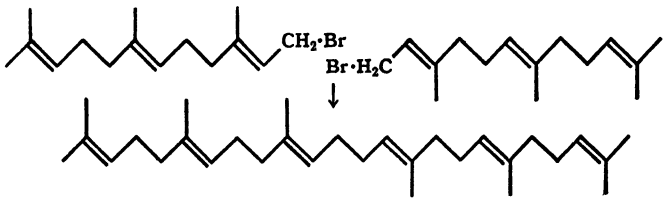
III IV

The dehydration of nerolidol gives farnesene, which on treatment with formic acid gives a monocyclic sesquiterpene the hydrochloride of which is identical with that of naturally occurring bisabolene (p. 944).

Farnesol (p. 944) is produced by an isomeric change (p. 840) when nerolidol is treated with acetic anhydride ; the corresponding

[1] Reductions of this kind may also often be conveniently and almost quantitatively accomplished by using hydrogen in the presence of a palladium catalyst which has been partially poisoned with a lead salt and quinoline : also by using sodium in liquid ammonia.

bromide, farnesyl bromide, when treated with magnesium in ether gives a mixture of hydrocarbons from which squalene hexahydrochloride, identical with that from natural squalene, can be isolated; *squalene*, $C_{30}H_{50}$, is an important dihydrotriterpene which occurs in the livers of the shark.

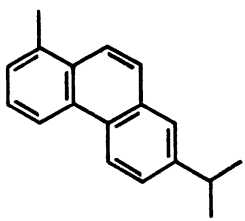


Squalene

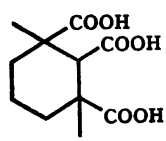
Resin Acids

The non-volatile residue of colophony or rosin from turpentine (p. 909) is a brown, brittle mass largely used for sizing paper and cotton and for the manufacture of plastics, varnish, soap, etc.; it consists largely of a complex mixture of *resin acids*, derived from diterpenes, $C_{20}H_{32}$, of which *abietic acid* may be taken as typical.

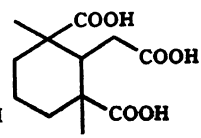
Abietic acid, $C_{20}H_{30}O_2$, is laevorotatory and melts at 173°. When it is dehydrogenated with sulphur or palladium-charcoal it yields *retene* (1-methyl-7-*iso*propylphenanthrene), $C_{18}H_{18}$, and when it is hydrogenated it gives a mixture of tetrahydroabietic acids; on oxidation with permanganate it is converted into two isomeric tetrahydroxy-acids, $C_{19}H_{29}(OH)_4COOH$; these facts prove the presence of two double bonds in the molecule of abietic acid. When it is oxidised with nitric acid, abietic acid gives the two *cyclo*hexane acids, (I) and (II), together with some *iso*butyric acid:



Retene

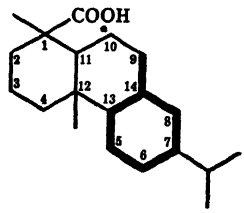


I

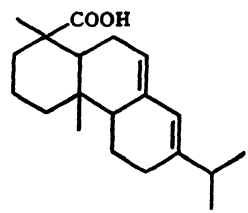


II

The framework of abietic acid can thus be shown by (III), the heavy lines serving to indicate those parts of the molecule within which the double bonds must be situated; the two carbon atoms which are lost (as carbon dioxide and methane respectively) in the conversion of abietic acid into retene are therefore those of the carboxyl group at 1 and the methyl group at 12:



III



IV

The production of *iso*butyric acid as one of the products of oxidation points to one of the double bonds being 6:7 or 7:8. The position of the carboxyl group is confirmed by the fact that esterification of the acid is difficult, as in other tertiary compounds, $CR_3 \cdot COOH$; moreover, if the carboxyl is converted into a methyl-group by the following series of changes (compare p. 954):

$$—COOEt \longrightarrow —CH_2OH \longrightarrow —CHO \longrightarrow —CH:N \cdot NH_2 \longrightarrow —CH_3,$$

and the product is then dehydrogenated, retene is again formed.

The molecular refraction and absorption spectrum of abietic acid give only indecisive evidence as to whether the double bonds are conjugated or not, and although abietic acid combines with maleic anhydride, it only does so at 130°, a temperature at which isomeric change might occur before reaction.

As a result of much further work, however, it is concluded that the structure of abietic acid is that shown in (IV).

Natural and Artificial Perfumes

The extraction of essential oils from plants, for their use as perfumes and essences, is an art which has been carried out from the remotest times, and is now a very important industry.

In many countries considerable tracts of land are utilised for the

cultivation of the plants required, and particularly in the South of France, tuberoses, violets, jasmine, etc., are grown in large quantities for the sake of their delicate perfumes. It seems probable, however, that before very long such natural products will be almost entirely displaced by synthetic ones, just as those of the indigo and the madder plant have been superseded by coal-tar products, and many natural medicinal compounds by manufactured substitutes.

The essential oils are extracted from the vegetable products in various ways. The oldest process for their separation was by steam distillation ; the vegetable matter was boiled with water in an earthenware still, and the oil was then collected from the aqueous distillate ; large metal stills are now used for this purpose, and in the case of oranges, lemons, limes, and other large fruits, the peel is first disintegrated mechanically in order to set free the essential oils. Another process, which is particularly useful when the proportion of perfume is very small, is to extract the vegetable matter with a volatile, odourless solvent, such as light petroleum, and then to distil the solvent. When such methods do not give good results, *enfleurage* is used ; the flowers (roses, violets, orange-blossoms, etc.) are placed in melted odourless fat (such as purified lard), and the latter is then separated from the flowers in hydraulic presses ; the essences are afterwards extracted from the fat with alcohol. Some flowers (jasmine, tuberose, etc.), however, continue to produce their perfume for a long time after they have been picked ; in such cases they are left in contact with a layer of cold fat (*cold enfleurage*), until the formation and absorption of perfume ceases.

Nearly all types of compounds composed of carbon, hydrogen, and oxygen are found in essential oils, and most of these naturally occurring substances, whether aliphatic or aromatic, have a pronounced and agreeable smell. Some of the simpler odoriferous aliphatic esters (p. 198) can be prepared from other sources, and have long been manufactured for use in confectionery.

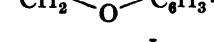
The artificial production or partial synthesis of such compounds is an expanding and important branch of industry which, as already mentioned, may lead to the complete supersession of the natural products.

The first important partial synthesis in this field was that of coumarin (m.p. 67°), which occurs in the Tonka-bean, and in sweet vernal grass, to which the pleasant smell of new-mown hay is partly

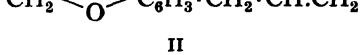
due ; this compound was prepared (Perkin, 1868) from salicylaldehyde and sodium acetate by a Perkin reaction, followed by the conversion of the resulting coumarinic acid into its lactone (p. 709).

Some years later various important perfumes were prepared from certain cheap and abundant naturally occurring substances. *Vanillin*, $C_6H_3(OMe)(OH)\cdot CHO$[OMe:OH = 3:4], for example, which occurs in vanilla pods, was prepared by Tiemann and Haarmann from *coniferin*, $C_{16}H_{22}O_8,2H_2O$, which occurs in the sap of various coniferae ; this compound is a phenolic glucoside of *coniferyl alcohol*, $C_6H_3(OMe)(OH)\cdot CH{:}CH\cdot CH_2\cdot OH$, and, on oxidation, gives *glucovanillin* (the group —CH:CH·CH_2·OH being converted into —CHO) ; this product is hydrolysed by acids, yielding vanillin and glucose. Vanillin is now manufactured from *eugenol*, $C_6H_3(OMe)(OH)\cdot CH_2\cdot CH{:}CH_2$[OMe:OH = 3:4], an important component of oil of cloves ; the eugenol is first heated with caustic alkali, to convert it into its isomeride, *iso*eugenol (p. 839), and the latter, in the form of its acetyl derivative, is then oxidised.

Heliotropin, (I), or piperonal (p. 602), which occurs in heliotrope (Cherry Pie), is manufactured in a similar manner from *safrole*, (II), a component of *sassafras officinale* and other essential oils ; the allyl is converted into the propenyl radical by isomeric change, as in the case of eugenol, and the latter is then oxidised with chromic acid.



I



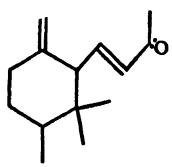
II

Terpineol is also manufactured from turpentine (p. 917).

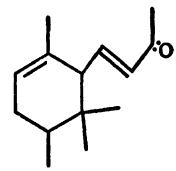
A very interesting synthetic perfume was discovered by Baur (*Ber.* 1891, 2832), who found that the 2:4:6-trinitro-derivative, obtained by nitrating *m*-tertiary butyltoluene, $C_6H_4(CH_3)\cdot CMe_3$, had a pronounced odour recalling that of musk, a very expensive perfume obtained from certain glands of the musk-deer. This artificial 'Musc Baur,' or some nearly related nitro-compounds having a similar odour, are now manufactured in large quantities and are very cheap compared with exaltone (p. 787), a far superior musk substitute.

The possible preparation of the odoriferous principle of violets

at one time occupied much attention and an optically active ketone, *irone*, was first isolated from the roots of *Iris florentina* by Tiemann and Krüger (*Ber.* 1893, 2675); this product was given the formula $C_{13}H_{20}O$, but in the light of later experiments it seems more probable that the molecular formula is $C_{14}H_{22}O$ and that it is a mixture of isomerides, (I*a*) and (I*b*).

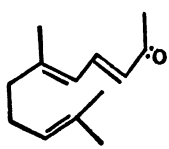


I*a*

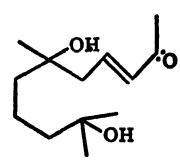


I*b*

Later it was found that two compounds, α- and β-*ionones*, both having an intense smell of violets, and related to irone in structure, could be cheaply prepared from citral, an abundant component of oil of lemon-grass and of lemon oil: Citral condenses with acetone in the presence of baryta, giving pseudo*ionone*, (II),[1] which combines with water, giving pseudo*ionone* '*hydrate*,' (III); when this compound is heated with dilute acid, ring-closure occurs, with the elimination of one molecule of water, and by the loss of another, in different ways, α-ionone, (IV), and β-ionone, (V), are formed.



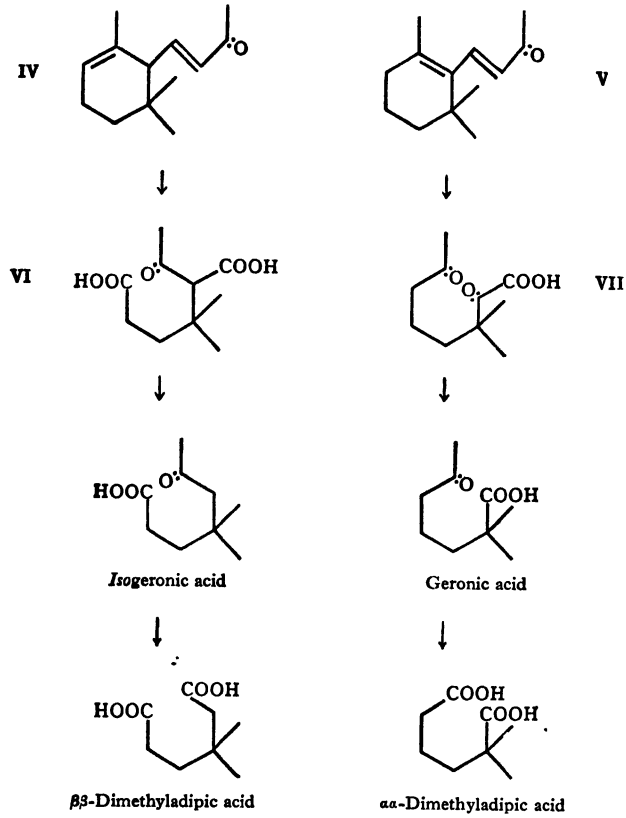
II



III

The structures of α- and β-ionone follow from those of their oxidation products; the former yields *iso*geronic acid, and the latter geronic acid, both of which are further oxidised by sodium hypobromite to ββ-dimethyladipic and αα-dimethyladipic acids respectively:

[1] A mixture of *cis*- and *trans*-forms from citral *a* and citral *b*.



The initial products of oxidation, (VI) and (VII), are unstable and cannot be isolated.

The ionones are now prepared on the large scale for use in perfumery, and some of their derivatives, the carotenes and vitamin A, for example (pp. 976, 978), are very important.

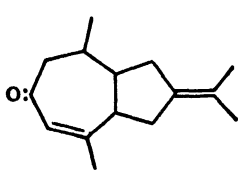
Many other compounds, differing greatly from one another in structure, are prepared by the ordinary processes of organic chemistry and used in perfumery; as examples, anisaldehyde (aubepine, hawthorn blossom), phenylethyl alcohol (which occurs in roses), methyl anthranilate (a component of orange flowers and of jasmine), and esters of salicylic acid may be mentioned.

Azulenes

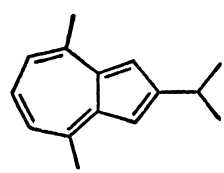
The blue colour of camomile oil was first observed about five hundred years ago and it is now known that many essential oils contain violet or blue compounds, or yield such substances on dehydrogenation with selenium, sulphur, etc. The colouring matters may be extracted from a petrol or ethereal solution of the oils with aqueous phosphoric acid and precipitated from the latter with water; with picric and styphnic acids, trinitrobenzene, etc., they give crystalline derivatives which may be used for their purification. These compounds are known as *azulenes* and are of great interest because of their colour and structure.

Vetivazulene, $C_{15}H_{18}$, is obtained by the action of sulphur on vetiver oil (from *andropogon muricatus*); it crystallises in violet needles, m.p. 32°. On catalytic reduction it unites with four molecules of hydrogen to give a hydrocarbon, $C_{15}H_{26}$; its refractivity and other physical properties suggest that it is dicyclic and if so one of the five double bonds which it would contain is resistant to reduction. With potassium permanganate it is oxidised to acetic, *iso*butyric and oxalic acids, and acetone; tetrahydrovetivazulene with ozone gives acetone, formic, *iso*butyric and α-methylglutaric acids. All such products give little information concerning its structure.

When vetiver oil is fractionated and appropriate ketonic fractions are purified by means of their semicarbazones, a ketone, *β-vetivone*, $C_{15}H_{22}O$, can be isolated. As a result mainly of the work of St. Pfau and Plattner, β-vetivone has been shown to be (I), and its molecule contains both a seven- and a five-membered ring.



I



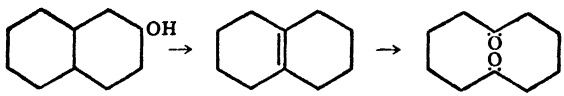
II

When its hydrazone is heated with sodium ethoxide and alcohol (Wolff-Kishner method),

$$>C{=}N\cdot NH_2 = >CH_2 + N_2,$$

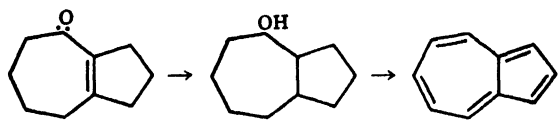
it gives a hydrocarbon, $C_{15}H_{24}$, which on dehydrogenation yields vetivazulene, (II), and eudalene (p. 946): the formation of the latter illustrates how changes in ring structures may occur during high temperature dehydrogenations. Conclusive evidence for the structure of vetivazulene is therefore not afforded by such a result, but the given constitution has, in fact, been confirmed by synthesis.

Azulene, $C_{10}H_8$, of which vetivazulene is a dimethyl*iso*propyl derivative, has been synthesised by a most ingenious method: β-decalol, dehydrated with zinc chloride, gives a mixture of isomeric octahydronaphthalenes, from which the Δ-9:10-compound, (I), can be separated and converted into *cyclo*decan-1:6-dione, (II), by ozonolysis:



I II

When this diketone is treated with aqueous sodium carbonate it undergoes an internal condensation giving 0,3,5-di*cyclo*-Δ-9-decen-4-one, (III). The corresponding saturated alcohol, (IV), obtained by reduction gives azulene, (V), on dehydrogenation with palladium-charcoal:



III IV V

Other azulene derivatives have been obtained by treating the ketone (III) with Grignard reagents and dehydrogenating the products.

CHAPTER 57

PLASTICS AND RUBBER

Plastics

A PLASTIC substance is one which, like putty, plasticine or celluloid, can be moulded by pressure or other mechanical means, at a suitable temperature, into a required form, which is then retained ; the word plastic, however, is now used as a noun to denote those materials which can be thus treated at some stage in their manufacture, and afterwards hardened if necessary (below). Some plastics are also known as synthetic resins, but the latter term is more restricted and cannot be applied, for example, to the cellulose plastics, since cellulose has not yet been synthesised.

Plastics are nearly always mixtures of substances of high molecular weight, ranging probably beyond 100,000 or so, and with rare exceptions they are amorphous. Those which soften when heated and harden again in the cold, without having undergone chemical change (so that the operations may be repeated many times), are classed as *thermoplastic*, and generally consist of ribbon-like molecules. Those which change in structure when they are heated, at some stage in their manufacture, and gradually harden as a result of irreversible chemical reactions, are termed *thermosetting*, and in their final condition are probably composed of lattice-like or tridimensional molecules.

The finished manufactured products may be colourless, or coloured ; transparent, or opaque. In addition to the organic compounds of which they are mainly composed, they may contain other ingredients, such as plasticisers, fillers and pigments. Plasticisers, as their name implies, are added to increase the fluidity or mobility of the material and thus facilitate the moulding or other mechanical operations ; also sometimes to decrease brittleness and impart flexibility. They are generally esters of high boiling-point, such as glycollates, phthalates and organic phosphates, or other viscous and high boiling liquids such as the polyglycols ; camphor is an important plasticiser, especially for cellulose esters (p. 962). Fillers, such as wood flour, lampblack, asbestos and mica, are often incorporated in order to modify the physical properties, such as brittle-

ness, resistance to shock, heat resistance and electrical characteristics ; the desired ornamental effect is generally attained by the addition of organic or mineral pigments.

The use of plastics is extending rapidly ; they are chemically inert, stable under ordinary conditions, insoluble in water, generally good thermal and electrical insulators, rigid or flexible, and not easily broken ; they can be cut to shape but are mostly moulded into the required form. They are employed for the production of articles of domestic and industrial use far too numerous to mention and are of particular importance in the electrical industry, in the manufacture of aeroplane parts, non-splintering glass, fabrics, photographic films, etc.

The reactions involved in the manufacture of plastics are mainly of two types, namely (1) condensation, and (2) polymerisation, as will be seen from the following brief account of some of the more important commercial products.

Condensation Plastics. In the process of condensation, as already shown, two or more molecules, identical or different, unite with the elimination of the elements of water, alcohol or some other simple compound, as in the formation of crotonaldehyde from acetaldehyde, and of mesityl oxide and phorone from acetone. Theoretically, in these and many other examples of this very common reaction, the process might continue indefinitely ; actually, as a rule, it very soon comes to an end and there is nothing unusual in the properties of the relatively simple products, which if solid are crystalline. When, however, formaldehyde (formalin) is heated with phenol in the presence of an acid or alkali, a long series of condensations results in the gradual formation of a mixture of various amorphous, very complex plastics. This material, first manufactured by Baekeland about 1908, and hence called *Bakelite*, was the first entirely synthetic industrial plastic.

The initial change in the production of Bakelite is probably a simple reaction between formaldehyde and phenol, which gives *o*-hydroxymethylphenol (saligenin), two molecules of which then condense, again in the *o*-position :

$$C_6H_5\cdot OH+CH_2O \longrightarrow HO\cdot C_6H_4\cdot CH_2\cdot OH,$$
$$2HO\cdot C_6H_4\cdot CH_2\cdot OH \longrightarrow HO\cdot C_6H_4\cdot CH_2\cdot C_6H_3(OH)\cdot CH_2\cdot OH.$$

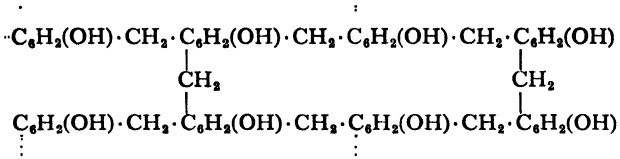
As this last compound, like saligenin, contains a $-CH_2\cdot OH$ group and a C_6H_4 radical in which a position *ortho* to the phenolic

hydroxyl is unsubstituted, a similar condensation may be repeated, and so on indefinitely with successive products. The result is the formation of a mixture of substances, the molecules of which are composed of very long chains, consisting (except at the ends) of the identical units shown between the dotted lines,

$$HO \cdot C_6H_4 \cdot CH_2 \cdot C_6H_3(OH) \cdot CH_2 \cdot C_6H_3(OH) \cdot CH_2 \cdot C_6H_4 \cdot OH.$$

When, therefore, the molecule is sufficiently large its empirical formula is practically identical with that of one of these units, since the composition of the slightly different end groups may be left out of consideration. Owing to its very high molecular weight the substance differs from ordinary crystalline compounds in its physical characteristics ; it is a plastic.

Now the properties of the products formed by the condensation of phenol and formaldehyde (formalin) vary very considerably with the nature (acid or alkali) of the condensing agent, proportions of the reactants and the temperature ; when instead of equimolecular quantities an excess of formalin is used, the aldehyde may react with some of the hydrogen atoms *para* to the hydroxyl radicals and the linear condensation products may thus become united by $—CH_2—$ groups at intervals throughout their length ; this would give rise to a sort of ladder arrangement and, by a continuation of such a reaction, lattice arrangements and tridimensional structures would be produced :



Cross linkages of this kind have an important effect on the properties of the plastic, rendering it much more sparingly soluble and raising the softening point, until finally a thermosetting material is obtained. Other phenols, such as the cresols, give similar substances.

Formaldehyde reacts with urea, in the presence of a catalyst,

$$CH_2O + NH_2 \cdot CO \cdot NH_2 = NH_2 \cdot CO \cdot NH \cdot CH_2 \cdot OH,$$

and by repeated condensations of the product there might be formed

molecules consisting of long chains of the units indicated by the dotted lines,

$$NH_2 \cdot CO \cdot NH \cdot CH_2 \cdot NH \cdot CO \cdot NH \cdot CH_2 \cdot NH \cdot CO \cdot NH \cdot CH_2 \cdot NH \cdot CO \cdot NH_2;$$

further condensation might then occur between the NH < groups and the formaldehyde whereby the chains become linked together. As the products are thermosetting plastics it is probable that they are cross-linked structures, formed from the linear molecules shown above.

A most important plastic of an amide type, but otherwise quite different from the urea-formaldehyde product, is obtained when a solution of adipic acid (prepared from phenol, p. 797) and hexamethylenediamine [1] is heated under pressure (Carothers); the liquid gradually becomes more and more viscous and the product, when melted, can be formed into threads and finally spun into fibres, which, structurally and physically, are very like those of silk, but twice as strong and unchanged by water. This material (and the fabric made therefrom) is known as *nylon* and was the first successful entirely synthetic fabric. The reactions which occur here are probably simple condensations which, repeated many times, give complex chain molecules, the units of which are as indicated :

$$\cdots\cdots CO \cdot [CH_2]_4 \cdot CO \cdot NH \cdot [CH_2]_6 \cdot NH \cdot CO \cdot [CH_2]_4 \cdot CO \cdot NH \cdot [CH_2]_6 \cdot NH \cdots\cdots$$

In spite of its apparent simplicity the satisfactory manufacture of nylon was only accomplished after vast expenditure of time and money, as the technical difficulties, etc., were very considerable.

A different type of condensation plastic, in which the units are linked by ester groups is produced from glycerol and phthalic anhydride or in general from polyhydric alcohols and polybasic acids or their anhydrides. Theoretically there are many different ways in which reactions between these two components may occur, giving either comparatively simple products, incapable of further change, or complex substances still capable of undergoing condensation. Considering the latter possibility only, two molecules of glycerol may react with one molecule of phthalic anhydride,

$$HO \cdot CH_2 \cdot CH(OH) \cdot CH_2 \cdot O \cdot CO \cdot C_6H_4 \cdot CO \cdot O \cdot CH_2 \cdot CH(OH) \cdot CH_2 \cdot OH;$$

[1] Hexamethylenediamine is also obtained from phenol, since it is prepared from adipic acid through the amide and nitrile.

this product may condense with phthalic anhydride and then with glycerol (at either end) and theoretically these processes may continue indefinitely; there would thus be formed long *linear* molecules of the units indicated above by the dotted lines, and these might then become cross-linked by condensation with the anhydride, giving lattice or tridimensional structures. The plastics obtained in this way are the *glyptals* or *alkyd* resins, which are used principally as varnishes and for joining sheets of asbestos and other materials.

Terephthalic acid and ethylene glycol give a linear condensation product which can be made into fibres and fabrics (*Terylene*) in a similar manner to nylon.

Polymerisation Plastics. In many cases of polymerisation, as, for example, in that of aldehydes, the process soon comes to an end because of the formation of closed chain compounds, such as trioxymethylene and paraldehyde; but when an aldol is formed this linear product still contains an aldehyde group and polymerisation might theoretically continue indefinitely; actually, so far as is known, it proceeds to a limited extent only, as in the production of formose from formaldehyde.

Ethylene and other olefinic compounds, however, give polymerides by a reaction indicated below, which seems to continue indefinitely,

$$\overset{\frown}{CH_2{:}CH_2}+H\cdot CH{:}CH_2 = CH_3\cdot CH_2\cdot CH{:}CH_2,$$

$$CH_3\cdot CH_2\cdot \overset{\frown}{CH{:}CH_2}+H\cdot CH{:}CH_2 = CH_3\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH{:}CH_2.$$

Straight chain molecules of high molecular weight which have the structure, $CH_3\cdot CH_2\cdot [CH_2\cdot CH_2]_n\cdot CH{:}CH_2$, are thus produced. When n is very large the difference between the molecular formula of the polymer and that of the corresponding normal paraffin, is negligible, since the composition of the latter is also expressed so very closely by $[CH_2]_n$. Such polyethylenes, therefore, are very similar to the paraffins in chemical properties, although their molecules contain one ethylenic link; they are thermoplastics and are used largely for insulating electrical cables, etc. *Polythene*, manufactured from ethylene, is an example of such polymerisation, but unlike the great majority of plastics it is crystalline.

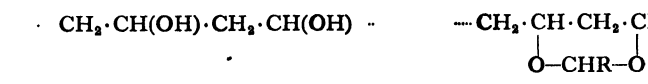
Poly*iso*butylenes, such as *vistanex*, are formed from *iso*butylene, $CMe_2{:}CH_2$, in a similar manner; they consist of units $—CMe_2\cdot CH_2—$ and resemble the paraffins in their chemical behaviour.

Styrene (phenylethylene, vinylbenzene), $C_6H_5 \cdot CH{:}CH_2$, undergoes ethylenic polymerisation, in which the phenyl group takes no part and gives a resinous plastic, *polystyrene*, composed of units $—CH_2 \cdot CHPh—$; this product is extensively used for electrical purposes as it has a very high dielectric constant.

The polymerisation of all such unsaturated hydrocarbons is usually carried out at elevated temperatures under high pressure in the presence of a catalyst as, for instance, boron trifluoride or aluminium chloride; but others such as peroxides, concentrated sulphuric acid, phosphates and silicates are also used.

Simple vinyl derivatives, such as vinyl chloride, $CH_2{:}CHCl$, and vinylidene dichloride, $CH_2{:}CCl_2$, also polymerise in the same way as ethylenic hydrocarbons, giving linear products composed of the units $—CH_2 \cdot CHCl—$ and $—CH_2 \cdot CCl_2—$ respectively.

Vinyl acetate, $CH_2{:}CH \cdot O \cdot CO \cdot CH_3$, is also a source of various plastics: by the usual ethylenic polymerisation it gives *polyvinyl acetate*, a product composed of units $—CH_2 \cdot CH(O \cdot CO \cdot CH_3)—$; the ester groups can then be hydrolysed, giving polyvinyl alcohol, two units of which, (I), react with one molecule of an aldehyde to form an acetal, (II),



I II

Various thermoplastics of different properties may thus be manufactured from polyvinyl alcohol; formaldehyde gives polyvinyl formal (*Formvar*, R = H), acetaldehyde, polyvinyl acetal (*Alvar*, $R = CH_3$), and butyraldehyde, polyvinyl butyral (*Butvar*, $R = C_3H_7$). The last-named product is used mainly as a laminator, for joining sheets of glass, in the manufacture of safety glass (Triplex), which does not splinter when it is broken, and many of these vinyl plastics have found wide application.

The polymerisation of esters of acrylic acid and alkyl substituted acrylic acids gives the important group of *acrylate* plastics; those from ethyl acrylate and methyl methylacrylate (p. 343), for example, consist of units $—CH_2 \cdot CH(COOEt)—$ and $—CH_2 \cdot CMe(COOMe)—$ respectively, and the latter (*Perspex*) is used more particularly in the manufacture of windows for aeroplanes, etc.

In the examples given above all the units of the complex molecules

are identical, but there is no reason why this should be so. A mixture of two (or more) simple olefinic compounds may give linear polymerides formed by the combination of molecules of both the components; a mixture of equimolecular proportions of vinyl chloride and vinyl acetate, for example, might give a product composed of the units (I), whereas that from a mixture of methyl methylacrylate and ethyl acrylate might consist of the units (II):



I II

Such mixed polymers are called inter- or co-polymers.

As the proportions of the two components can be varied at will, plastics having almost any desired physical properties may thus be produced from vinyl derivatives alone.

Many vinyl plastics can be converted into materials with rubber-like properties by the incorporation of plasticisers, but the products, although plastic and elastic, cannot be vulcanised (p. 965).

Passing now from olefinic substances containing only one active double bond in the molecule to those which contain two, it will be seen that a linear polymer formed from the latter still retains one ethylenic link *in every unit*; butadiene, for example, would give (III) and chlorobutadiene, (IV):



III IV

The properties of the unsaturated plastics thus formed are different from those of the saturated polymerides of mono-olefinic compounds, and are similar in many respects to those of natural rubber; it is mainly from such di-olefines and their substitution products that the very important synthetic rubbers are manufactured (p. 968).

The complex molecules of cellulose consist of long chains which are possibly cross-linked, and the units of which have the empirical formula, $C_6H_{10}O_5$ (p. 899); these units contain alcoholic hydroxylic groups which can be esterified with acetic anhydride, nitric acid, etc., or made into ethers, and some of the products are used in the manufacture of plastics such as cordite, celluloid, xylonite, etc. Of the partly synthetic compounds of this kind cellulose acetate is perhaps the most important because of its use in the manufacture

of artificial silk (rayon), cinema films and many other commercial products. Other fibres derived from cellulose have already been described (p. 330).

Casein (p. 645) is a highly complex substance of animal origin composed of units having an amide structure, comparable to that of nylon ; after it has been moulded it can be hardened by treatment with formaldehyde. It is commonly used for the manufacture of buttons, umbrella handles, ash trays, etc. Other proteins are also used for the production of fibres, films, etc.

Plastics containing Silicon. Mono-, di-, and tri-alkyl and aryl substitution products of silicon tetrachloride, prepared with the aid of Grignard reagents, are readily hydrolysed by water, and the corresponding hydroxides quickly undergo condensation in the presence of acids or alkalis giving open and closed chain products. The mono-hydroxy-compounds (silicols) thus give the simple oxides, $SiR_3 \cdot O \cdot SiR_3$, only, but the diols, $SiR_2(OH)_2$, afford complex mixtures of both types,

$$HO \cdot SiR_2 \cdot [O \cdot SiR_2]_n \cdot O \cdot SiR_2 \cdot OH \qquad SiR_2 < \begin{matrix} O \cdot SiR_2 \\ [O \cdot SiR_2]_n \end{matrix} > O$$

and the trihydroxides are rapidly converted into highly complex products of unknown structure (Kipping).

The mixtures so obtained from the lower alkyl derivatives are oils (known as *silicones*), soluble in many organic liquids, and do not crystallise at polar temperatures ; they have characteristics different from those of mineral and vegetable oils, show very little change in viscosity with changes in temperature, and are now manufactured, mainly in the U.S.A., for various commercial purposes.

When oxidised with air and a catalyst, or treated in various other ways, these oils, mainly open chain compounds, afford gelatinous or resinous plastics as the result of further condensation and of the displacement of alkyl groups by oxygen with the formation of cross-linked molecules. These products differ from the generality of plastics in being much more stable towards heat ; as they have exceptional electrical insulating properties, are very inert chemically and do not attack metals, they are of considerable importance, particularly in the electrical industry. The more volatile substituted silicon chlorides, in the state of vapour or dissolved in an organic liquid, may be applied directly to glass, porcelain, etc., for the production of a water-repellant film ; the halide is decomposed by the

moisture on the article so treated and an adherent film of silicone is thus produced.

The Manufacture of Plastic Materials. There are four main mechanical methods by which plastic articles may be manufactured ; they vary with the nature of the plastic and the shape of the article to be made.

(1) *Moulding.* This is the chief method and employs mainly a phenol-formaldehyde plastic. A moulding powder is prepared by mixing a partly condensed (still thermoplastic) phenol-formaldehyde product with a filler (usually wood-flour), plasticiser, pigment, etc. This mixture is then placed in a mould and submitted to pressure and heat (up to 180° or so) whereon the thermosetting process (*cure*) occurs. The cure requires from 1 minute to 1 hour or more, according mainly to the thickness of the moulded article : the two halves of the mould are separated and the finished product ejected. This operation requires very heavy and expensive equipment.

(2) *Casting.* This method is also largely used for phenol-formaldehyde resins which, in the liquid (partially condensed) state are mixed with a plasticiser, poured into moulds and maintained at 60–80° during several days until cured ; as a rule no filler is used. The moulds are often made of lead.

(3) *Injection Moulding.* A granulated thermoplastic material is fed into a heated cylinder and forced into moulds (cooled if necessary). This is a very rapid method and is used largely for cellulose acetate and methyl methylacrylate plastics.

(4) *Extruding.* A thermoplastic material, either alone or mixed with a suitable solvent, is heated and forced through a die by a screw ; rods, tubing, etc., are thus made and wire, etc., may be coated with plastic.

Rubber

India Rubber, *Rubber*, or *Caoutchouc*, is prepared from a watery emulsion, known as rubber *latex*, a product of many tropical and sub-tropical trees, such as the Euphorbiaceae, of which *Hevea brasiliensis* is the main species and the almost exclusive source of commercial natural rubber. *Guttapercha* and *balata* are closely related to rubber, but differ from it in physical properties.

The latex is obtained by making incisions in the bark of the tree and collecting the 'milky' liquid which exudes ; it consists mainly of rubber, 27–35% ; fatty matter soluble in acetone, 1·2–1·7% ; protein-

like substances, 1·5–2% ; water, and a very little mineral matter. Some samples also contain inositol (p. 798) and/or *l*-methylinositol and dimethylinositol. When it is treated with very dilute acetic acid, the latex coagulates and the precipitated rubber is then boiled with water, kneaded, and pressed into blocks or rolled into sheets ; the latter may be cured (rendered aseptic) by a smoking process.

This crude material may be purified by extracting it with boiling acetone, to remove fats and resins, and then treating it with chloroform or benzene ; the proteins are not dissolved and, from the decanted colloidal solution, the rubber may be precipitated by the addition of alcohol. The product still contains some protein matter, which may be removed by hydrolysis with cold methyl alcoholic potash, but the rubber cannot then be obtained completely free from alkali.

According to Pummerer the preparation of ' pure ' rubber is best carried out as follows : Uncoagulated latex is stirred with 8% sodium hydroxide solution, in an atmosphere of nitrogen ; the liquid is then diluted with three times its volume of water, stirred at 50° during 8–10 hours, and then placed aside. The rubber separates at the surface as a cream, and, after having been treated in this way several times, it is free from protein. The cream is then diluted with water, stirred, separated, and left in a dialyser during several hours ; after coagulation with acetone or acetic acid it is extracted with acetone, to remove resins, dissolved in benzene and fractionally precipitated with a mixture of alcohol and acetone.

Rubber thus purified is colourless, optically inactive, and has no definite melting-point ; it is ' soluble ' in benzene, chloroform, and carbon disulphide. Its remarkable elasticity under ordinary conditions is gradually lost with a rise or fall of temperature ; this behaviour seriously impaired its usefulness for most purposes, and the great importance of rubber at the present time is due to a discovery of Goodyear in 1839 ; namely, that if rubber is heated with white-lead and sulphur, elasticity is retained over a greater range of temperature than before and it is also less readily attacked by chemical reagents. Such *vulcanised* rubber is now manufactured by heating the natural material with sulphur (2·5–15%) under pressure, at about 130–155°, during 6 to 12 hours ; by increasing the proportion of sulphur to 25–40%, *ebonite* and *vulcanite* are obtained, and coloured vulcanised products may be prepared by the incorporation of various substances, such as the sulphides of

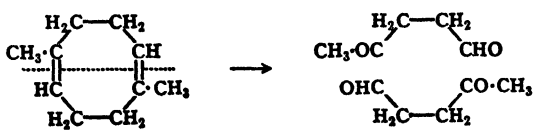
antimony and mercury. Rubber may also be vulcanised by treating it (thin sheets or tubing) with a solution of sulphur monochloride in carbon disulphide, or by the successive action of sulphur dioxide and hydrogen sulphide (Peachey). The process of vulcanisation may be very much hastened and thus cheapened by the addition of certain *accelerators*, such as thiocarbanilide, but very little is known as to the chemical changes which result.

Nowadays increasing quantities of rubber latex are concentrated by evaporation or centrifugion to save carriage, sterilised by the addition of ammonia and shipped to countries where it can be more efficiently treated; the manufactured articles there produced are superior in quality to those made from sheets of imported rubber.

Rubber has the empirical formula, C_5H_8, but its molecular formula is not known. It gives with hydrogen bromide a compound, $(C_5H_9Br)_n$, and with bromine, $(C_5H_8Br_2)_n$. Samples purified by ordinary methods give no appreciable depression of the freezing-point in benzene solution, but various specimens, obtained by Pummerer's process, gave values by Rast's method in camphor or benzylidenecamphor, and by Beckmann's method in menthol, corresponding with a molecular weight of 600–2400.

When rubber is destructively distilled it yields a complex mixture of hydrocarbons, which contains isoprene, dipentene, and a sesquiterpene, *hevene*; isoprene at ordinary temperatures slowly polymerises, giving a rubber-like product, as observed by Tilden.

Harries treated rubber, dissolved in chloroform, with ozone and obtained an explosive oil, which gradually solidified in a vacuum to a glassy mass; the molecular weight of this substance agreed with that of an ozonide, $C_{10}H_{16},O_3,O_3$; when decomposed with water this ozonide gave laevulic aldehyde and its peroxide. These facts accord with the view that the ozonide is derived from 1:5-*dimethyl*-Δ-1:5-cyclo-*octadiene*,

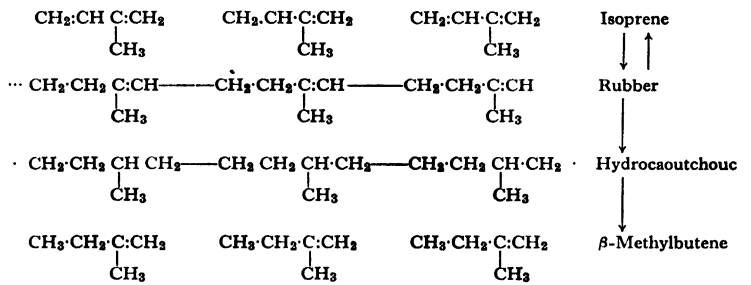


but it seems to be more probable that the rubber molecule, as suggested by Pickles, is an open chain structure, composed of modi-

fied isoprene units, from which such an ozonide might well be formed :

$$CH_2\cdot CH{:}C\cdot CH_2{-}CH_2\cdot CH{:}C\cdot CH_2{-}CH_2\cdot CH{:}C\cdot CH_2\cdots$$
$$\qquad\qquad\quad CH_3 \qquad\qquad\quad CH_3 \qquad\qquad\quad CH_3$$

When rubber is heated with hydrogen at about 270° under high pressure, in the presence of platinum or palladium, it is converted into a hydrocarbon, named *hydrocaoutchouc*, $(C_5H_{10})_n$, which is still colloidal and cannot be distilled in a vacuum. This compound is not acted on by bromine, concentrated nitric acid, or potassium permanganate in the cold, and thus behaves like a paraffin or a *cyclo*-paraffin. It is slowly decomposed at about 350–400°, giving a mixture of many olefines, $(C_5H_{10})_n$; the most complex component of this mixture has a molecular formula of $C_{50}H_{100}$, or thereabouts, and the simplest component is *β-methylbutene*, which, on oxidation, gives methylethyl ketone. The transformation of isoprene into rubber, of rubber into hydrocaoutchouc, and of the latter into β-methylbutene, may be represented in the following manner (Staudinger, *Ber.* 1924, 1203) :



It seems very probable, therefore, that rubber is a mixture of various compounds derived from isoprene, but no definite conclusion can yet be drawn as to the number of isoprene units which form the molecules ; as far as is known the latter are long open chain structures, but if so, it would be difficult to account for the formation of the ozonide, $C_{10}H_{16},O_3,O_3$, unless it is a dimeride of an ozonide, C_5H_8,O_3.

Later investigations with certain synthetic rubbers showed that their behaviour towards ozone is similar to that of the natural product. Thus the ozonide of rubber from butadiene yields

(succindialdehyde and) succinic acid, and that from dimethylbutadiene rubber gives mainly acetonylacetone, while the ozonide of natural rubber gives laevulic aldehyde, as already stated :

Butadiene rubber—

$$—CH_2·CH{:}CH·CH_2—CH_2·CH{:}CH·CH_2— \longrightarrow COOH·CH_2\ CH_2·COOH$$

Dimethylbutadiene rubber—

$$—CH_2·CMe{:}CMe·CH_2—CH_2\ CMe{:}CMe\ CH_2— \longrightarrow COMe\ CH_2·CH_2·COMe$$

Natural rubber—

$$—CH_2·CH{:}CMe·CH_2—CH_2\ CH{:}CMe\ CH_2— \longrightarrow COMe·CH_2\ CH_2·CHO$$

These results seem to show that the natural and the synthetic products have much the same type of structure : on the other hand, isoprene rubber, destructively distilled, gives mixtures which differ from those obtained from natural rubber, since they contain saturated hydrocarbons.

Synthetic Rubber

Towards the close of the nineteenth century there were indications that the supply of rubber, at that time obtained almost entirely from the Amazon district, would not meet the ever-increasing demands, and there was therefore a probability that if a suitable method could be devised, synthetic rubber could be profitably manufactured. During the interval between the two great wars, however, owing to the extensive plantations which had been laid out in many tropical countries, there was more than enough natural rubber (about one million tons in 1932) to provide all the world's needs, and its price was so low that it would have been impossible for any synthetic product to compete with it.

In spite of such economic considerations, however, much research had been done during this period both in Germany and elsewhere, partly because it was always possible that a more useful material even than natural rubber might be discovered, and indeed several processes were being worked for the manufacture of rubbers with special properties. Following the fall in 1941 of the chief rubber-growing countries, Malaya, the Dutch East Indies, etc., the more promising syntheses were put into very large-scale operation, mainly in the U.S.A.

The first synthetic rubbers were obtained by the polymerisation of simple dienes (p. 962), such as butadiene and isoprene, but later

work has shown that better results are usually obtained by the co-polymerisation of mixtures of butadiene and various mono-olefinic compounds such as styrene. The more important products, their components and a few of their trade designations are shown below : they have a structure probably allied to that of natural rubber, contain double bonds and can be vulcanised.

Butadiene-Styrene co-polymer	Buna-S, Perbunan
Butadiene-Acrylonitrile co-polymer	Buna-N
Butadiene-*Iso*butylene co-polymer	Butyl rubber
Chlorobutadiene polymer	Duprene, Neoprene

In the earlier processes polymerisation either in the liquid or vapour phase, or in solution, was effected with suitable catalysts such as sodium ; nowadays emulsion polymerisation is used in which the diene or a mixture of it with an olefine is emulsified in water with soap or other similar reagent and then heated at 40–60° during 10–15 hours with hydrogen peroxide, ammonium persulphate or an organic peroxide or peracid, with the addition of a trace of carbon tetrachloride, sodium cyanide, etc. The product is a latex which resembles that of natural rubber and can be coagulated in a similar manner.

The various synthetic rubbers differ from one another and also from natural rubber in many ways, and by suitable compounding a material having almost any desired character can be obtained.

The preparation of two of the most important compounds used in the manufacture of synthetic rubbers, butadiene and chloroprene, is described below, together with interesting proposals for that of isoprene ; styrene has already been mentioned (p. 419) and acrylonitrile is prepared from cyanoethanol (p. 244).

Butadiene, $CH_2{:}CH\cdot CH{:}CH_2$, (b.p. −3°), is formed in small proportions when a mixture of ethylene and acetylene is passed through a red-hot tube. It was at one time manufactured from butyl alcohol, obtained from starch (p. 119). This alcohol, with hydrogen chloride, gave butyl chloride which was subsequently chlorinated ; the mixture of dichlorides, which probably contained the compounds shown below, yielded crude butadiene when it was passed over heated soda-lime :

$$CH_3\cdot CH_2\cdot CH_2\cdot CH_2Cl \longrightarrow \begin{cases} CH_3\cdot CH_2\cdot CHCl\cdot CH_2Cl \\ CH_3\cdot CHCl\cdot CH_2\cdot CH_2Cl \\ CH_2Cl\cdot CH_2\cdot CH_2\cdot CH_2Cl \end{cases}$$

In the case of 1:2-dichlorobutane, the formation of butadiene would also involve some isomeric change.

Butadiene is now manufactured by three methods: (1) Aldol, from acetaldehyde, is converted into 1:3-butylene glycol by catalytic reduction, and the latter, passed over heated lime, gives the diolefine,

$$CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}CHO \longrightarrow CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_2{\cdot}OH \longrightarrow CH_2{:}CH{\cdot}CH{:}CH_2.$$

(2) Acetylene is polymerised to *vinylacetylene*, by treatment with cuprous and ammonium chlorides, and by catalytic reduction this hydrocarbon is converted into butadiene,

$$2C_2H_2 \longrightarrow CH_2{:}CH{\cdot}C{:}CH \longrightarrow CH_2{:}CH{\cdot}CH{:}CH_2.$$

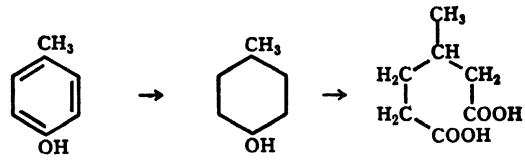
(3) Petroleum is cracked under such conditions that it yields directly 5–12% of butadiene, or the butane and butene, formed under the usual conditions, are employed. In the latter case the butane is dehydrogenated at 600° with a catalyst of aluminium and chromium oxides, and the butene thus formed is converted into butadiene with a similar catalyst at a slightly higher temperature. The butene from butane (and that obtained directly from petroleum) may also be converted into butadiene by combining it with chlorine and then heating the 2:3-dichlorobutane with barium chloride.

2-Chlorobutadiene, $CH_2{:}CH{\cdot}CCl{:}CH_2$ (*chloroprene*), is obtained on the large scale by treating *vinylacetylene* with hydrochloric acid under particular conditions,

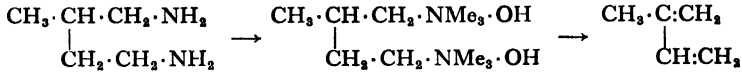
$$CH{:}C{\cdot}CH{:}CH_2 + HCl = CH_2{:}CCl{\cdot}CH{:}CH_2.$$

Isoprene, $CH_2{:}CMe{\cdot}CH{:}CH_2$ (*2-methylbutadiene*), boils at 33–34° and is formed by strongly heating turpentine or rubber, or by passing dipentene (p. 913) over heated platinum. It may be manufactured from the crude amyl alcohol obtained from fusel oil (p. 120), by a method analogous to that by which butadiene is obtained from butyl alcohol; the amyl chlorides, produced by treating the alcohols with hydrogen chloride, are chlorinated and the mixture of dichlorides is passed over heated soda-lime.

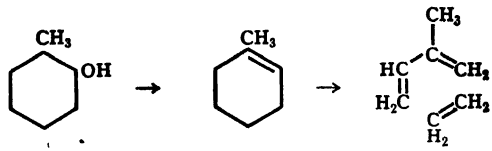
Isoprene may also be prepared in various other ways: (1) *p*-Cresol is reduced with hydrogen in the presence of nickel, and the *4-methylcyclohexanol* so obtained is oxidised to *methylcyclohexanone*, and then to *β-methyladipic acid*,



The diamide of this acid with sodium hypochlorite gives 2-*methyl*-1:4-*diaminobutane*, and the quaternary hydroxide, obtained from this base by exhaustive methylation, is then destructively distilled :



(2) *o*-Cresol is reduced catalytically to 2-*methyl*cyclo*hexanol*; this product, passed over heated alumina, yields Δ-1-*tetrahydrotoluene* (methyl*cyclo*hexene), which is decomposed at a high temperature, giving isoprene and ethylene,



As the last two methods start from materials which are not abundant, it seems unlikely that they could be used successfully in the large scale operations for which they were devised ; the manufacture of a synthetic rubber from isoprene has therefore been abandoned.

CHAPTER 58

CAROTENOIDS, PYRONES, ANTHOCYANINS, AND DEPSIDES

Carotenoids

THE term *carotenoid* (or *lipochrome*) is applied to certain yellow, orange, red or brown pigments of a particular type which occur widely distributed in the animal and vegetable kingdoms. Such compounds are found in all kinds of plants, and, in those which also contain chlorophyll, are intimately associated with that most important substance ; in others, such as the fungi, in which chlorophyll is absent, the carotenoids are mainly responsible for the colour. In the animal kingdom the yellow colour of many fats—butter, for example—is due to their presence.

Mainly from the results of the work of Kuhn, Karrer, and their collaborators, it has been shown that all carotenoids possess in their molecules numerous (7–11) conjugated double linkages, to which they owe their colour. Some of the carotenoids are hydrocarbons, some are di- or poly-hydroxy-compounds, and some are carboxylic acids.

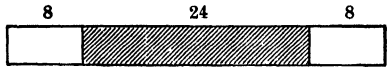
Lycopene, $C_{40}H_{56}$, forms carmine prisms, melting at 175°, and was first isolated by Willstätter from tomatoes, which owe their colour to its presence ; it also occurs in bitter-sweet and rose hips and many other plants. On exposure to dry oxygen it rapidly absorbs 32·5% of its weight (11 atoms) of this gas and becomes colourless. When a solution of lycopene in *cyclo*hexane is treated with hydrogen in the presence of a platinum catalyst, each molecule of the hydrocarbon combines with *thirteen* molecules of hydrogen, and a colourless paraffin, *perhydrolycopene*,[1] $C_{40}H_{82}$, is produced. This fact proves that lycopene is an open chain polyene, in the molecule of which there are thirteen double bindings.

On ozonolysis lycopene (1 mol.) gives acetaldehyde, acetic acid, acetone (at least 1·6 mol.), and laevulic acid, whereas with chromic acid it gives acetic acid (6 mol.). These products show that the molecule contains the following groups :

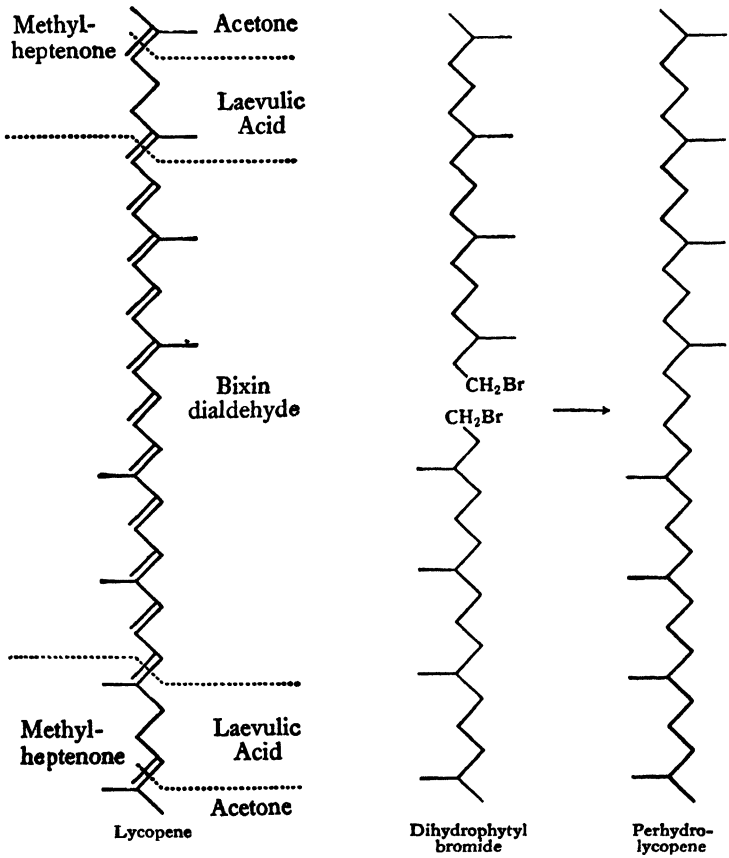
$$2Me_2C{=}, \qquad {=}CMe\cdot CH_2\cdot CH_2\cdot CH{=}, \qquad 6\text{—}CMe{=}$$

[1] The prefix ' perhydro ' denotes that all the double (or treble) bonds in the lycopene molecule have been reduced.

Cautious oxidation with chromic acid gives *2-methyl-Δ-2-hepten-6-one* (1 mol.) and *lycopenal*, $C_{32}H_{42}O$ (1 mol.), and the latter is further broken down into methylheptenone (1 mol.) and *bixin dialdehyde*, $C_{24}H_{28}O_2$ (1 mol.); it is clear, therefore, that the two molecules of methylheptenone have originated from the ends of the lycopene chain and that of bixin dialdehyde from the middle portion, thus:



Now the formation of each methylheptenone molecule involves



the loss of one —CMe= group and two double bonds from the lycopene molecule, so that the central portion (C_{24}) must contain four —CMe= groups and an uninterrupted series of conjugated linkages to account for the nine remaining double bonds. The application of the isoprene rule then leads to the symmetrical formula for lycopene (p. 973).

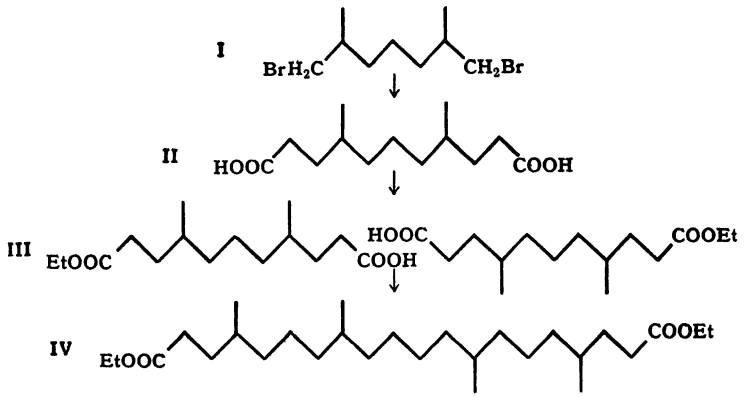
The absorption spectrum and other physical properties of lycopene, when compared with those of synthetic polyenes in general, accord with the given structure, which is now fully established.

A hydrocarbon, b.p. 240° (0·3 mm.), probably identical with perhydrolycopene, has been synthesised from *phytol* (p. 1083), the structure of which has been established by synthesis: Phytol, which occurs in chlorophyll, is reduced catalytically to dihydrophytol, which is converted into its bromide with phosphorus pentabromide; bromine is then eliminated from two molecules of the bromide by the Wurtz-Fittig reaction, yielding a hydrocarbon, $C_{40}H_{82}$, as indicated (p. 973).

It should be noted that the molecule of lycopene is built up from eight isoprene *residues* which form two identical groups, $C_{20}H_{28}$, united together symmetrically, although lycopene, unlike terpenes, could not be formed by the mere polymerisation of isoprene.

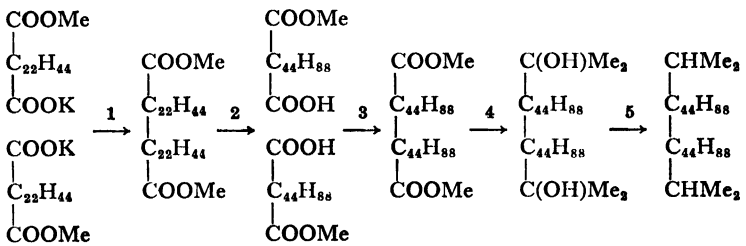
Bixin, $C_{25}H_{30}O_4$, occurs in *Bixa orellana* and crystallises in violet needles, m.p. 198°; on hydrolysis it gives methyl alcohol and nor*bixin* (footnote, p. 926), $C_{24}H_{28}O_4$, a dibasic acid of which therefore bixin is the monomethyl ester. On catalytic hydrogenation bixin unites with nine molecules of hydrogen and the *perhydrobixin* which is thus formed gives *perhydro*nor*bixin* on hydrolysis.

Perhydro*nor*bixin has been synthesised as follows: Trimethylene dibromide is condensed with diethyl sodiomethylmalonate and the product is converted into the diethyl ester of αα′-dimethylpimelic acid, in the usual manner; this ester is then reduced to the alcohol which is treated with phosphorus tribromide. From the resulting dibromide, (I), with the aid of diethyl malonate, the dibasic acid, (II), is prepared and converted into its monoethyl ester, (III); the electrolysis of the potassium salt of this acid gives perhydro*nor*-bixin diethyl ester, (IV), which, although it contains four asymmetric groups, is identical with that prepared from natural bixin.



This synthesis not only proves the constitution of bixin but also confirms that of lycopene, as the bixin dialdehyde obtained from the latter can be oxidised to *nor*bixin.

A very interesting paraffin, $C_{94}H_{190}$, has been synthesised from the potassium salt of perhydrobixin by the following reactions :



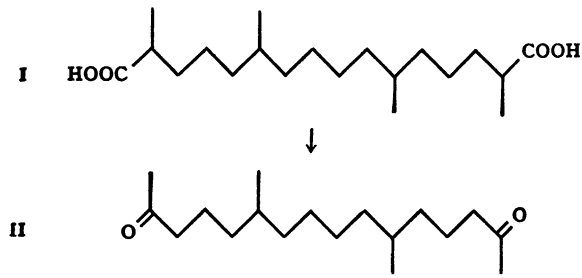
1 and 3. Electrolysis (Kolbe reaction). 2. Partial hydrolysis. 4. MeMgI. 5. HI.

Crocetin, $C_{20}H_{24}O_4$, is found in saffron, in the form of its digentiobioside. Its constitution has been established by the conversion of perhydro*nor*bixin into perhydrocrocetin by a series of well-known reactions. A carboxylic acid, $R \cdot CH_2 \cdot COOH$, is converted into the α-hydroxy-acid, which is esterified (methylated) with diazomethane ; the resulting methyl ester is then treated with an excess of methyl magnesium iodide and the tertiary alcohol so formed is oxidised (with lead tetra-acetate) first to the next lower aldehyde and then to the corresponding acid :

$$R \cdot CH_2 \cdot COOH \longrightarrow R \cdot CHBr \cdot COOH \longrightarrow R \cdot CH(OH) \cdot COOH \longrightarrow R \cdot CH(OH) \cdot COOMe \longrightarrow R \cdot CH(OH) \cdot C(OH)Me_2 \longrightarrow R \cdot CHO \longrightarrow R \cdot COOH.$$

By the application of this series of reactions, and then repeating them with the product, the molecule of perhydro*nor*bixin, $C_{24}H_{48}O_4$, loses four —CH_2— groups (two at each end of the structure) and gives *perhydrocrocetin*, $C_{20}H_{40}O_4$.

When perhydrocrocetin, (I), is submitted to the same series of reactions (shown above), the product is a diketone, (II), the production of which, in the place of a dialdehyde, obviously proves the presence of methyl (or other alkyl) groups at these points in the chain :



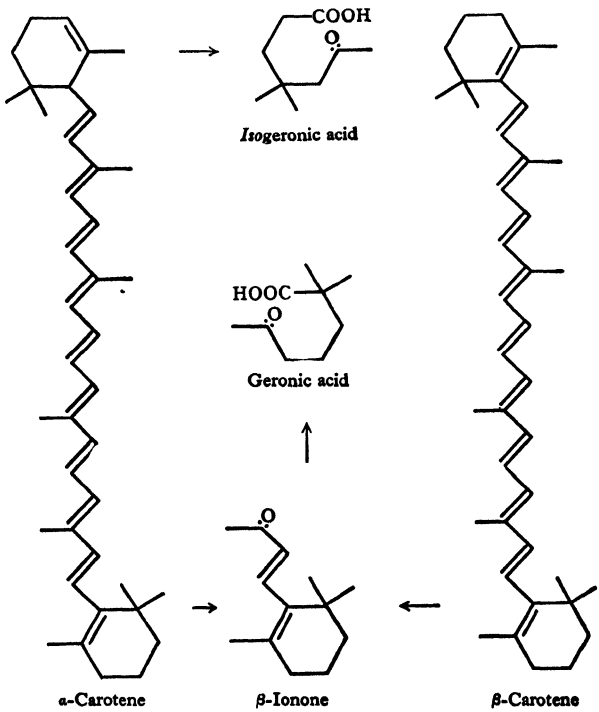
Carotene, $C_{40}H_{56}$, usually occurs with chlorophyll, and also gives rise to the colour of many yellow flowers, roots (such as carrots), and fats (such as butter). Three isomeric carotenes have been isolated, and they are most easily separated by the very important method of chromatographic analysis (p. 980). α-Carotene, m.p. 184°, is more soluble in petroleum than the β-isomeride ; it is highly dextrorotatory and shows a very high rotatory dispersion (p. 743), $[\alpha]_{6563}+284°$, $[\alpha]_{6075}+458°$. β-Carotene, m.p. 187°, and γ-carotene, m.p. 178°, are optically inactive. The proportion of the forms varies in different plants.

The α- and β-isomerides are closely related, and the structural formulae assigned to them (p. 977) are based on the following results, obtained mainly from an investigation of the mixture :

On exposure to dry oxygen, carotene absorbs about 35% of its weight (12 atoms) of the gas, with the emission of a distinct odour of violets (p. 952). When reduced with hydrogen in the presence of a platinum catalyst, each molecule combines with *eleven* molecules of hydrogen, giving a colourless saturated hydrocarbon, *perhydrocarotene*, $C_{40}H_{78}$; from this fact it is concluded that the molecule of carotene contains eleven olefinic bindings, and two closed chains. The ozonolysis of (β-)carotene gives *geronic acid* (p. 952), the yield

of which corresponds with that calculated for the oxidation of two β-ionone rings. Oxidation with permanganate under various conditions gives acetic, oxalic, αα-dimethylsuccinic, and αα-dimethylglutaric acids, together with β-ionone (p. 952).

From these results, the structure of β-carotene is represented by the symmetrical formula shown below, which is closely related to that of lycopene, and indeed may be derived from the latter by ring-closure of the two ends of the chain. The molecule of α-carotene, which is dissymmetric, differs from that of the β-isomeride only as regards the structure of that ionone ring which gives *iso*geronic acid on oxidation. γ-Carotene is monocyclic, and, structurally, consists of half a molecule of β-carotene joined to half a molecule of lycopene.

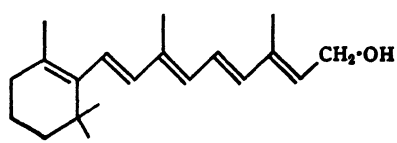


The given structures have been fully confirmed by a series of brilliant investigations by Kuhn and his collaborators.

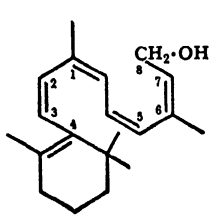
Many of the carotenoids are converted into an equilibrium mixture of isomerides when their solutions in, for example, benzene or petroleum ether are boiled during 30–60 minutes; a similar isomerisation occurs under the influence of catalysts such as iodine, or heat. During these changes decompositions also take place. Such isomerism is probably due to changes of configuration about one or more of the double bonds.

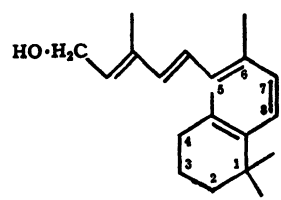
Vitamin A, $C_{20}H_{30}O$, occurs in the free state, and as esters, in the liver oils of many fish, notably the cod and halibut, and also in whale oil; it may be prepared by removing the hydrolysable matter and sterols from the liver extracts, followed by a chromatographic separation or distillation in a molecular still under 0·00001 mm. pressure. It has been obtained in crystals, m.p. 63–64°, from ethyl formate at a low temperature. Both α- and β-carotene yield vitamin A in the animal body, as does indeed any carotenoid which contains a β-ionone ring and five conjugated double bonds. With a solution of antimony trichloride in dry chloroform, vitamin A gives a deep blue colour (Carr-Price reaction, p. 653), which has been much used for estimating the vitamin; carotenoids give a similar colour.

When submitted to ozonolysis, vitamin A yields geronic acid in the amount required by one β-ionone ring per molecule and on catalytic hydrogenation it absorbs five molecules of hydrogen. From such facts, an examination of physical data, and relationship to the carotenes, the given structure of the vitamin was proved (Karrer):



Vitamin A

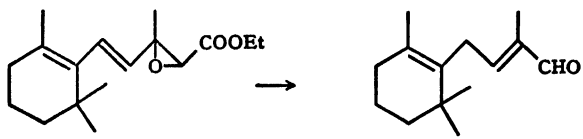




In the presence of hydrochloric acid and alcohol, vitamin A (concentrate) is transformed into a cyclic derivative which, on dehydrogenation with selenium, gives 1:6-*dimethylnaphthalene*; these changes are accounted for by Karrer's formula from which such a substance could be derived in either (or both) of the ways indicated (p. 978).

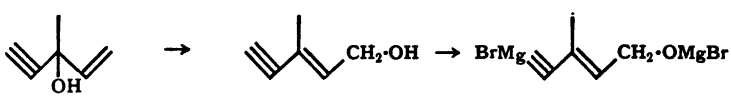
Vitamin A, identical in all respects with the natural product, has been synthesised as follows (Isler et al., Helv., 1947, **30**, 1911):

(1) β-Ionone is treated with ethyl chloroacetate and sodium methoxide at −60°, the resulting glycidic ester, (I), is hydrolysed, and the acid is heated with copper powder under reduced pressure; the product is an aldehyde, (II), during the formation of which the ethylenic linkage migrates and occupies the αβ-position to the aldehyde group:



I II

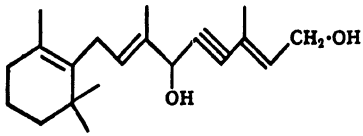
(2) Acetylene is condensed with methylvinyl ketone in liquid ammonia solution in the presence of sodium, and the product of hydrolysis, the tertiary alcohol, (III), is isomerised with sulphuric acid (p. 942), and thus converted into (IV), which, treated with an excess of ethyl magnesium bromide gives (V):



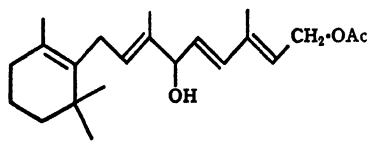
III IV V

(3) The aldehyde, (II), reacts normally with (V), and in the product of hydrolysis, (VI), the acetylenic link is then partially reduced to an olefinic bond; the acetyl derivative, (VII),[1] heated with iodine in petrol solution is converted into the acetate of vitamin A, from which, after hydrolysis, the pure crystalline vitamin is isolated with the aid of its crystalline β-naphthoate.

[1] A $-CH_2 \cdot OH$ group is much more easily acetylated than a $>C \cdot OH$ group.



VI



VII

Vitamin A_2 occurs associated with vitamin A in fresh-water fish: its structure only differs from Vitamin A in that it has another conjugated double bond in the ring.

Chromatographic Analysis. When a solution of an organic solid is filtered through a tightly packed column of a suitable absorbent such as alumina, calcium carbonate or lime, the solute is often deposited on the absorbent in a particular layer or zone (Tswett): the location of this zone depends upon the nature of the solute and that of the solvent and it may be made to travel gradually down the column by successive washings with the same (or a different) solvent. If now a mixture of two or more solutes in a suitable solvent (often benzene or petroleum ether) is submitted to the same process, the solutes are deposited in bands which may be further separated from one another by suitable washing (*development*). In the case of differently coloured solutes the bands may be cut off and the separated solutes extracted therefrom; such a process has proved invaluable in the separation of carotenoids (p. 976), chlorophylls (p. 647), and other pigments from one another (*chromatographic analysis*).

With colourless compounds a separation occurs in the same way, but as it is impossible to see the limits of the bands, various methods are used to determine their boundaries. Thus various colourless compounds may exhibit different fluorescent effects in ultra-violet light; or the whole column may be extruded from the tube and painted longitudinally with some indicator which reacts differently with the contents of the various zones.

Diphenylpolyenes

Some most interesting *diphenylpolyenes*, the molecules of which contain several conjugated systems of carbon atoms, have been prepared by Kuhn, R., and his collaborators (*J.* 1938, 605), principally in order to compare their behaviour with that of the carotenoids.

The molecules of these compounds contain two phenyl groups each of which is combined with a terminal carbon atom of the open chain ; unlike the di-olefines, butadiene, isoprene, etc., they do not polymerise readily, so that they are more suitable than such compounds for the object in view.

1:6-**Diphenylhexatriene**, $C_6H_5 \cdot CH{:}CH \cdot CH{:}CH \cdot CH{:}CH \cdot C_6H_5$, has been prepared in many different ways ; it can be obtained from cinnamic aldehyde, which on reduction is converted into *hydrocinnamoin*,

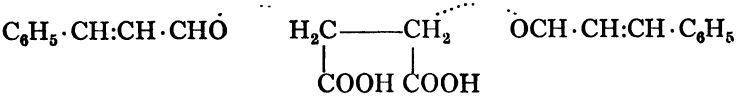
$$C_6H_5 \cdot CH{:}CH \cdot CH(OH) \cdot CH(OH) \cdot CH{:}CH \cdot C_6H_5,$$

just as benzaldehyde is transformed into hydrobenzoin (p. 501) ; this dihydroxy-compound is converted into diphenylhexatriene when its suspension in ether is treated with phosphorus di-iodide, as the organic di-iodide which is probably formed, spontaneously loses iodine. In a similar way,

$$Ph \cdot CH{:}CH \cdot CH(OH) \cdot CH{:}CH \cdot CH(OH) \cdot CH{:}CH \cdot Ph,$$

prepared from acetylene dimagnesium bromide and cinnamic aldehyde, followed by a partial reduction of the acetylenic linkage, gives *diphenyloctatetrene*.

An important general method for the preparation of polyenes is, by the condensation of aromatic aldehydes (2 mol.) with a dicarboxylic acid (1 mol.) in the presence of acetic anhydride and litharge, at temperatures above about 140° ; in this reaction two molecules of carbon dioxide, as well as $2H_2O$, are eliminated :



Instead of cinnamic aldehyde, its condensation product with acetaldehyde, $C_6H_5 \cdot CH{:}CH \cdot CH{:}CH \cdot CHO$ or crotonaldehyde, $C_6H_5 \cdot CH{:}CH \cdot CH{:}CH \cdot CH{:}CH \cdot CHO$, may be employed ; the former, with succinic acid, gives $C_6H_5 \cdot [CH{:}CH]_6 \cdot C_6H_5$, and the latter, $C_6H_5 \cdot [CH{:}CH]_8 \cdot C_6H_5$ (1:16-*diphenylhexadecaoctene*) ; other dicarboxylic acids, such as dihydromuconic acid (p. 814), may also be used instead of succinic acid, and by this method compounds, $Ph \cdot (CH{:}CH)_n \cdot Ph$, in which $n = 1$ to 8 were obtained, but the reaction cannot be used for the higher analogues.

Some of the latter have been prepared as follows: Unsaturated aromatic aldehydes such as those mentioned above are converted into thio-aldehydes with the aid of hydrogen sulphide, and the products are heated with copper,

$$2\text{Ph}\cdot(\text{CH:CH})_n\cdot\text{CHS} \longrightarrow \text{Ph}\cdot(\text{CH:CH})_{2n+1}\cdot\text{Ph};$$

in this way compounds in which $n = 5$ and 7 were prepared.

It is noteworthy that in such syntheses the resulting diphenylpolyene is only obtained in one form, although theoretically many might be expected, owing to the possibilities of *cis-trans*-isomerism; 1:4-diphenylbutadiene, prepared by various other methods, is known in the three forms predicted by theory, but of the six possible stereoisomerides of diphenylhexatriene, only one is obtained by the above general methods and this has been shown by X-ray analysis to be the *all trans*-compound.

Diphenylethylene or stilbene is colourless, and 1:4-diphenylbutadiene is only faintly yellow, but diphenylhexatriene is distinctly yellow, and the higher diphenylpolyenes are intensely coloured, yellow, orange, or copper-red compounds, in which respect they resemble the carotenoids; 1:22-diphenyldocosaundecene, $\text{Ph}\cdot(\text{CH:CH})_{11}\cdot\text{Ph}$, however, is violet-black (m.p. 318°) and 1:30-diphenyltriacontapentadecene, $\text{Ph}\cdot(\text{CH:CH})_{15}\cdot\text{Ph}$, is greenish-black. The polyenes dissolve in concentrated sulphuric acid, giving solutions the colours of which pass from yellow to blue as the number of olefinic bindings in the molecule increases; the more complex carotenoids also give blue colourations.

On reduction with sodium- or aluminium-amalgam, the diphenylpolyenes behave in a very remarkable manner; a hydrogen atom is added at each end of the chain, whereby both the $C_6H_5\cdot CH{:}CH—$ groups become $C_6H_5\cdot CH_2—CH{:}$, so that not only 1:4- (p. 813), but 1:6-, 1:8-, and 1:10-addition may take place in a complex conjugated system. The *dibenzylpolyenes* thus obtained are *colourless* and, unlike the diphenyl derivatives, readily undergo atmospheric oxidation, especially when they are slightly impure; when submitted to ozonolysis they give phenylacetic acid, together with a little phenylacetaldehyde, and the yield of the former alone is more than 75% of that theoretically possible on the assumption that the two hydrogen atoms are added at the ends of the chain only; in the presence of a catalyst the dibenzylpolyenes are completely reduced by hydrogen to the saturated hydrocarbons.

On reduction with molecular, instead of nascent, hydrogen, with the aid of a palladium catalyst, the diphenylpolyenes behave quite differently; some of their molecules undergo complete reduction, according to the quantity of hydrogen absorbed, whilst the others are unchanged.

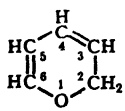
The addition of bromine to the diphenylpolyenes has not been fully investigated, but seems to take a different course from that of nascent hydrogen; that is to say, two bromine atoms do not combine with the terminal $C_6H_5 \cdot CH{:}CH—$ groups only.

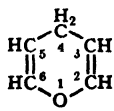
The diphenylpolyenes are oxidised by permanganate, but apparently less readily than the simple olefines; diphenylhexatriene, one of the more stable of these compounds, in acetone solution, is not attacked by permanganate at ordinary temperatures until after the lapse of some forty minutes.

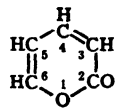
Another very interesting reaction of the diphenylpolyenes is described later (p. 1027).

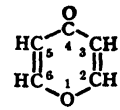
Pyrones

The term *pyran* is applied to the unknown *unsaturated* closed chains represented below, and the *pyranose* sugars are derived from the corresponding saturated structure (p. 874). The *unsaturated* closed chain compounds related to the pyrans are named *α-pyrone* and *γ-pyrone* respectively:


α-Pyran


γ-Pyran

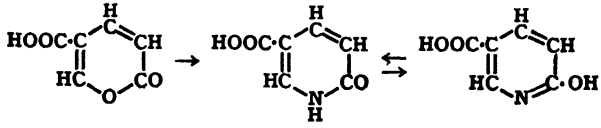

α-Pyrone


γ-Pyrone

Many derivatives of α- and γ-pyrone occur in nature, and many have also been prepared synthetically; such compounds, although containing olefinic bindings, do not behave like olefines, and do not react with hydroxylamine and other ketonic reagents. It is clear from its structure that α-pyrone is an unsaturated lactone and in the γ-isomeride the carbonyl group is conjugated with the cyclic oxygen atom; both substances, therefore, behave like lactones rather than like ketones.

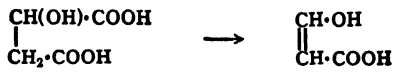
Both α- and γ-pyrone derivatives give with ammonia the cor-

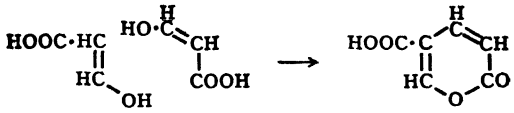
responding derivatives of a *hydroxypyridine* (or of its tautomeride, *pyridone*); *coumalic acid*, for example, gives 6-*hydroxynicotinic acid*,



and 2:6-*dimethyl-γ-pyrone* gives 4-*hydroxylutidine* (p. 985).

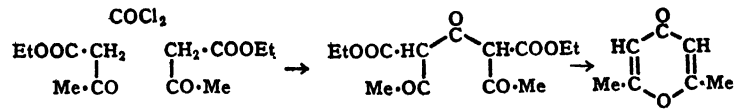
α-*Pyrone*-5-*carboxylic acid* (*coumalic acid*) is formed by the action of concentrated sulphuric acid on malic acid, possibly with the intermediate production of hydroxymethyleneacetic acid :





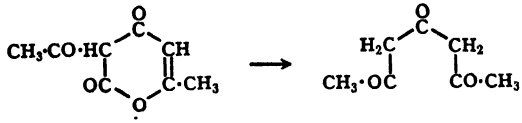
It melts at 206°, gives yellow salts with alkalis, and when heated alone is converted into α-pyrone (*coumalin*) and carbon dioxide. 6-*Phenyl-α-pyrone* occurs in *coto* bark.

2:6-**Dimethyl-γ-pyrone** can be obtained by treating the copper derivative of ethyl acetoacetate with carbonyl chloride and hydrolysing the product with sulphuric acid ; the acid thus formed readily loses carbon dioxide, giving diacetylacetone, which, probably in a di-enolic form, then loses the elements of water :



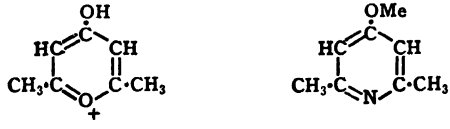
Dimethylpyrone can also be obtained from *dehydracetic acid*, $C_8H_8O_4$, which is produced, together with other compounds, when the vapour of ethyl acetoacetate is passed through a suitably heated iron tube. This so-called ' acid,' which has probably the given

structure, is decomposed by hydriodic acid, with the loss of carbon dioxide and the formation of diacetylacetone, which then gives dimethylpyrone:



Dimethylpyrone (m.p. 132°), as shown by Collie and Tickle (*J.* 1899, 710), combines directly with mineral and with organic acids, giving crystalline salts, such as the *hydrochloride*, $C_7H_8O_2$,HCl, and the *oxalate*, $(C_7H_8O_2)_2$,$C_2H_2O_4$; these salts are partially, but not completely, hydrolysed in aqueous solution, as shown by cryoscopic and conductivity measurements.

From time to time various formulae have been assigned to the cation of these salts; that shown, (I), is supported by the fact that the *methiodide*, $C_7H_8O_2$, MeI, corresponding with the hydrochloride, is transformed into *methoxylutidine*, (II), by treatment with ammonium carbonate in the cold:

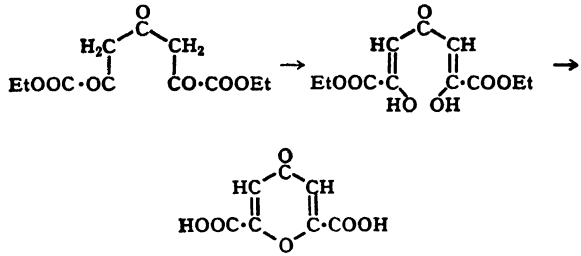


I II

The ring common to such (symmetrical) compounds is possibly a mesomeric form of two identical contributors as suggested for benzene.

Other oxonium derivatives are known, such as the compound Me_2O,HCl (formed from dimethyl ether and hydrogen chloride), and possibly the Grignard reagents.

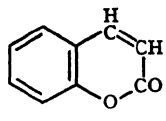
γ-Pyrone-2:6-dicarboxylic acid (*chelidonic acid*) occurs in *Chelidonium maius*. It is obtained from diethyl acetonedioxalate, which is prepared by the condensation of acetone with diethyl oxalate in the presence of sodium ethoxide; when this ester is heated with hydrochloric acid, it is hydrolysed and also loses the elements of water:



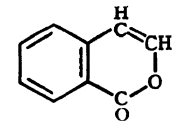
Chelidonic acid gives *acetonediacetic acid* and pimelic acid on reduction, and is decomposed by hot alkalis giving oxalic acid and acetone. When heated alone it loses carbon dioxide, giving first, *γ-pyrone-2-carboxylic acid* (*comanic acid*), and then **γ-pyrone** (m.p. 32°, b.p. 215°).

3-*Hydroxy-γ-pyrone*-2:6-*dicarboxylic acid*, or *meconic acid*, occurs in opium (p. 610).

Benzopyrones are formed, theoretically, by the condensation of the benzene and the pyrone nuclei. In this way α-pyrone gives rise to the coumarins (p. 709) and the less important *iso*coumarins.

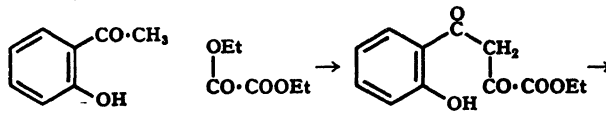


Coumarin



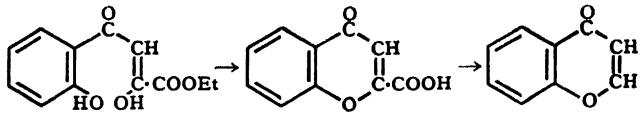
*Iso*coumarin

Chromone or *benzo-γ-pyrone*, is derived from γ-pyrone. It has been synthesised as follows: *o-Hydroxyacetophenone*,[1] (I), is condensed with diethyl oxalate in the presence of sodium, and the product, (II), is treated with alcoholic hydrochloric acid; the *chromonecarboxylic acid*, (IV), which is thus formed (from III) gives chromone, (V), when it is heated:



I II

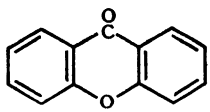
[1] Ethyl sodioacetoacetate is condensed with *o*-nitrobenzoyl chloride, and the product, $NO_2 \cdot C_6H_4 \cdot CO \cdot CH(COOEt) \cdot CO \cdot CH_3$, is hydrolysed: the resulting *o-nitroacetophenone* is converted into *o*-hydroxyacetophenone by the usual method. *o*-Hydroxyacetophenone is also obtained from phenyl acetate by the Fries reaction (p. 845).



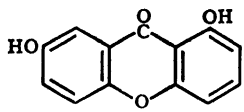
III IV V

Xanthone, *dibenzo-γ-pyrone*, is produced when *oo'*-diaminobenzophenone is diazotised and the solution of the diazonium salt is heated, as the *oo'*-dihydroxybenzophenone, which is first formed, loses the elements of water; it is also produced when a mixture of phenol and salicylic acid is heated with concentrated sulphuric acid. It crystallises in colourless needles, melting at 173°.

One of its dihydroxy-derivatives, *euxanthone*, occurs as a glycoside, *euxanthic acid*, the [illegible] salt of which is a yellow pigment (*piuri*, *Indian yellow*), deposited from the urine of oxen fed on mango leaves.

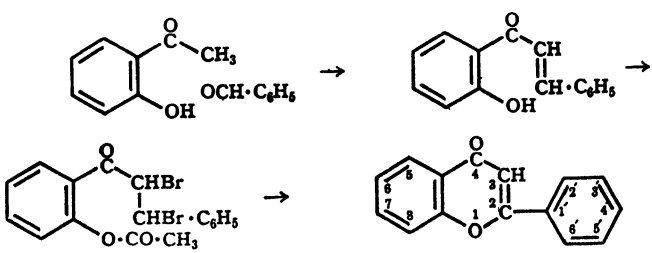


Xanthone



Euxanthone

Flavone (2-*phenylchromone*) was first obtained synthetically by Kostanecki. *o*-Hydroxyacetophenone is condensed with benzaldehyde in the presence of alcoholic potash, and the product, *benzylidene-o-hydroxyacetophenone*, is converted into its acetyl derivative; when the latter is brominated and the dibromo-derivative is treated with alkali, flavone is produced:



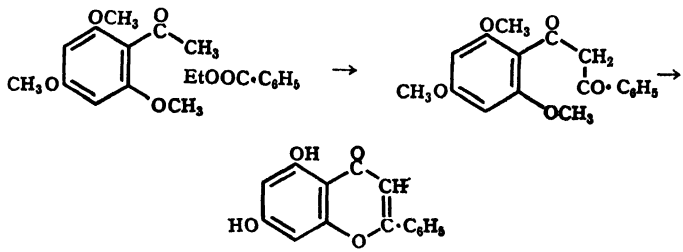
Flavone melts at 97° and occurs on the stalks and leaves of primula.

Anthoxanthidins and Anthoxanthins

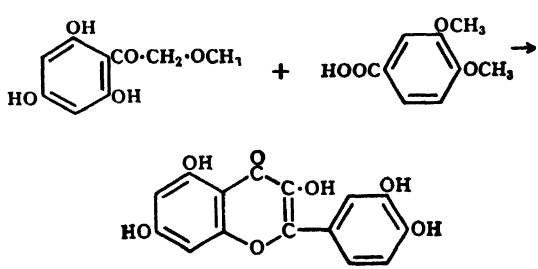
The **anthoxanthidins** are pigments derived from flavone, and many of them occur in plants, usually as their glycosides, the **anthoxanthins** : *chrysin*, 5:7-*dihydroxyflavone*, in the buds of the poplar ; *luteolin*, 5:7:3′:4′-*tetrahydroxyflavone*, in mignonette ; and *quercetin*, 3:5:7:3′:4′-*pentahydroxyflavone*, as its rhamnoside, *quercitrin*, in the blossom of the horse-chestnut.

Many such substances were first synthesised by Kostanecki.

Chrysin, for example, is formed by heating with hydriodic acid the product of the condensation of *phloroacetophenonetrimethyl ether* with ethyl benzoate in the presence of sodium ethoxide :



Anthoxanthidins have also been synthesised by Robinson and his co-workers by heating phloroacetophenone (2:4:6-*trihydroxyphenylmethyl ketone*), or one of its derivatives, with a mixture of the sodium salt and the anhydride of an aromatic acid. Thus phloroacetophenone, sodium benzoate, and benzoic anhydride yield a product which on hydrolysis gives chrysin ; similarly *ω-methoxyphloroacetophenone* and the sodium salt and anhydride of veratric acid (p. 612) give a product which, when demethylated, yields quercetin (*J.* 1926, 2334),



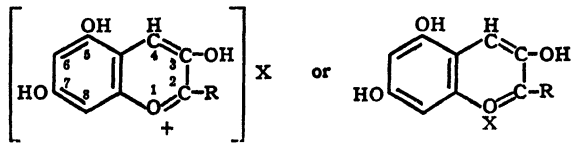
Many of the anthoxanthidins are decomposed when air is passed through their alkaline solutions, the pyrone nucleus undergoing disintegration ; a substituted benzoic acid and phloroglucinol [1] are thus obtained, and from the known structures of the products that of the anthoxanthidin may often be determined.

Anthocyanidins and Anthocyanins

The many beautiful colours of flowers and fruits are due mainly to a group of pigments known as the **anthocyanins.** These compounds combine phenolic and basic properties and form both alkali salts and well-crystallised salts with acids ; the latter are usually employed in their isolation. The free anthocyanins are violet, their alkali salts blue, and their salts with acids, red. A single anthocyanin, therefore, may often give rise to very different colours, which depend on its state of combination ; the colour of the blue cornflower, for example, is due to a metallic salt of *cyanin*, but, in the form of its salts with acids, cyanin gives rise to the colour of the red rose and geranium. The colour, however, is not entirely dependent on the degree of acidity of the cell-sap ; it may also be affected by the presence of colloids, other pigments, and the physical condition of the anthocyanin.

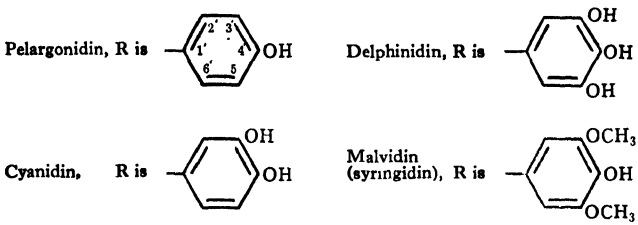
The anthocyanins are hydrolysed by hydrochloric acid, giving a sugar and a salt of an **anthocyanidin** ; *cyanin*, for example, yields glucose, and the anthocyanidin salt, *cyanidin chloride*. When they are further broken down by hot alkali they give phloroglucinol or one of its methyl ethers, and in addition a phenolic acid, or a methyl ether of a phenolic acid, which is characteristic of the particular anthocyanidin : *pelargonidin*, for example, gives *p*-hydroxybenzoic acid, *cyanidin* gives protocatechuic acid, and *delphinidin* gives gallic acid.

Mainly as a result of the researches of W. [illegible], it has been found that the anthocyanidin salts are substituted *hydroxybenzopyrylium* or *hydroxyflavylium* compounds of the general formula,



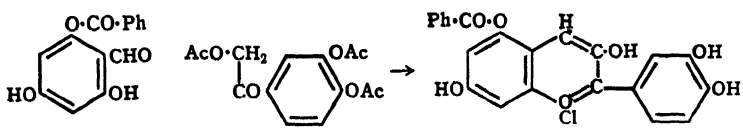
[1] Phloroglucinolcarboxylic acid, the formation of which might be expected, is decomposed in boiling aqueous solution, carbon dioxide being eliminated.

in which the group —R is an aromatic residue, containing one or more hydroxyl or/and methoxyl radicals, as shown below, and X is an acidic radical (compare p. 985):



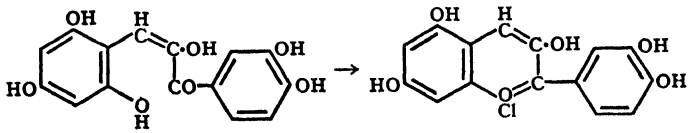
Almost all the anthocyanidins are derived from pelargonidin, cyanidin, or delphinidin, by the substitution of methyl radicals for hydroxylic hydrogen atoms.

The anthocyanidin salts were first synthesised by long and troublesome methods, but Robinson and his collaborators worked out simpler processes of which the synthesis of cyanidin chloride (*J.* 1928, 1526) may be taken as an example. Phloroglucinaldehyde, prepared from phloroglucinol by Gattermann's reaction (p. 502), is first benzoylated by the Schotten-Baumann method, and the product, 2-*benzoyloxy*-4:6-*dihydroxybenzaldehyde*, (I), is condensed with ω:3:4-*triacetoxyacetophenone*, (II) (p 993), in the presence of hydrogen chloride in ethyl acetate solution; 5-*benzoylcyanidin chloride*, (III), is thus produced, as the acetyl groups are eliminated during the reaction:



I II III, 5-Benzoylcyanidin chloride

The benzoyl group is then hydrolysed with aqueous-alcoholic alkali, which also breaks the pyrylium ring, giving (IV); on treatment with hydrochloric acid the pyrylium ring is re-formed with the production of cyanidin chloride, (V),

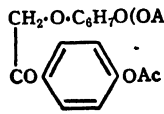


IV V, Cyanidin chloride

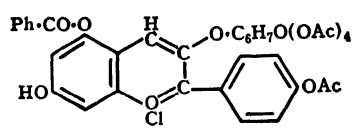
Using similar methods, pelargonidin chloride and delphinidin chloride have also been synthesised from the appropriate hydroxyacetophenone derivatives.

The anthocyanins are mono- or di-hexosides, or biosides, of the anthocyanidins, containing sugar residues in the 3- or 3:5-positions (p. 989): a single anthocyanidin may therefore give rise to two or more anthocyanins. The positions of the sugar residues in the molecules have been conclusively proved by the synthesis of the anthocyanins themselves (Robinson and Robertson, *J.* 1928, 1460):

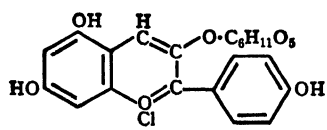
ω-[*Tetra-acetyl-β-glucosidoxy*]-4-*acetoxyacetophenone*, (VI), prepared as described later (p. 993), is treated as before with 2-*benzoyloxy*-4:6-*dihydroxybenzaldehyde* (I, p. 990), and the acetyl derivative, (VII), so formed is converted into the anthocyanin salt, (VIII), by successive treatment with alkali and acid.



VI



VII

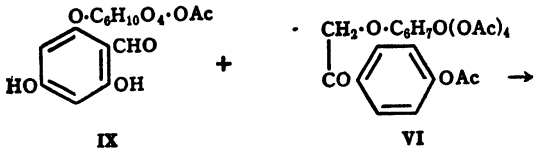


VIII, Callistephin chloride

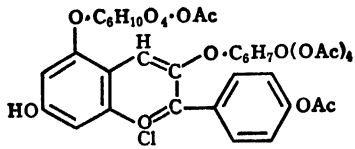
The product is identical with the naturally-occurring anthocyanin salt, callistephin chloride; it yields pelargonidin chloride and glucose on hydrolysis.

Pelargonin chloride, a diglucoside, has been synthesised as follows (Robinson and Todd, *J.* 1932, 2488): 2-*Monoacetyl-β-glucosidyl-*

phloroglucinaldehyde, (IX) (p. 993), is condensed in the usual manner with *ω-[tetra-acetyl-β-glucosidoxy]-4-acetoxyacetophenone*, (VI),

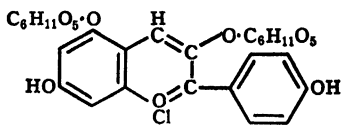


IX VI



X

and the product, (X), is converted into the anthocyanin salt, pelargonin chloride, by successive treatment with cold alkali and acid,

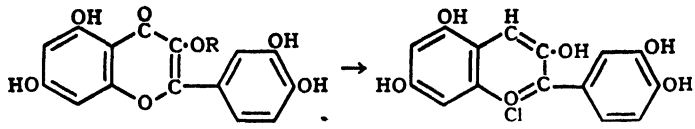


Pelargonin chloride

The presence of a free hydroxyl group in the 3-position (p. 989) apparently renders an anthocyanin open to attack by oxidising agents, such as ferric chloride, and this reaction may therefore be used to ascertain whether or not a sugar residue occupies that position.

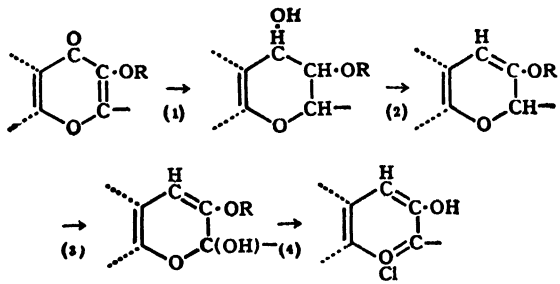
Conclusions as to the positions of the sugar groups can also be drawn from a careful comparison of the colour changes, with a variation of hydrogen ion concentration, of anthocyanins of known and unknown structures.

The anthocyanidins are closely related to the flavone pigments (anthoxanthidins), and the latter may often be converted into the anthocyanidins by reduction: *rutin*, for example, a glycoside of quercetin (p. 988), treated with sodium amalgam and alkali, is converted into a product which, with air and hydrochloric acid, yields cyanidin chloride, rhamnose and glucose,



Rutin (R = $C_{12}H_{21}O_9$) Cyanidin chloride

The changes in the pyrone nucleus probably involve reduction (1), loss of water (2), atmospheric oxidation (3), salt formation (with its redistribution of valencies), and hydrolysis (4),



The preparation of some of the compounds used in the syntheses of the anthocyanidins and anthocyanins is very briefly described below.

ω:3:4-*Triacetoxyacetophenone* (p. 990) has been obtained by condensing chloroacetic acid with catechol in the presence of phosphorus oxychloride and then heating the resulting halogen derivative with acetic anhydride and potassium acetate :

$$C_6H_4(OH)_2 \longrightarrow CH_2Cl\cdot CO\cdot C_6H_3(OH)_2 \longrightarrow AcO\cdot CH_2\cdot CO\cdot C_6H_3(OAc)_2$$

ω-*Hydroxy*-4-*acetoxyacetophenone* has been prepared as follows: Chloroacetyl chloride is treated with anisole and an excess of anhydrous aluminium chloride; during the reaction the methyl group is displaced by [illegible]. The —OAc group is then substituted for the chlorine atom as above, the acetyl compound is hydrolysed, and the sodium derivative of the phenolic product is acetylated :

$$MeO\cdot C_6H_5 \longrightarrow HO\cdot C_6H_4\cdot CO\cdot CH_2Cl \longrightarrow$$
$$HO\cdot C_6H_4\cdot CO\cdot CH_2\cdot OAc \longrightarrow AcO\cdot C_6H_4\cdot CO\cdot CH_2\cdot OH$$

This acetyl derivative, treated with tetra-acetyl-1-bromo-α-glucose (p. 879) in benzene solution in the presence of silver carbonate, gives ω-[*tetra-acetyl-β-glucosidoxy*]-4-*acetoxyacetophenone* (p. 991).

2-*Monoacetyl-β-glucosidylphloroglucinaldehyde* is obtained (to-

gether with the corresponding tetra-acetyl derivative) by the condensation with potash of phloroglucinaldehyde and tetra-acetyl-α-bromoglucose in acetone solution ; during this reaction the hydrolysis of three acetyl groups takes place. It is to be noted that the phloroglucinaldehyde derivatives are β-glucosides, although an α-glucoside is used in their preparation (footnote, p. 895), because a Walden inversion has occurred.

Depsides

By the interaction of the hydroxyl group of one molecule of a phenolic acid and the carboxyl group of another, a carboxy-derivative of a phenolic ester, $HOOC \cdot C_6H_4 \cdot O \cdot CO \cdot C_6H_4 \cdot OH$, may be obtained ; theoretically this compound might react with another molecule of the same or of a different phenolic acid, and by repetitions of such reactions there would be formed highly complex products,

$$HOOC \cdot C_6H_4 \cdot O \cdot [CO \cdot C_6H_4 \cdot O]_n \cdot CO \cdot C_6H_4 \cdot OH,$$

related to the phenolic acids, just as the polypeptides are related to the amino-acids (p. 620). To such compounds Fischer and Freudenberg gave the name *depside* (Gr. *depsein*, to tan), because many of them resembled the tannins (p. 998); they are distinguished as di-, tri-, etc. depsides, according to the number of their constituent phenolic acid residues.

Certain depsides had been previously obtained by the action of phosphorus oxychloride on a phenolic acid, but such products were indefinite in character and probably complex mixtures. Fischer controlled the course of depside formation by first ' protecting ' or ' blocking ' the phenolic group with the *carbomethoxy*-radical, —CO·OMe, which could be easily removed again by hydrolysis without bringing about the fission of the more stable depside link.

The phenolic acid is first treated with methyl chloroformate and cold dilute aqueous alkali; the resulting carbomethoxy-derivative, (I), is converted into the acyl chloride, (II), by treatment with phosphorous pentachloride in chloroform solution, and the product is then condensed with another molecule of the same or of a different phenolic acid in the presence of alkali. The substituted didepside thus formed, (III), may be hydrolysed with cold aqueous normal alkali, and thus converted into a didepside, or may be transformed into its acid chloride, and utilised in further analogous syntheses of tri-, tetra-, and poly-depsides.

I $MeO\cdot CO\cdot O\cdot C_6H_4\cdot COOH$ II $MeO\cdot CO\cdot O\cdot C_6H_4\cdot COCl$

III $MeO\cdot CO\cdot O\cdot C_6H_4\cdot CO\cdot O\cdot C_6H_4\cdot COOH$

The acid chloride, (II), may also be used for many other preparations; it reacts with esters of amino-acids, for example,

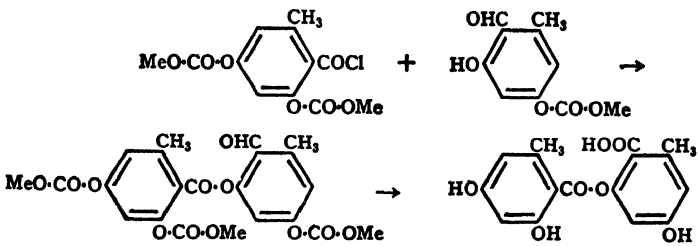
$$MeO\cdot CO\cdot O\cdot C_6H_4\cdot COCl + 2NH_2\cdot CH_2\cdot COOEt =$$
$$MeO\cdot CO\cdot O\cdot C_6H_4\cdot CO\cdot NH\cdot CH_2\cdot COOEt + HCl,NH_2\cdot CH_2\cdot COOEt,$$

and with benzene in the presence of aluminium chloride it gives substituted benzophenones. The carbomethoxy-group in the product is then displaced by careful hydrolysis.

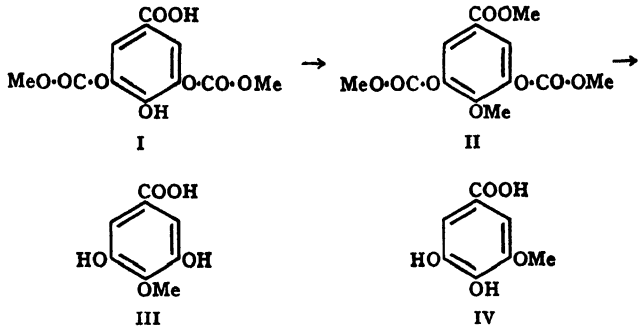
Phenolic groups situated in the *m*- or *p*-position to a carboxyl radical are easily carbomethoxylated, but those in the *o*-position are not; thus protocatechuic acid and gallic acid (p. 536) are both fully substituted by the method given above, whereas salicylic acid remains unchanged; by using a large excess of methyl chloroformate in benzene solution in the presence of dimethylaniline, however, the carbomethoxy-derivatives of salicylic acid and other *o*-phenolic acids may be prepared. Partially carbomethoxylated polyphenolic acids are prepared either by the use of carefully controlled quantities of the reagents, or by the graded hydrolysis of the fully substituted compounds; in the latter process, a carbomethoxy-group in the *p*-position to the carboxyl radical is often the more or the most easily displaced.

In some cases the hydroxyl in the *o*-position to a carboxyl group does not react readily with the acid chloride; this difficulty is overcome by condensing a carbomethoxy-derivative of a phenolic *aldehyde* with that of the acid chloride and then oxidising and hydrolysing the product.

o-*Di-orsellinic acid* was thus prepared from *dicarbomethoxyorsellinyl chloride* (p. 997) and p-*monocarbomethoxyorsellinaldehyde*:



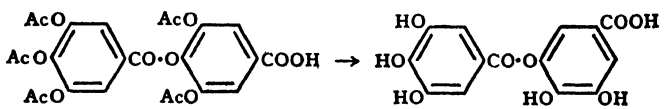
The *orientation* of partially carbomethoxylated phenolic acids, and of the depsides, may be accomplished with the aid of diazomethane. A dicarbomethoxylated gallic acid, (I), for example, yields the methyl derivative, (II), which, on hydrolysis, gives (III):



I II III IV

The structure of (III), and hence that of (II) and of (I), can then be established, because (III) can give only one monomethyl ether, or other phenolic derivative, whereas (IV) could give two isomerides. Similarly a study of the hydrolysis products of a completely *methylated* depside will settle the constitution of that compound.

Now, when the pentacarbomethoxy-derivative of *p*-digallic acid is hydrolysed, instead of giving *p*-digallic acid, as would be expected, it is converted into *m*-digallic acid; similarly, when penta-acetyl-*p*-digallic acid, (V), is hydrolysed with cold dilute ammonia, the product is not the expected p-*galloylgallic acid*, but m-*galloylgallic acid*, (VI), as hydrolysis is accompanied by the transference of the galloyl group from the *p*- to the *m*-hydroxy-group:



V VI

Such isomeric changes (p. 845) are quite common among the depsides, the investigation of which is thus rendered much more difficult.

Most of the didepsides, such as di-orsellinic acid, are crystalline, sparingly soluble in cold water, and give colour reactions with ferric chloride. They are easily hydrolysed by an excess of dilute

alkali, and with diazomethane they yield first their methyl esters, and then methyl ethers of these esters, all the phenolic being converted into —OMe groups. The didepsides of gallic, protocatechuic, and β-resorcylic acid (2:4-dihydroxybenzoic acid) precipitate dilute gelatine solutions, and solutions of quinine acetate (properties shown by tannin).

Tri- and tetra-depsides may also be prepared by the general methods. The tetradepside,

$$HO\cdot(MeO)C_6H_3\cdot CO\cdot O\cdot C_6H_4\cdot CO\cdot O\cdot C_6H_4\cdot CO\cdot O\cdot C_6H_4\cdot COOH,$$

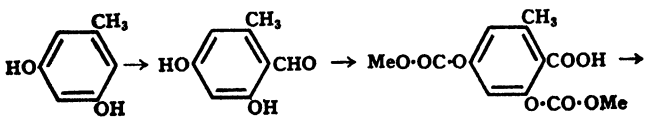
for example, is obtained by condensing *carbomethoxyvanilloyl*-p-*hydroxybenzoyl chloride*, (I),[1] with p-*hydroxybenzoyl*-p-*hydroxybenzoic acid*, (II), and then displacing the carbomethoxy-group by hydrogen,

I $MeO\cdot CO\cdot O\cdot(MeO)C_6H_3\cdot CO\cdot O\cdot C_6H_4\cdot COCl$

II $HO\cdot C_6H_4\cdot CO\cdot O\cdot C_6H_4\cdot COOH$

The chief natural sources of the depsides so far discovered are the lichens; *lecanoric acid*, $C_{16}H_{14}O_7$, for example, occurs in *Roccella* and *Lecanora*, and *evernic acid*, $C_{17}H_{16}O_7$, together with orsellinic acid, in *Evernia prunastri*. The constitutions of these acids have been established by the following syntheses:

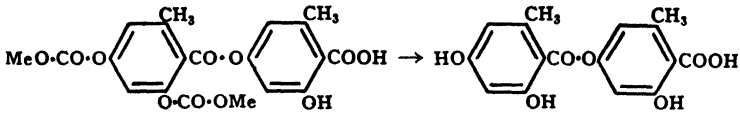
Orcinol, $C_6H_3(CH_3)(OH)_2$, (I), which can be obtained from 3:5-dinitrotoluene; is treated with chloroform and potash (Reimer-Tiemann), or with hydrogen cyanide and hydrogen chloride in the presence of aluminium chloride (Gattermann), and the resulting *orsellinaldehyde*, (II), is converted into its dicarbomethoxy-derivative which is oxidised; the product, (III), the dicarbomethoxy-derivative of orsellinic acid, is converted into its chloride, which, condensed with orsellinic acid, gives (IV):[2]



I II III

[1] Vanillic acid is $C_6H_3(COOH)(OCH_3)\cdot OH[OCH_3:OH = 3:4]$.

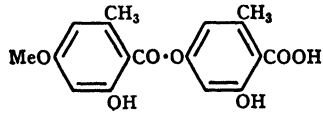
[2] Orsellinic acid yields two isomeric monomethyl ethers and must therefore have the structure assigned to it: if it were 2:6-dihydroxy-4-methylbenzoic acid, as would be possible from its method of synthesis from orcinol, only one ether could exist.



IV V

The didepside, (v), thus obtained, after the displacement of the carbomethoxy-groups, is identical with naturally-occurring lecanoric acid, which, therefore, is a *p*-diorsellinic acid, because it differs from *o*-diorsellinic acid prepared as described above (p. 995), and yet gives orsellinic acid on hydrolysis.

Lecanoric acid and evernic acid yield, with diazomethane, the same ester, *methyl trimethyllecanorate*, so that evernic acid is a methyl derivative of lecanoric acid, (v). Further, evernic acid, on hydrolysis, yields orsellinic acid together with *everninic acid*, which is known to be a *p*-methyl derivative of orsellinic acid ; the constitution of evernic acid, therefore, is



The above, and many other interesting syntheses, were rendered possible by the application of Fischer's simple method of protecting or blocking a phenolic group by the introduction of a radical which, subsequently, could be easily displaced.

Tannins

A brief description of tannin has already been given (p. 536) As long ago as 1854, Strecker suggested that some tannins were compounds of glucose and gallic acid, but owing to experimental difficulties it was impossible to prove that these two substances were not merely mixed together in the natural product. By dissolving pure commercial tannin from Chinese galls (oak-apples) in a slight excess of alkali carbonate and extracting the solution with ethyl acetate, Fischer obtained preparations containing no free carboxyl groups and which, on hydrolysis with 5% sulphuric acid, gave 7–8% of glucose and 93–92% of gallic acid ; it was thus shown that this particular tannin is probably a compound of one molecule of

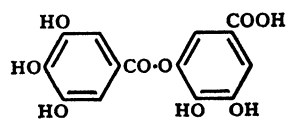
glucose with five molecules of *digallic acid* (a didepside), corresponding in structure with penta-acetyl or pentabenzoyl glucose.

Pentagalloylglucose was then prepared by carefully hydrolysing the carbomethoxy-derivative, obtained by the condensation of tricarbomethoxygalloyl chloride with glucose, in the presence of chloroform and quinoline,

$$C_6H_{12}O_6+5C_6H_2(O\cdot CO_2Me)_3COCl \longrightarrow$$
$$C_6H_7O[O\cdot CO\cdot C_6H_2(O\cdot CO_2Me)_3]_5 \longrightarrow C_6H_7O[O\cdot CO\cdot C_6H_2(OH)_3]_5$$

This compound showed a strong resemblance to tannin in that it had an astringent taste, and precipitated solutions of gelatin and of alkaloids; it was probably a mixture of α- and β-tetra-galloyl-galloylglucosides.

When tannin is methylated with diazomethane, a *methylotannin* is obtained (Herzig) which is indifferent towards alkali and therefore contains no free phenolic or carboxyl groups; on hydrolysis it yields glucose, *trimethylgallic acid*, and a *dimethylgallic acid*, in which the methoxy-groups are in positions 3 and 4 (COOH = 1). The digallic acid component of tannin, therefore, is probably a *m*-digallic acid,



Pentamethyl-m-*digallic acid* was therefore prepared from *trimethylgalloyl chloride* and 3:4-*dimethylgallic acid*, and its acid chloride was condensed with both α- and β-glucose in the manner described above. Two isomeric *penta*[*pentamethyl*-m-*digalloyl*]-*glucoses* (both of which were probably mixtures of α- and β-glucosides) were thus obtained; the preparation from β-glucose was very similar to methylotannin, but their identity could not be established.

Attempts to synthesise tannin itself, by the condensation of *penta-acetyl*-m-*digalloyl chloride* with β-glucose, followed by the displacement of the acetyl groups, gave a *penta*-m-*digalloylglucose* which was possibly an isomeride of natural tannin, but it differed from the latter in specific rotation; the structure of gallotannin, therefore, was not established. Certain tannins are derived from the catechins, which are hydrogenated anthocyanidins.

In the course of these experiments on the synthesis of tannin

various compounds of very high molecular weight were prepared, as, for example, *penta[pentamethyl*-m-*digalloyl]glucose*, M.W. 2050 (p. 999). By the condensation of tribenzoylgalloyl chloride (a substance which is easily prepared, and which crystallises well) with mannitol, a compound of molecular weight 2966 was probably obtained, but its composition could not be proved by analysis. When, however, p-*iodophenylmaltosazone* is similarly condensed with tribenzoylgalloyl chloride, the product contains halogen, and its composition can be fixed by iodine determinations.

Hepta[tribenzoylgalloyl]-p-*iodophenylmaltosazone*,

$$C_{12}H_{13}O_2(:N_2HC_6H_4I)_2[O\cdot CO\cdot C_6H_2(O\cdot CO\cdot C_6H_5)_3]_7$$

thus prepared, has a (calculated) molecular weight of 4020; that found from measurements of the freezing-points of its bromoform solutions agreed with this value, a fact which shows that the results of cryoscopic measurements are trustworthy even in the case of such complex molecules. The molecular weight of this compound, moreover, far surpassed that of any substance of known constitution which at that time had been synthesised.

CHAPTER 59

AROMATIC STRUCTURE AND SUBSTITUTION

Aromatic Structure

THE theory of resonance as applied to benzene and other aromatic compounds has been briefly outlined in Part II, but it must not be thought that the problems of the structure and reactions of benzene and its derivatives are thereby solved.

Prior to the advent of this theory the chemical behaviour of the aromatic hydrocarbon had been compared or contrasted with that of various unsaturated compounds such as dipropargyl (p. 379). The inferences drawn from such studies were however of questionable value because of the possible effects of the ring structure on all the properties and reactions of one of the compounds only.

In order to avoid this obvious disadvantage W[illiam] H[enry] Perkin and his collaborators (*Ber.* 1911, 3423; 1913, 517), after a very laborious investigation, prepared a hydrocarbon, C_8H_8, which they regarded as *cyclo*-octatetrene (p. 817) [1] and which therefore could be regarded as far more comparable with benzene in structure than any open chain hydrocarbon; but here again there was a complete dissimilarity in practically every respect. *Cyclo*-octatetrene combines with hydrogen in the presence of palladium, whereas benzene does not; it reduces permanganate, immediately forms an additive compound with bromine, and in other ways has nothing in common with the aromatic hydrocarbon. This contrast is now explained as follows: The molecule of benzene fulfils the conditions of resonance and exists in the mesomeric form. It is a symmetrical planar molecule as is shown by the X-ray examination of the crystal structure of benzene derivatives; also by the study of their infra-red spectra and measurements of their electron diffraction. The fact that substances such as diphenyl, *p*-dimethyl-, *p*-dichloro- and *p*-dibromo-benzenes, 1:3:5-trialkyl- and tribromo-benzenes have zero dipole moments also points to the planar distribution of the ring and the substituents. On the other hand, it has been shown mathematically that the molecule of *cyclo*-octatetrene cannot assume

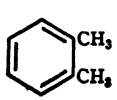
[1] *Cyclo*-octatetrene has since been obtained by the polymerisation of acetylene and all the pioneer results of Willstätter have been confirmed.

a mesomeric state ; a wide difference in properties between benzene and the cyclic olefine might therefore be expected.

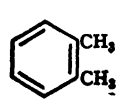
Some experimental evidence, in addition to that already given, that benzene has the postulated mesomeric structure (p. 390), is afforded by measurements of the carbon to carbon distances in its molecule ; if there were alternate double and single links in the ring, as in Kekulé's formula, the carbon-carbon distances should also alternate between 1·54 A.U., the single bond distance found in paraffins, and 1·33 A.U., the double bond distance found in olefines. In fact the bonds are all of equal length, namely 1·39 A.U., a value which lies between that of a single and that of a double bond.

Further physical evidence that the carbon atoms in benzene are not united by ordinary ethylenic bonds is afforded by the value of the heat of combustion of the hydrocarbon, which, as already stated, is 39,000 cal. less than that calculated for a compound of the Kekulé structure. Moreover, the heats of hydrogenation of benzene, *cyclo*hexene and ethylene are respectively 49,800, 28,590 and 32,580 cal. ; if benzene contained three ethylenic linkages similar to that of *cyclo*hexene, the heat of hydrogenation would be expected to be of the order of 86,000 cal., giving a value of nearly 36,000 cal. for the resonance energy.

Chemical evidence that benzene is a mesomeric compound is, of course, impossible to obtain as all the reactions of the hydrocarbon may be considered as the normal behaviour of such a structure. Nevertheless an interesting attempt to obtain such evidence was made by Levine and Cole (*J. Am. Chem. Soc.* 1932, 338) who studied the ozonisation of *o*-xylene. They found that the ozonide of this hydrocarbon when decomposed with water, gives glyoxal, methylglyoxal and diacetyl, all of which can be isolated in the form of their *p*-nitrophenylhydrazones, and it was shown later by Wibaut that the relative quantities of the products are such as would be expected from a mixture of equal quantities of (I) and (II) :



I



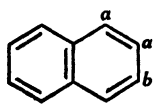
II

This result might be accounted for by assuming (1) That the mesomeric bonds, as such, undergo fission during ozonisation ;

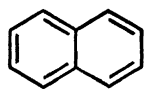
since all bonds are of the same type, the results would be as stated ; (2) That the mesomeric molecule passes into its Kekulé contributors, (I and II), prior to reaction and that ozonisation then proceeds normally ; if so, the postulated structurally isomeric *o*-xylenes are formed in equal quantities.

Unfortunately, therefore, the results are of little value as evidence either for or against the view that the benzene molecule exists in a mesomeric state.

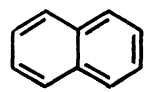
An attempt to show that the chemical behaviour of a mesomeric substance is determined by that of all its theoretically possible contributory forms has been made by Pauling, Brockway and Beach (*J. Am. Chem. Soc.* 1935, 2708) in the case of condensed ring hydrocarbons. Naphthalene, for example, may be represented by the following structures, all of which may contribute to the mesomeric state :



I



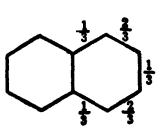
II



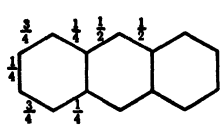
III

In (I) and (II) double bonds connect the $\alpha\beta$-atoms (a, a) and in (III) a single bond does so ; the reverse conditions apply to the $\beta\beta$-atoms (a, b). On the assumption that each structure contributes about equally, as doubtless do the identical structures (II) and (III), the $\alpha\beta$-links in the mesomeric form will have two-thirds, and the $\beta\beta$-links (and others) one-third of the character of a double bond as indicated in (IV) by the given numerical fractions. These conclusions are supported by the known facts concerning the positions at which naphthalene derivatives couple.

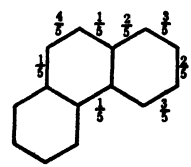
In the cases of anthracene and phenanthrene the characters of the various bonds in the respective resonance forms, (V) and (VI), can be deduced in a similar manner and indicated as before :



IV



V



VI

Here again the results give bond characters apparently in agreement with the known chemical properties of the hydrocarbons, such as the nearly olefinic nature of the 9:10-link in phenanthrene, which is shown by the ready oxidation of the hydrocarbon to diphenic acid; such deductions, however, are open to criticism (Lennard-Jones and Coulson, *Transactions of the Faraday Society*, 1939, 35, 817).

Substitution in the Benzene Series

The orientating or directing influence of an atom or group, already combined with the benzene nucleus, on the position which is taken up by a second substituent, has already been considered, and a simple empirical rule, concerning the position taken up by the entering group, has been given (p. 433).

Hammick and [illegible] (*J.* 1930, 2358) proposed another empirical rule: A mono-substitution product of benzene may be represented by $C_6H_5 \cdot A$ (A = halogen) or $C_6H_5 \cdot AB$; in the latter A is *any* atom directly united to the nucleus and B is an atom, or one of several atoms, directly combined with A, as for example the H of a CH_3 or the O of an NO_2. If now any atom B is in a *higher* group of the periodic table than is A, then further substituents enter the *meta*-position: when A and B are in the same periodic group, then if B is of lower atomic weight than A, *meta*-substitution again occurs. If no such atom B satisfies one of these conditions, substitution is *ortho-para*, and the same occurs if B is absent: further, if AB carries an ionic charge, a positive charge gives *m*- and a negative charge *op*-substitution. The following table gives a few illustrations of the application of this rule:

Group —AB	—NO_2	—CN	—Cl	—CH_3	—OH	—CH:CH—	—$CHCl_2$
A	N	C	Cl	C	O	C	C
B	O	N	—	H	H	C & H	H & Cl
Substitution occurs	*m*-	*m*-	*op*-	*op*-	*op*-	*op*-	*op*- *m*-

It must not be forgotten that in a great many cases both *op*- and *m*-substitution occur at the same time in variable proportions, so that the above rules only give an indication of which is the predominant reaction.

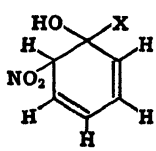
Many explanations or theories of aromatic substitution based mainly on Kekulé's formula have been put forward during the last sixty to seventy years; of these, only a few of the more important are considered here.

Holleman (1910), after prolonged investigation, summarised his conclusions as follows :

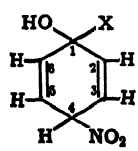
In every compound, C_6H_5X, X is directly united with a doubly-bound carbon atom, and it is known that the behaviour of such an atom or group is very greatly influenced by the immediate proximity of the ethylenic binding ; the chlorine atom in $CH_2{=}CCl{-}CH_3$, for example, is very resistant to double decomposition compared with that in $CH_2{=}CH{-}CH_2Cl$. It may be assumed, therefore, that X influences the double binding, since a mutual action between different groups in a molecule is a general phenomenon.

Now in such a group, C_6H_5X, the substituent X may facilitate or hinder addition, and from what is known about conjugated bindings (p. 813), addition in the 1:4, (II), as well as in the 1:2, (I) position may be influenced, whereas addition in the 2:3-position, (III), will not, since X is not directly combined with the olefinic linkage. Consequently, the velocity of the *additive* reaction in the *o*- and *p*-positions will be increased or decreased, but addition in the *m*-position will not be influenced.

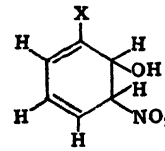
It is very probable that substitution is preceded by addition. Thus, in nitration, the first products may be those shown below ; these lose the elements of water, whereby the less stable olefinic 6-ring reverts to the benzene structure. The velocity of the additive reactions in the three cases represented will determine the type of substitution.



I



II



III

If X increases the velocity, substitution is *op* (I and II), and exclusively so if X has a very large accelerating effect, for in that case the quantity of *m*-product will be negligible. If the effect of X is not so great, the proportion of *m*-derivative, (III), will be greater. If, on the other hand, X retards addition, the proportion of *m*-derivative will be large, and the slowness of *m*-substitution in general will be explained.

Just as in processes of addition to conjugated systems, the formation of 1:4- products is accompanied by that of 1:2-, so also in the

aromatic compounds. The relative proportions in which *o*- and *p*-compounds are formed varies within very wide limits and depends on the nature of X, on that of the substituting reagent, on the temperature, and other conditions. All these factors influence the results but do not cancel the accelerating effect of X. If the *m*-compound is the main product, the *o*-derivative is often formed at the same time. This is also explained since primary addition may give NO_2 at 2 or at 3.

Holleman himself points out that his views do not make it possible to *predict* the effect of a given substituent any more than it is possible to predict the nature of the effect of a catalyst.

In 1919 Vorländer discussed the question whether or not electrical charges within the molecules of the reacting substances were the directing agents in aromatic substitution (*Ber.* 1919, 263). This possibility had been considered previously by Hübner, Nölting, and others, and it had been pointed out that groups such as $-NO_2$, $-SO_3H$, and —COOH, which are *m*-orientating, might be regarded as electro-negative (or acidic) because they occurred in the anions of acids :

$$\overset{-}{N}O_3\overset{+}{H},\ \overset{-}{S}O_4\overset{+}{H}_2,\ R\cdot\overset{-}{C}O\overset{+}{O}H.$$

The basic group, $-NH_2$, which is *op*-orientating, was then considered to be electro-positive, and by implication or otherwise the halogens, —OH, $-CH_3$, and other *op*-orientating groups were also regarded as electro-positive.

Such a classification of aromatic substituents, however, was an arbitrary one ; the —OH group and the halogens might at that time, with much more reason perhaps, have been considered to be negative radicals.

Vorländer also discussed this question as to whether a given atom or group should be labelled positive or negative, and he represented some of the principal aromatic substituents as follows :

op-Orientating $-\overset{-}{N}H_2$, $-\overset{-}{O}H$, $-\overset{-}{O}Me$, $-\overset{-}{C}H_3$ and the halogens ;

m-Orientating $-\overset{+}{N}O_2$, $-\overset{+}{C}O\cdot\overset{-}{O}H$, $-\overset{+}{S}O_2\cdot\overset{-}{O}H$.

He argued that nitric acid should be represented by $\overset{+}{H}O\overset{-}{N}O_2$, and that when it reacts with benzene it behaves like a true hydroxy-base, the benzene playing the part of an acid ; similarly in the case

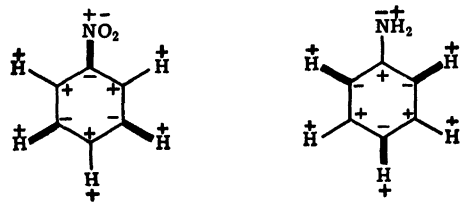
of sulphuric acid. He also pointed out that in acyl chlorides the R·CO— group plays the part of, say, Na in NaCl, and is therefore positive. As further evidence that the three *m*-orientating groups given above should be regarded as positive, he drew attention to the fact that their directive action is the same as that of the very strongly positive quaternary ammonium radical.

He then classified some forty aromatic substituents as positive or negative according to their *known* orientating effect on nitration or bromination ; when represented in the manner shown above, the positive or negative character of the substituent is that of the *atom* which is directly combined with carbon of the nucleus, so that substituents previously regarded as *negative* were now classed as *positive* and *vice versa*. On such a basis Vorländer founded the following rules of substitution :

I. In the formation of disubstitution products of benzene by halogenation or nitration, the entering substituent is directed mainly into the *m*-position by positive, into the *o*- and *p*-positions by negative side chains already present in the molecule.

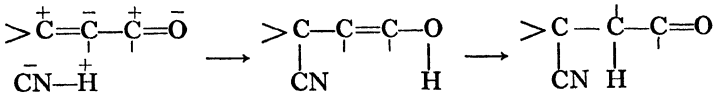
II. The carbon atoms of the nucleus behave negatively towards a positive, and positively towards a negative substituent.

In order to account for this behaviour he assumed that the positive or negative influence of the substituent extended to all the carbon atoms of the nucleus, which become *alternately* − or + as shown below :



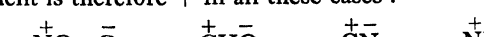
The nuclear H atoms in any such substitution product are now no longer bound with equal, but by different strengths, as indicated by the light and heavy lines ; those joined to the carbon atoms by heavy lines are in a state of greater tension (electrical potential difference), and will be more readily displaced than the others ; they have stronger positive charges and will react more energetically with bromine, for example, to form HBr, or with nitric acid to form H_2O. Consequently the positive substituent, NO_2—, causes *m*-, whereas the negative substituent, NH_2—, causes *op*-orientation.

At about the same time, in order to explain certain abnormal reactions of aliphatic compounds, Lapworth (*Proc. Manchester Literary and Philosophical Society*, Vol. 64, 1920) put forward his views on *induced alternate polarities*. According to him a particular atom (the ' key ' atom) at the end of a chain in a molecule, may have a positive or a negative effect, which is transmitted along that chain. In the molecule of an $\alpha\beta$-unsaturated ketone, for example, the ' key ' atom, oxygen, induces an alternating effect, so that in its reactions the compound shows, or appears to show, polar properties; thus the combination of such a ketone with hydrogen cyanide often does not give a cyanohydrin but may be expressed by

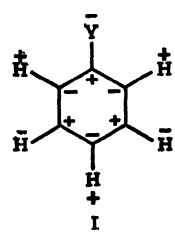


The signs + and −, however, do not imply that the atoms so marked actually carry electrical charges, but that these atoms seem to display these relative polar characters at the instant of the chemical change in which they take part.

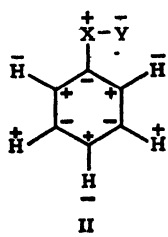
These views were then applied to benzene derivatives, and that atom of the substituent which is directly united to carbon of the nucleus was given a + or − sign according to that which had been assigned to the ' directive ' or ' key ' atom. Thus in the nitro- and aldehyde groups the oxygen atom is the key atom, whereas in the cyanogen group the key atom is nitrogen and in a quaternary chloride it is the nitrogen atom of the positively charged ammonium group; the substituent is therefore + in all these cases:



The polarity induced by the ' key ' atom is then extended to all the carbon and hydrogen atoms of the nucleus, which are marked + or − alternately:



I



II

Compounds of the type (I), reacting with $\overset{-}{HO}\cdot\overset{+}{NO_2}$, $\overset{-}{HO}\cdot\overset{+}{SO_3H}$, or halogen will therefore give *op*-, whereas those of type (II) will give *m*-derivatives, H^+ combining with the negative, and C^- with the positive radical or atom, as ..... by Holleman.

Modern views on aromatic substitution are based on considerations of how the inductive and mesomeric effects of substituents will influence the availability of electrons at different positions in the nucleus. Aliphatic hydrocarbons do not readily undergo substitution and their derivatives of the type RX usually react by a nucleophilic mechanism in which a negative reagent or ion attacks where there is a deficiency of electrons. Aromatic hydrocarbons in general are readily substituted and the ease of substitution is frequently increased by groups which are not themselves displaced ; the very different behaviour of benzene and of phenol towards nitrating and halogenating agents is an example. Aromatic substitution is usually brought about by *electrophilic* reagents which are themselves deficient in electrons and which therefore attack where electrons are most available ; such groups are Br^+, NO_2^+, HSO_3^+, $CH_3\cdot CO^+$, $Ph\cdot N_2^+$, etc. Simultaneously with the electrophilic attack on the nucleus, or immediately after it, a proton is lost from the point of attack, as is shown in the following examples :—

$$C_6H_6+Br^+ = C_6H_5Br+H^+,$$
$$C_6H_6+NO_2^+ = C_6H_5\cdot NO_2+H^+,$$
$$C_6H_6+HSO_3^+ = C_6H_5\cdot SO_3H+H^+,$$
$$C_6H_6+CH_3\cdot CO^+ = C_6H_5\cdot CO\cdot CH_3+H^+,$$
$$Me_2N\cdot C_6H_5+Ph\cdot N_2^+ = Me_2N\cdot C_6H_4\cdot N_2\cdot Ph+H^+,$$

The evidence for nitration being effected by the nitronium ion, NO_2^+, is strong and the existence of this ion has been proved in many ways. Firstly, cryoscopic measurements of solutions of nitric acid in sulphuric acid show that the depression of the freezing-point is four times larger than would be produced by undissociated nitric acid : this is explained by the following reaction,

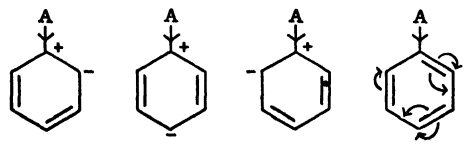
$$HNO_3+2H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + 2HSO_4^- ;$$

secondly, examination of the Raman spectra of solutions of nitric acid in sulphuric acid and comparisons with many other spectra have shown the presence of the NO_2^+ ion in such solutions, and thirdly, the kinetics of nitration can only be explained by assuming that the nitronium ion is the nitrating agent. In cases of substitution

other than nitration the evidence is less conclusive, but, for example, in halogenation and in the Friedel-Crafts reaction where catalysts are employed, these probably act by removing the negative ion as a complex, $AlCl_4^-$, $FeCl_3Br^-$, or by forming complexes with one of the reactants, $RAlCl_4$.

The influence of a substituent on the distribution of electrons in the nucleus depends on the nature of the substituent and may be considered under four headings.

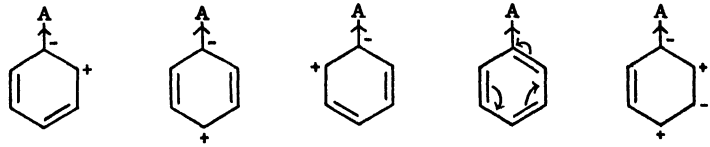
(1) *The substituent A has an electron-repelling inductive effect.* The end forms which, with the usual Kekulé forms, contribute to the total mesomeric state are (I), (II) and (III) and the final mesomeric form is represented by (IV),



I II III IV

At the instant of reaction electromeric change to (I), (II) or (III) occurs and an electrophilic reagent attacks at the 2-, 4-, or 6-positions where electrons are available : *op*-substitution results. It is seen that in (I), (II) and (III) the 1-carbon atom to which A is attached has only a sextet of electrons so that probably the contributions of these forms to the total mesomerism will not be great, but sufficient to control the orientation of further substitution. It is also to be noted particularly that the 3- and 5-carbon atoms are unaffected in all cases : it is impossible to write a structure with a negative charge on these atoms without exceeding the octet rule. The general inductive effect will, however, cause a drift of electrons away from A increasing their availability over the whole nucleus, but to a much greater extent in the *o*- and *p*-positions, making substitution more rapid than in benzene itself. Toluene, which is a compound containing a group of this sort, for example, is converted into mononitrotoluene nearly 25 times as fast as benzene is nitrated to nitrobenzene.

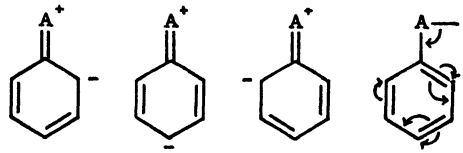
(2) *The substituent A has an electron-attracting inductive effect.* The end forms are (V), (VI) and (VII) and the final mesomeric form (VIII),



V VI VII VIII IX

Again octets are not maintained in (V), (VI) and (VII) as the 2-, 4- and 6-carbon atoms respectively have only a sextet of electrons; the only atom with available electrons is that at 1- to which the group A is attached and at which substitution cannot occur without displacement of A: such a displacement does indeed sometimes occur. In the electromeric forms the 3- and 5-positions are again unaffected, but owing to the deficiency of electrons at the 2-, 4- and 6-carbon atoms electrons are most available at the *m*-positions; even here, however, their availability is not great and is diminished and made less than in any position in benzene itself by the general inductive effect towards A. Substitution cannot therefore occur at 2-, 4- or 6- and is forced to take place at 3- and 5-: it will however be slower than in benzene. Examples of compounds containing groups with this effect are the quaternary salts of $Ph \cdot NMe_3^+$, $Ph \cdot PMe_3^+$, $Ph \cdot AsMe_3^+$, etc., all of which show slow *m*-substitution. It might be thought that forms such as (IX) in which the 3-position has a negative charge and is therefore activated would be possible contributors to the mesomerism, but in this there are two carbon atoms with only a sextet of electrons and it is assumed that it is too unstable to make an appreciable contribution.

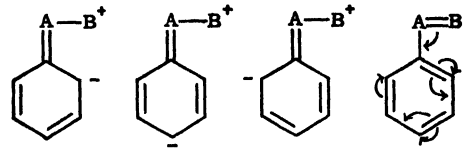
(3) *The substituent A has an unshared pair of electrons on the atom directly attached to the nucleus.* In this case the unshared pair can be concerned in the mesomerism and forms (X), (XI) and (XII) are contributors to the final state indicated by (XIII) (compare p. 695*f*), Octets are maintained in all forms (even on the group A) which



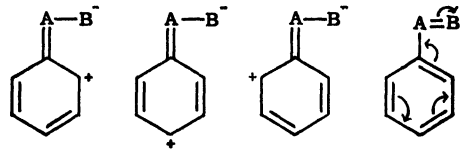
X XI XII XIII

therefore probably contribute more to the final mesomeric state than the forms discussed above in which sextets of electrons are found. In the electromeric forms (X), (XI) and (XII) electrons are available at the 2-, 4- and 6-positions respectively and *op*-substitution will occur ; furthermore it will be much more rapid than in benzene owing to the high electron density at these positions. Aniline and phenol are examples of compounds containing groups of this sort and their extremely easy and rapid *op*-substitution is familiar and illustrated by the formation of tribromo-derivatives in cold aqueous solution, by diazo-coupling, etc.

(4) *The atom A directly attached to the nucleus has another atom attached to it by a multiple link.* Here a pair of electrons of the double (or triple) bond can participate in the mesomerism in either of two ways as indicated in (XIV)-(XVII) or (XVIII)-(XXI),



XIV XV XVI XVII



XVIII XIX XX XXI

In none of the contributors are all octets maintained : the atom with the positive sign has only a sextet of electrons. It is clear that case (*a*) represented by (XIV)-(XVII) resembles type (1) and *op*-substitution will result : styrene, $C_6H_5 \cdot CH{:}CH_2$, is a substance of this kind. The case (*b*) represented by (XVIII)-(XXI) is similar to type (2) and slow *m*-substitution will occur : all compounds containing the carbonyl group directly attached to the nucleus, as, for example, benzaldehyde, acetophenone, benzoic acid and ethyl benzoate are of this type, owing to the mesomeric effect of that group. Benzene is mononitrated nearly 300 times as fast as is ethyl benzoate, under the same conditions.

The various effects described above may be summarised as follows:

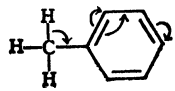
	Type	*Example*	*Orientating Effect*
(1)	Ph←A	Ph·CH_3	*op-*
(2)	Ph→A	Ph·NMe_3X	*m-*
(3)	Ph↶A	Ph·OH	*op-*
(4*a*)	Ph↶A=B	Ph·CH:CH_2	*op-*
(4*b*)	Ph↷A=B↶	Ph·COOEt	*m-*

Such then is the general theory of aromatic substitution and it remains to examine some individual cases in more detail and to see how some of the separate effects just described may be superimposed on one another.

The inductive effect of the halogens might be expected to place them in type (2), but they are, in fact, *op*-directing: it must therefore be assumed that a mesomeric effect of type (3) is more powerful, but as the inductive effect is in the opposite direction the mesomeric effect is partly nullified and the slow *op*-substitution found experimentally results. Chlorobenzene is mononitrated at only 3 per cent. of the speed of benzene under the same conditions. It usually happens that when an inductive and a mesomeric effect are both present the latter controls the electromeric effect.

In nitrobenzene and benzenesulphonic acid the substituents both have strong dipoles, $-{}^{+}NO_2{}^{-}$ and $-{}^{+}SO_2{}^{-}-OH$ respectively; their inductive effect is of type (2) and their mesomeric effect of type (4*b*). The effects therefore reinforce one another and slow *m*-substitution results, which is, of course, in accord with experiment.

It has been suggested that the strong *op*-directive effect in toluene may not be entirely due to the inductive effect, but that a methyl group attached to a conjugated system may exert a mesomeric effect by a process known as *hyperconjugation*: the electrons of the C—H bonds of the methyl group are assumed to be less localised than those of a C—C bond and permit of greater electron release in the *op*-positions (XXII). The same effect might account for the large fall in acid strength in passing from formic to acetic acid.

XXII 

When the series toluene, benzyl chloride, benzylidene dichloride, benzotrichloride is considered it might be expected that the inductive effect of the halogen atoms would gradually convert the electron repulsion of the unsubstituted side chain into an attraction, with consequent change from predominantly *op-* to predominantly *m*-substitution. That this is indeed the case is shown by the following figures for the percentage of *m*-compound formed by nitration of the relevant substances,

$C_6H_5 \cdot CH_3$	$C_6H_5 \cdot CH_2Cl$	$C_6H_5 \cdot CHCl_2$	$C_6H_5 \cdot CCl_3$
4	14	34	64

Experiment therefore confirms the theoretical conclusions, but it might perhaps have been expected that benzotrichloride would have been more strongly *m*-directing than it is in fact.

The inductive effect of the chlorine atoms in the above cases has only been transmitted through one carbon atom and it might be anticipated that such an effect would gradually diminish if a saturated side chain of increasing length is introduced between a chlorine atom or a group with a similar inductive effect, and the nucleus. That this is so is shown by the figures for the percentage of *m*-nitration in two series of compounds which both have a strongly electron attracting group in the side chain,

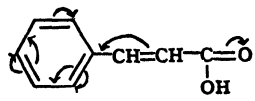
$Ph \cdot NMe_3X$	$Ph \cdot CH_2 \cdot NMe_3X$	$Ph \cdot CH_2 \cdot CH_2 \cdot NMe_3X$	$Ph \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NMe_3X$
100	88	19	5

$Ph \cdot NO_2$	$Ph \cdot CH_2 \cdot NO_2$	$Ph \cdot CH_2 \cdot CH_2 \cdot NO_2$
93	48	13

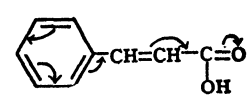
Incidentally these figures are entirely opposed to the alternate polarity views, according to which the second compound in each series should give *op-*, and the third should give predominantly *m*-substitution.

It would not, however, be anticipated that the same damping of the inductive effect would be shown in an unsaturated side chain in which the substituent is conjugated with the nucleus, but in fact

such is even more the case. Thus benzoic acid is *m*-, but cinnamic acid *op*-directing, as is $Ph \cdot CH{:}CH \cdot NO_2$; the effect of the strongly electron attracting carboxyl or nitro-group is completely lost although it is directly conjugated with the nucleus and the following (most unlikely) state (I) must be assumed, instead of the much more obvious (II),



I

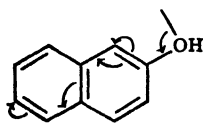


II

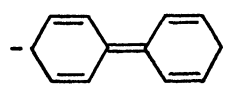
The mononitration of cinnamic acid is however about ten times slower than that of benzene and there must then be a general inductive effect in the opposite direction to the mesomeric effect.

A case which falls well in line with theory is the decrease of reactivity produced by acetylating aniline; this is due to the electron attraction of the carbonyl group which makes the unshared pair of the nitrogen atom less available for participation in the mesomerism of the nucleus.

The theory outlined above may be extended to polycyclic compounds such as naphthalene and diphenyl and to heterocyclic aromatic substances. Thus the substitution of α-naphthol and α-naphthylamine in the 2- and 4-positions is easily understood and the substitution of β-naphthol at 1- or 6- is also clear (III): in diphenyl forms such as (IV) contribute to the mesomerism and give *op*-direction in both rings,



III



IV



V

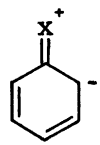
In the case of pyridine the strongly acidic solutions used in nitrations, etc., convert the base into a salt (V) in which the nitrogen atom then has a similar *m*-directing and deactivating effect to that in the quaternary ammonium derivatives and nitrobenzene. In pyrrole, however, where the lone pair is already participating in the mesomerism of the ring no salt formation is possible and

forms such as those shown on p. 591 account for the great reactivity of both the α- and β-positions.

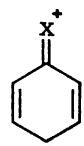
As an example of a nucleophilic, as contrasted with the usual electrophilic, substitution in the aromatic series the action of potash on nitrobenzene in the presence of air to give nitrophenol may be mentioned ; in this case the substituting group is the OH^- ion, and an oxidising agent (air) must be present to oxidise the H^- which is formed, to water. Attack should therefore be at positions of least electron density, that is to say the *o*- and *p*-positions from which electrons are withdrawn ; the product is in fact *o*-nitrophenol. The action of sodamide on pyridine to give α-aminopyridine is similarly nucleophilic.

A few other applications of the electronic theory to aromatic chemistry may be considered.

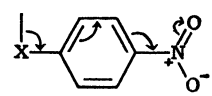
The stability of the aromatic halides is attributed to contributions of forms such as (I) and (II) to the mesomerism ; both the S_N1 and S_N2 reactions are made difficult as in the vinyl compounds.



I

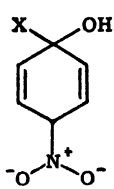


II

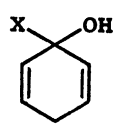


III

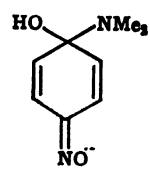
When electron-attracting groups such as NO_2 are present in the *o*- and/or *p*-position it would appear that the above effect should be enhanced and the halides be more stable ; the reverse is, of course, the case and it must be assumed that the carbon atom of the nucleus to which the halogen is attached becomes more positive by withdrawal of electrons, (III), thus allowing easier S_N2 reaction by a nucleophilic reagent. A more convincing explanation is perhaps found if the transition state is considered ; this is as shown,



IV



V



VI

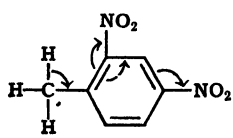
(IV), and the negative charge can be on oxygen, whereas on the unsubstituted halide it must be on carbon, (V).

A similar case of easy hydrolysis is provided by *p*-nitrosodimethylaniline and here again the negative charge of the transition state can be on oxygen, (VI). Such considerations show how the electronic theory can rarely be applied with complete safety unless all the experimental facts are known ; almost as many new facts can be predicted from applications of analogy to organic reactions as from theoretical considerations.

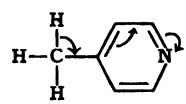
A case of activation of hydrogen atoms in a side chain is provided by 2:4-dinitrotoluene which condenses with benzaldehyde to give 2:4-dinitrostilbene,

$$Ph \cdot CHO + H_3C \cdot C_6H_3(NO_2)_2 = Ph \cdot CH{:}CH \cdot C_6H_3(NO_2)_2 + H_2O \ ;$$

the strongly electron-attracting nitro-groups conjugated through the nucleus with the methyl group cause incipient ionisation of the hydrogen atoms of the latter, (I). Similar activation is shown by the 2- and 4-methylpyridines, (II), and quinolines by the electron attraction of the heterocyclic nitrogen atom,



I



II

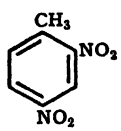
CHAPTER 60

THE ORIENTATION OF BENZENE DERIVATIVES. POLYCYCLIC HYDROCARBONS

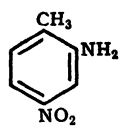
Orientation of Benzene Derivatives

It may be taken for granted that practically every known di-substitution product of benzene, $C_6H_4X_2$ or C_6H_4XY, has already been orientated by the methods described on pp. 394-399, and that the structure of a new di-derivative might be readily determined by converting the compound into one of those of known orientation. Many tri-substitution products, in which two, or all, of the substituent atoms or groups are identical, have also been orientated by Körner's method.

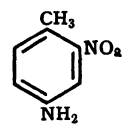
There are, however, various simpler processes by which the structures of compounds, C_6H_3XYZ, may be determined. When toluene is nitrated it gives three mononitro-derivatives ; the *o*- and *p*-compounds, which are the principal products, can be converted into one and the same dinitro-derivative, which, therefore, must be the 1:2:4-compound, (I). This dinitro-derivative, on reduction with ammonium sulphide, affords a mixture of two bases, $C_6H_3(NH_2)(NO_2)\cdot CH_3$; one of these is also obtained by the nitration of *o*-toluidine, in the form of its acetyl derivative, and must therefore be represented by (II), whereas the other base is produced in a similar manner from *p*-toluidine and must have the structure (III).



I



II



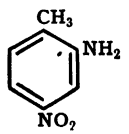
III

From each of these bases many other compounds may be prepared, such as $CH_3{:}NH_2{:}NH_2$, $CH_3{:}OH{:}NO_2$, and $CH_3{:}Cl{:}NO_2$, and the orientation of all such derivatives is thus established by synthesis.

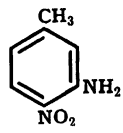
In many cases such simple methods are not available, and the following procedure is adopted : One of the substituents, say X, in the compound, C_6H_3XYZ, is displaced by hydrogen ; the product, C_6H_4YZ, is then identified as the *o*-, *m*-, or *p*-compound,

as the case may be, from a study of its properties, especially, if possible, by a mixed melting-point determination. A second substituent, say Y, in the compound, C_6H_3XYZ, is then displaced by hydrogen, and, as before, the product, C_6H_4XZ, is identified as the *o*-, *m*-, or *p*-compound. The data may then be sufficient for the orientation of the tri-derivative, but if not, the substituent Z is displaced by hydrogen and the nature of the product, C_6H_4XY, is established.

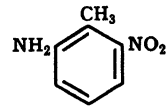
A compound, $C_6H_3(NH_2)(NO_2)\cdot CH_3$, for example, might be first converted into $C_6H_4(NO_2)\cdot CH_3$ by [illegible] the amino-group by hydrogen with the aid of the diazonium salt; the product is, say, *p*-nitrotoluene. The original compound is then acetylated, the nitro- is reduced to an amino-group, and the latter is then displaced by hydrogen as before; the product is (the acetyl derivative of), say, *o*-toluidine. These data show that the compound is (I). Similarly, it will be seen that each of the compounds, (II) to (VI) inclusive, could be orientated by identifying the products of two such operations, but in the case of the remaining four, (VII), (VIII), (IX), and (X), the results would be inconclusive, because (VII) and (VIII) would give *o*-nitrotoluene and *m*-toluidine, and (IX) and (X) would give *m*-nitrotoluene and *o*-toluidine:



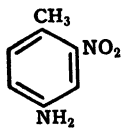
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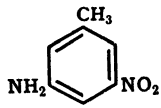
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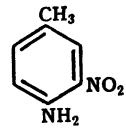
III



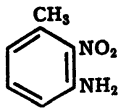
IV



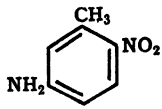
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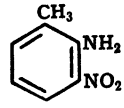
VI



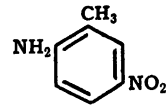
VII



VIII



IX

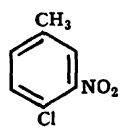


X

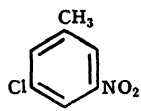
In order, therefore, to distinguish between (VII) and (VIII), or between (IX) and (X), it would be necessary to determine the relative positions of the $-NH_2$ and $-NO_2$ groups. For this purpose the $-NH_2$ group might be displaced by bromine, and the product oxidised to the acid, $C_6H_3Br(NO_2)\cdot COOH$, which is then reduced to $C_6H_3Br(NH_2)\cdot COOH$ with stannous chloride and hydrochloric acid; this compound, heated with soda-lime, might give either *o*- or *p*-bromoaniline, p. 1022). The relative positions, $CH_3{:}NO_2$, $CH_3{:}NH_2$, and $NO_2{:}NH_2$, having thus been determined, the orientation of the original compound has been accomplished.

Although only well-known general reactions are applied in such operations, it may happen that one or more of them may not take place in a normal manner; in the case just considered, the oxidation of the methyl group might be difficult or might involve the complete decomposition of the compound, and the results of the high temperature reaction with soda-lime might be very unsatisfactory. If so, a different procedure might be tried: The original compound might be reduced to the diamine and the diacetyl derivative of the latter submitted to oxidation; the product, heated with soda-lime, might then give *o*- or *p*-phenylenediamine, for the identification of which the diacetyl or dibenzoyl derivative might be used; the structure of the tri-derivative, (VII), (VIII), (IX) or (X), would then be determined.

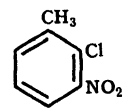
A similar but more restricted series of operations is often necessary even when the tri-substitution product has been prepared from a known di-derivative. Thus when *m*-nitrotoluene is chlorinated it may give one or more of the following isomerides,



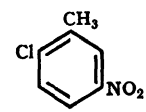
I



II



III



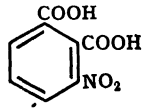
IV

and, for its orientation, each of the products must be converted either into one, or into two di-derivatives, as the case may be. If, when the nitro-group is displaced by hydrogen, one of the products gives *p*-chlorotoluene, it must be (I), whereas if *m*-chlorotoluene is formed it must be (II); if, however, the di-derivative is *o*-chlorotoluene, it will be necessary to ascertain the relative positions of the chlorine atom and the nitro-group in order to distinguish between (III) and (IV); for

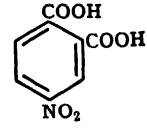
this purpose the nitrochloro-derivative might be oxidised to the acid, $C_6H_3Cl(NO_2)\cdot COOH$, and the latter reduced to the amino-compound with stannous chloride and hydrochloric acid. The amino-acid might then give *o*- or *p*-chloroaniline, when it was heated with soda-lime, a result which would decide between formulae (III) and (IV).

When two of the substituents in the tri-derivative are identical the orientation of the latter cannot of course be carried out on the lines just given, unless *one* of these substituents can be converted into another, which is readily displaceable by hydrogen. The orientation of a compound, $C_6H_3Me(NO_2)_2$, would be possible in that way, because one of the nitro-groups may be reduced, leaving the other unchanged, and a compound, C_6H_3XYZ, would thus be formed. When, however, one of the two identical groups cannot be thus differentiated, the tri-derivative may often be orientated by making use of other compounds of *known* structure.

The nitrophthalic acid (m.p. 219°) obtained by the oxidation of nitronaphthalene gives an anhydride, and is therefore a derivative of *o*-phthalic acid ; further, it can be prepared by the nitration of phthalic acid and must therefore be represented by (I) or (II).



I



II

Now from the base (IX, p. 1019), with the aid of the Sandmeyer reaction, the amino- is displaced by the cyano-group and the latter is hydrolysed to —COOH ; the methyl group is then oxidised and a nitrophthalic acid identical with that obtained from nitronaphthalene results. The nitrophthalic acid from naphthalene has therefore the structure (I).

An alternative process, namely the conversion of the tri-derivative of unknown structure into one which has already been orientated, is often used. Thus *m*-cresol is readily chlorinated, giving a mixture of monochloro-derivatives, which may contain four isomerides, corresponding with those obtained from *m*-nitrotoluene (p. 1020). One of these compounds (which can be isolated by fractional distillation) is treated with dimethyl sulphate and alkali and the product is then oxidised with permanganate ; the

chloromethoxybenzoic acid which is thus obtained is found to be identical with the acid, COOH:OMe:Cl = 1:3:4, so that the chlorine atom in this chloro-*m*-cresol is in the *p*-position to the methyl radical.

This last method, as a rule, is the most convenient one for such orientations, as it may be necessary to change one group only of the tri-derivative ; its applicability becomes more and more general, of course, with every increase in the number of compounds which have been orientated.

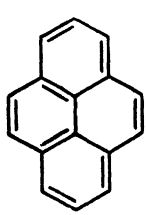
The structures of the higher substituted benzene derivatives are determined by analytical, synthetical, and comparative methods similar to those used in the case of the tri-derivatives.

The displacement of an aromatic substituent by hydrogen is a very important operation in many orientations. This is a simple matter in the case of halogens (p. 426) and $—NH_2$ or $—NO_2$ groups (p. 455), but for the displacement of —COOH and of —OH by hydrogen a high temperature is required, and the operations may lead to unsatisfactory results ; for such processes nitro-compounds must first be reduced to amino-compounds, otherwise complete decomposition may occur. For the displacement of an alkyl group, the compound must usually be oxidised to the corresponding acid ; this is not always possible, and in any case an amino-group, if present, must be protected by acetylation or benzoylation, and a hydroxyl group by methylation, before oxidation is attempted. Alkyloxy-groups cannot be directly displaced, and must be converted into phenolic groups before the compound is heated with zinc-dust.

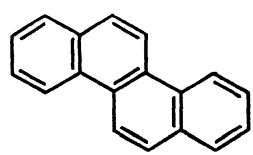
Polycyclic Hydrocarbons

Some of the many hydrocarbons obtained from coal-tar have been described, but others of a more complex nature have been isolated from this source and many have been synthesised.

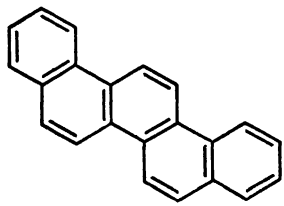
Those obtained from coal-tar usually contain condensed benzene nuclei, as in the examples shown below :



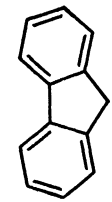
Pyrene, $C_{16}H_{10}$



Chrysene, $C_{18}H_{12}$



Picene, $C_{22}H_{14}$



Fluorene, $C_{13}H_{10}$

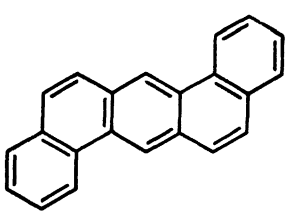
Pyrene crystallises in pale yellow plates, m.p. 149°, and is formed by treating diphenyl-*oo'*-diacetyl chloride with aluminium chloride and reducing the resulting diketone with hydriodic acid and red phosphorus.

Chrysene (1:2-benzphenanthrene), m.p. 250°, may be synthesised by strongly heating 1-phenyl-2-α-naphthylethane or indene, or by other methods which are mentioned later (pp. 1030, 1033, 1034).

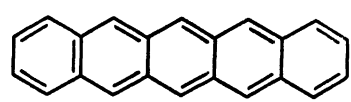
Picene (1:2:7:8-dibenzphenanthrene), m.p. 365°, is formed, among other compounds, by heating α-methylnaphthalene with sulphur or by the interaction of naphthalene, ethylene dibromide, and aluminium chloride.

Fluorene, m.p. 116°. is produced by passing diphenylmethane through a heated tube or from diphenyl, methylene dichloride and aluminium chloride.

The two isomeric *dibenzanthracenes*, (I) and (II), are of interest in that (I) is colourless, reacts slowly with maleic anhydride, and causes cancer when applied to the skin (of mice), whereas (II) is deep blue, reacts instantly with maleic anhydride, and has no carcinogenic activity :



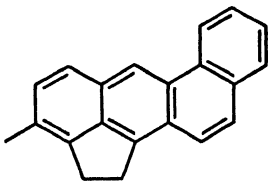
I



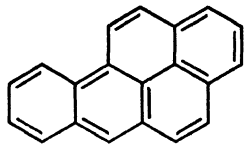
II

Other powerfully carcinogenic compounds are methylcholanthrene, a derivative of the steroids (p. 1087), and benzpyrene,

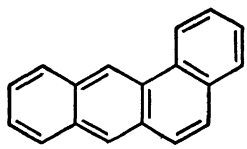
which has been isolated from pitch; all these carcinogenic substances are derivatives of 1:2-benzanthracene, which itself has no carcinogenic activity.



Methylcholanthrene

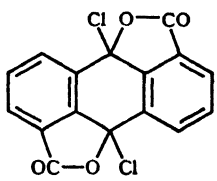


Benzpyrene

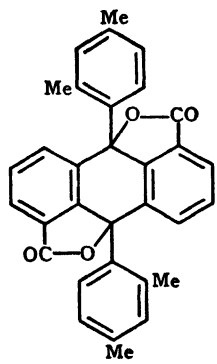


Benzanthracene

Coronene (' hexabenzobenzene ') is a very interesting and highly complex hydrocarbon, which has been synthesised by Scholl and Meyer, K. (*Ber.* 1932, 902). The chloride of anthraquinone-1:5-dicarboxylic acid reacts in a tautomeric form, (III), with *m*-xylene in the presence of aluminium chloride, yielding chiefly (IV),



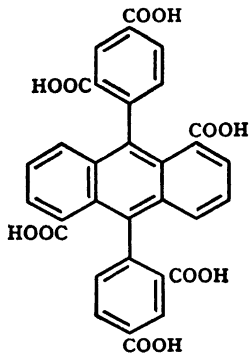
III



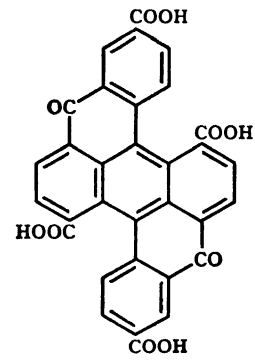
IV

This product is oxidised to the corresponding tetracarboxylic-dilactonic acid, which, on reduction, is converted into the hexacarboxylic acid, (v).

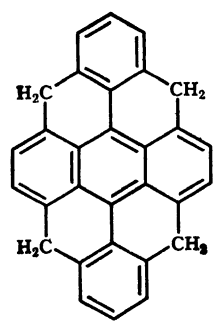
When (v) is treated with 20% oleum, it gives (vi), from which (vii) is formed, on reduction with hydriodic acid and phosphorus :



V

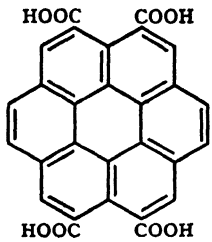


VI

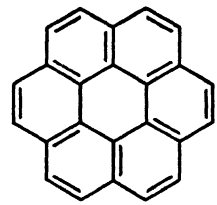


VII

This compound (vii), heated with soda-lime and copper powder, loses four atoms of hydrogen, giving a coronene derivative, in the molecule of which there are nine closed chains. On oxidation with nitric acid, two of the closed chains undergo fission and a tetracarboxylic acid, (viii), is formed ; when this acid is heated with soda-lime it gives coronene, (ix).



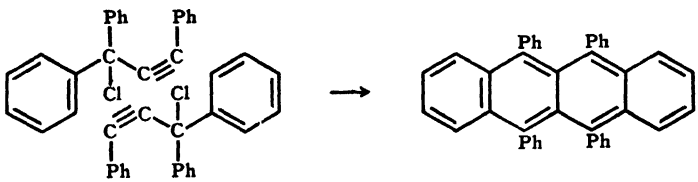
VIII



IX

Coronene is pale yellow, fluorescent, and exceedingly stable.

Some other very interesting hydrocarbons have been investigated by Moureu, Dufraisse, and their collaborators (*Compt. Rend.* 1926, 1440, and later). One of these compounds, *rubrene* or 9:10:11:12-tetraphenylnaphthacene (tetraphenylbenzanthracene), is formed by heating the chloride of *diphenylphenylethinyl carbinol* (see below) in a vacuum,



Rubrene

Rubrene, as its name implies, is a red compound, which shows a yellow fluorescence in benzene solution ; it is oxidised by chromic acid to *o*-dibenzoylbenzene and carbon dioxide. A solution of rubrene (R) in benzene absorbs oxygen when it is exposed to light, and a colourless peroxide, *oxyrubrene* (RO_2), which crystallises with half a molecule of benzene, can be isolated from the solution. When it is suddenly heated at about 180°, oxyrubrene decomposes into rubrene and oxygen with the emission of a greenish-yellow light. The interconversion of rubrene and oxyrubrene in the above simple manner recalls that of haemoglobin and oxyhaemoglobin.

The carbinol mentioned above can be obtained by treating benzophenone with sodiophenylacetylide, CNa:CPh, and decomposing the additive compound with water ; the carbinol is converted into the chloride with the aid of phosphorus trichloride.

Terphenyl, Quaterphenyl, etc.

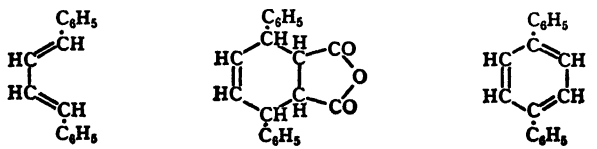
Chain-like polycyclic aromatic hydrocarbons can be obtained from nuclear aromatic halogen compounds by the Wurtz-Fittig reaction, or by the Ullmann modification of that reaction (p. 420). *Terphenyl* or 1:4-*diphenylbenzene*, $C_6H_5 \cdot C_6H_4 \cdot C_6H_5$, is formed when a mixture of *p*-dibromobenzene and bromobenzene is heated with sodium, and *quaterphenyl*, $C_6H_5 \cdot C_6H_4 \cdot C_6H_4 \cdot C_6H_5$, is obtained, together with some sexiphenyl, when 4:4′-di-iododiphenyl is heated with silver powder at about 240°; in this latter reaction some of the iodine is displaced by hydrogen.

Quinquiphenyl, $C_6H_5 \cdot C_6H_4 \cdot C_6H_4 \cdot C_6H_4 \cdot C_6H_5$, is prepared from a mixture of 4-iodoterphenyl and 4-iododiphenyl with the aid of silver at high temperatures, whereas *sexiphenyl*, $C_6H_5 \cdot [C_6H_4]_4 \cdot C_6H_5$ (m.p 465°), is obtained from 4-iodoterphenyl alone, under similar conditions, or by heating a mixture of 4-iododiphenyl (2 mol.) and 4:4′-di-iododiphenyl (1 mol.) with copper at 220°.

Methyl derivatives of hydrocarbons of this type may be obtained similarly; 4:4′-*dimethylsexiphenyl*, $CH_3 \cdot C_6H_4 \cdot [C_6H_4]_1 \cdot C_6H_4 \cdot CH_3$, for example, is prepared from 4:4′-methyliodiphenyl (2 mol.) and 4:4′-di-iododiphenyl (1 mol.) with the aid of copper.

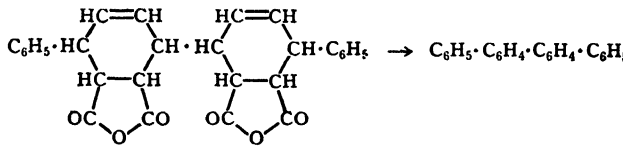
The methyl groups in the molecules of such compounds can be oxidised with chromic anhydride in glacial acetic acid solution; the carboxylic acids thus derived from quaterphenyl and higher members of this polycyclic series are very sparingly soluble in ordinary solvents, and their sodium salts are practically insoluble in boiling water. A summary of the more important work on these compounds is given by Pummerer and Seligsberger (*Ber.* 1931, 2477).

A much more interesting general method for the preparation of such polycyclic aromatic hydrocarbons is based on the Diels-Alder reaction. 1:4-Diphenylbutadiene combines directly with maleic anhydride, giving a product which can be hydrolysed to the corresponding acid; when the calcium salt of the latter is strongly heated with lime and zinc-dust, it is converted into terphenyl:



Kuhn and Wagner-Jauregg applied this method to the diphenylpolyenes (p. 980) and found that these compounds combined with maleic anhydride, one molecule of the latter being added to every *complete* conjugated system, —CH:CH·CH:CH—, of the polyene, during which reaction the pronounced colour of the hydrocarbon disappeared ; the 1:4-additive products thus obtained were hydrolysed, and the calcium salts of the acids were heated with lime and zinc-dust, and thus converted into polycyclic hydrocarbons (*Ber.* 1930, 2662).

Diphenylhexatriene, like diphenylbutadiene, combines with only one molecule of maleic anhydride, but diphenyloctatetrene, in the molecule of which there are two complete conjugated systems, combines with two, giving an additive product,



from which quaterphenyl can be obtained by the given method. It is interesting to note that derivatives of terphenyl occur in the colouring matter of certain fungi.

Synthesis of Di- and Poly-cyclic Compounds

Many methods are available for the synthesis of (di- and) polycyclic aromatic or hydroaromatic ring systems ; the most important general reactions for the production of the former are the following :

(1) The condensation of two molecules of an aromatic hydrocarbon by the direct elimination of hydrogen at relatively high temperatures : examples are the preparation of diphenyl from benzene, phenanthrene from *o*-ditolyl or stilbene, fluorene from diphenylmethane, chrysene from phenylnaphthylethane or indene and of picene from α-methylnaphthalene (p. 1023).

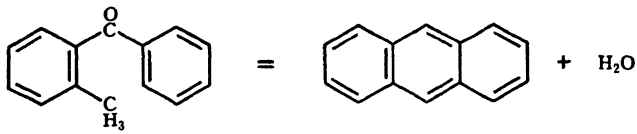
(2) The Wurtz-Fittig reaction, as in the production of diphenyl from bromobenzene and of anthracene and phenanthrene from *o*-bromobenzyl bromide ; the yields are usually poor, but are improved when copper is used instead of sodium (Ullmann, p. 420).

(3) The Friedel-Crafts reaction, as in the preparation of anthracene from benzyl chloride, or from benzene and tetrabromoethane ;

also of fluorene from diphenyl and methylene dichloride and of picene from naphthalene and ethylene dibromide (p. 1023).

(4) The use of diazonium salts, as in the Pschorr synthesis of phenanthrene. This reaction has been extended to the preparation of derivatives of that hydrocarbon and other diazonium salts may behave in an analogous manner. *o*-Nitrophenyldiazonium chloride, for example, with cuprous chloride gives mainly *oo'*-dinitrodiphenyl and not *o*-chlorobenzene ; similarly many phenyldiazonium salts, which give a normal Sandmeyer reaction, afford diphenyl derivatives with alcohol and copper powder ; phenyldiazonium sulphate with the latter gives diphenyl, and with formic acid and copper powder, a mixture of diphenyl, terphenyl, quaterphenyl, etc.

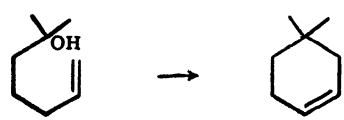
(5) The decomposition of *o*-methylbenzophenones by heating them alone or with zinc-dust (Elbs) :



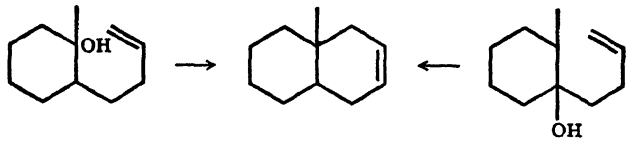
(6) The dehydrogenation of hydroaromatic ring systems (below) with sulphur or selenium, or with palladium-charcoal, a method of great importance in the determination of the structure of the sesquiterpenes, etc.

The more important general methods for the production of hydroaromatic compounds are :

(1) The cyclisation of compounds such as geraniol, linalool, nerolidol, etc., as already shown (p. 941), readily gives six-membered ring compounds, and illustrates a general type of change which occurs when (*a*) two double bonds or (*b*) one double bond and a $>C(OH)\cdot CH<$ group (which easily loses water) are suitably situated in the same molecule. Simple examples are the conversion of the methylheptenol, (I), into 1:1-dimethyl-Δ-3-*cyclo*hexene, (II), with phosphoric acid, and of the unsaturated tertiary alcohols, (III) and (IV), into 9-methyl-Δ-2-octahydronaphthalene :

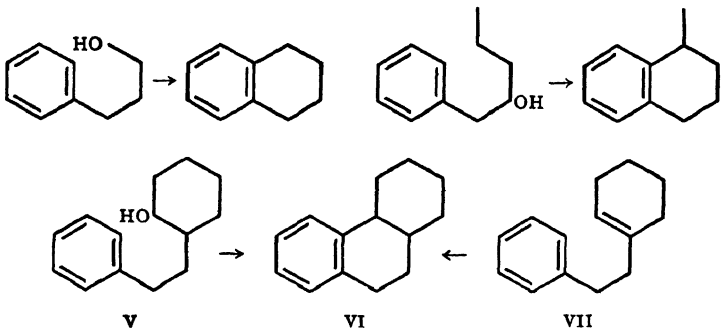


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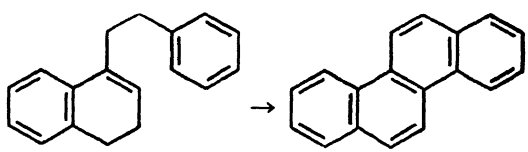
III IV

A reaction of a very similar type occurs when a suitable side chain aromatic alcohol or olefine is treated with sulphuric acid, stannic chloride, aluminium chloride, etc. :

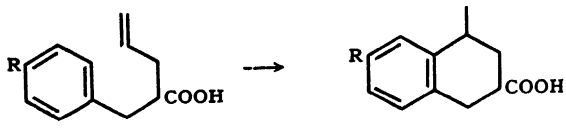


V VI VII

The synthesis of naphthalene from phenylbutylene (p. 541) is of a similar type, but dehydrogenation also occurs. The compound, (v), used in the synthesis of (vi), was prepared by condensing the potassium derivative of ethyl *cyclo*hexanone-2-carboxylate with β-phenylethyl bromide followed by ketonic hydrolysis and reduction, whereas (vii) was obtained by the dehydration of the alcohol from β-phenylethyl magnesium bromide and *cyclo*hexanone. On dehydrogenation (vi) gives phenanthrene. Retene (p. 948) and *cyclo*pentenophenanthrene (cf. p. 1089), as well as chrysene, picene, etc., have been synthesised by a similar method :



Darzens has performed many syntheses of a like nature in which sulphuric acid at about 45° is used as the condensing agent ; thus (viii), in which R=Me, $CHMe_2$, or OMe, gives (ix) :



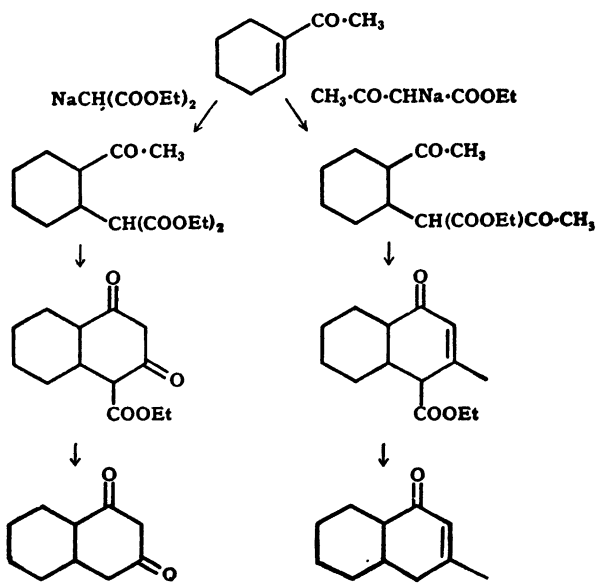
VIII IX

A very interesting hydrocarbon in which condensation had occurred in the *meta*-position was synthesised by Cook and Hewett from 1-benzyl*cyclo*hexanol with phosphorus pentoxide at 160° ;



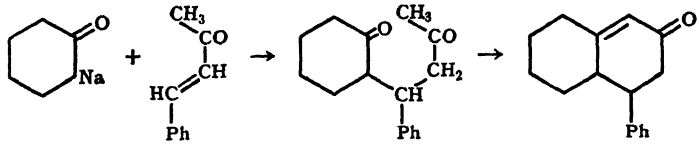
This reaction is one of the very rare cases in which ring formation occurs in other than the *o*-position.

(2) Many cyclic 1:5-ketonic esters or diketones undergo inner condensations in the same way as their open chain analogues (p. 799), as illustrated by the following examples (Linstead, Kon, Ruzicka):



In the first case acetyl-Δ-1-*cyclo*hexene[1] is condensed with diethyl sodiomalonate and in the second with ethyl sodioacetoacetate (Michael reactions): cyclisation then occurs with the elimination of alcohol and water respectively.

A slightly different method has been used by Robinson: the sodio-derivative of a saturated ketone, usually prepared with the aid of sodamide, is added to an $\alpha\beta$-unsaturated ketone, by a modified Michael reaction, whereon the resulting 1:5-diketone undergoes spontaneous ring formation. Thus, sodio*cyclo*hexanone condenses with methylstyryl ketone (benzylideneacetone) to give finally (x):

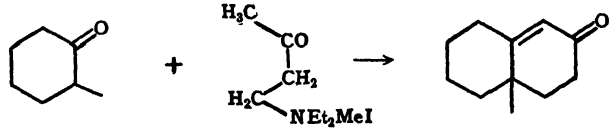


X

Attempts to extend this method to simple unsaturated ketones, such as methylvinyl ketone, were unsuccessful as such substances were polymerised by sodamide; it was found, however, that a Mannich base methiodide could be used as a source of such a ketone. Thus when acetone is heated with diethylamine hydrochloride and formaldehyde, condensation to the hydrochloride of a compound known as a Mannich base occurs,

$$CH_3\cdot CO\cdot CH_3+CH_2O+Et_2NH,HCl = CH_3\cdot CO\cdot CH_2\cdot CH_2\cdot NEt_2,HCl+H_2O:$$

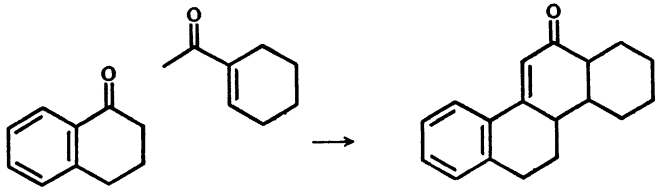
the free base, with methyl iodide, gives the quaternary salt, which is then condensed with the ketone in the presence of sodamide:



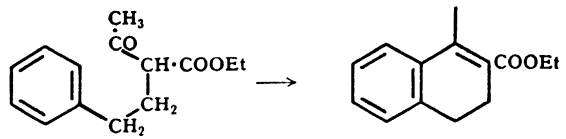
Presumably the methiodide decomposes into the unsaturated ketone during the reaction and is acted on by the sodioketone before polymerisation can occur.

[1] *Cyclo*hexene with acetyl chloride in the presence of stannic chloride yields 2-chloroacetyl*cyclo*hexane which is heated with pyridine.

A more complex synthesis is exemplified by the condensation of acetyl*cyclo*hexene and α-tetralone to give finally a ketodecahydrochrysene, which may be reduced (Clemmensen) and dehydrogenated to chrysene,

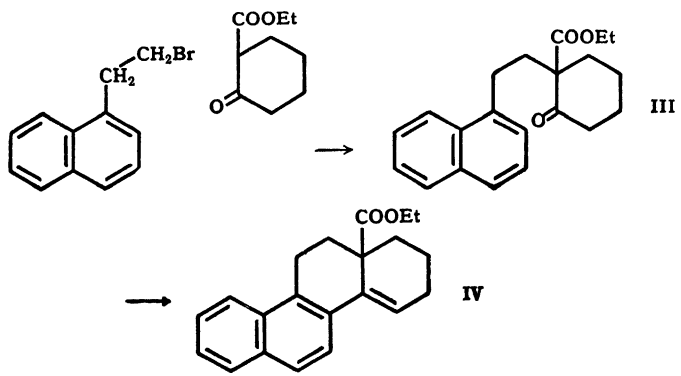


(3) Suitable aromatic ketonic esters also undergo cyclisation, in which water is eliminated from the enolic form ; thus the condensation product of β-phenylethyl bromide and ethyl sodioacetoacetate, (I), yields (II) :



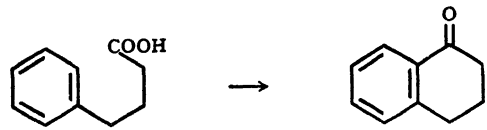
I II

Ruzicka and his co-workers condensed β-1-naphthylethyl bromide with ethyl *cyclo*hexanone-2-carboxylate to give (III), which when boiled with 50% sulphuric acid gave (IV) and then yielded chrysene on dehydrogenation and decarboxylation :

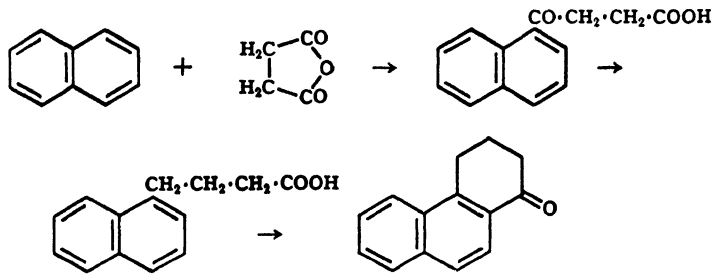


III IV

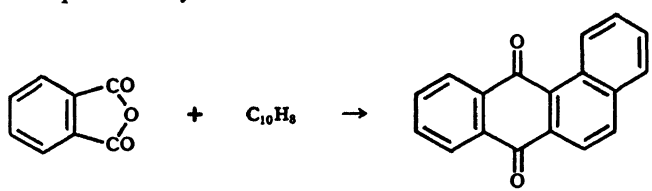
(4) Cyclic ketones have been made from acids with sulphuric acid as the condensing agent or from acid chlorides and aluminium chloride in the same way as α-indanone and its homologues (F. S. Kipping). These reactions may be typified by the preparation of α-tetralone and are very general:



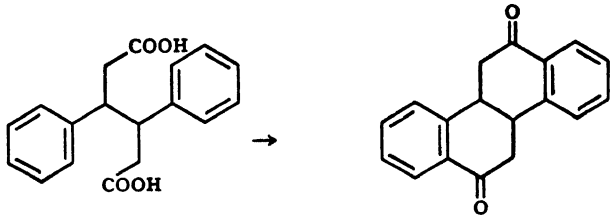
The resulting ketones may be reduced by Clemmensen's method and the products dehydrogenated to aromatic hydrocarbons; or the ketone may be acted on with a Grignard reagent and afterwards dehydrated and dehydrogenated. In this way numerous naphthalene and phenanthrene derivatives have been prepared. R. D. Haworth and his co-workers have condensed naphthalene derivatives with succinic anhydride (aluminium chloride), reduced the keto-acid and cyclised the product with sulphuric acid:



Phthalic anhydride can be condensed in the same way (cf. p. 561), and the quinone may then be converted into benzanthracene:

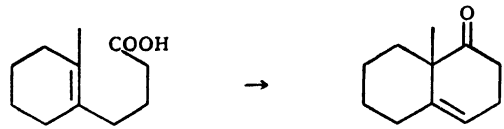


A slightly more complex case is presented by the double cyclisation of (v) by either method; the product on reduction and dehydrogenation yields chrysene:



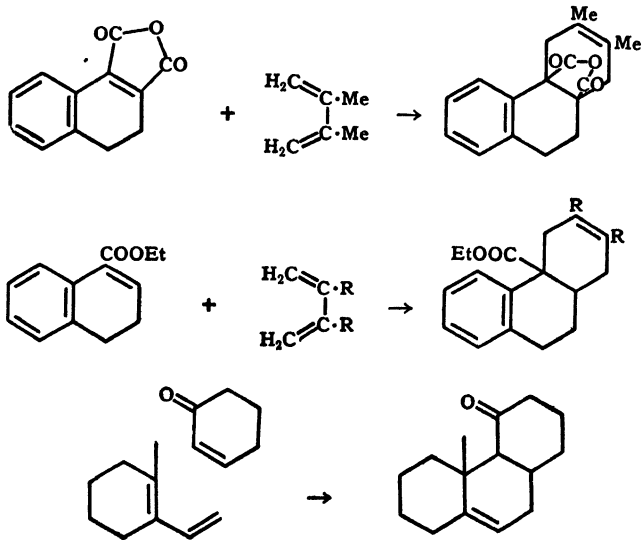
V

Similar reactions have been carried out with hydroaromatic acids : thus the chloride of (VI) gives (VII) on treatment with stannic chloride :



VI VII

(5) The Diels-Alder diene synthesis has been applied to the preparation of many polycyclic hydroaromatic compounds : examples which need no description are appended :



(6) Numerous polycyclic compounds have been prepared by the application of the methods of cyclic ketone formation from dibasic acids, either by the destructive distillation of a suitable salt of the acid or by the Dieckmann process (p. 780).

CHAPTER 61

ALKALI METAL COMPOUNDS, FREE RADICALS AND STERIC HINDRANCE

Alkali Metal Compounds

THE alkyl derivatives of zinc and mercury which have already been described (p. 233) were discovered by Frankland in 1849, and, until they were superseded by the much more accessible Grignard reagents, were compounds of great importance in many ways. In 1858, Wanklyn showed that sodium decomposed zinc diethyl with the separation of zinc, but a sodium alkyl was not isolated ; later, Acree found that, with sodium, mercury diphenyl in boiling benzene solution yielded sodium phenyl as an insoluble powder. During more recent times, Schlenk and Ziegler (and their co-workers) have studied such metallic compounds independently, and the following is a brief account of their results.

Sodium ethyl, C_2H_5Na, is gradually formed when mercury diethyl, dissolved in light petroleum, is heated with sodium in the absence of oxygen. Other sodium and potassium alkyls can be obtained in a similar manner. They are colourless solids, insoluble in organic solvents, decompose when they are heated, and inflame on exposure to the air; when treated with water, alcohol, or ether, they give paraffins,

$$RNa+(C_2H_5)_2O = RH+C_2H_4+C_2H_5\cdot ONa.$$

The corresponding lithium alkyl compounds, with the exception of lithium methyl, are soluble in petroleum and benzene without decomposition. *Lithium ethyl*, C_2H_5Li, crystallises from benzene, has a sharp melting-point, and distils unchanged in the absence of oxygen. *Sodium phenyl* and *lithium phenyl*, prepared from mercury diphenyl, are colourless, insoluble in indifferent solvents, and inflame in the air, but *sodium benzyl* is an intensely red crystalline compound, which reacts with tetramethylammonium chloride, giving *tetramethylbenzylammonium*, which is also a red solid,

$$C_6H_5\cdot CH_2Na+NMe_4Cl = NMe_4\cdot CH_2\cdot C_6H_5+NaCl.$$

Another method for the preparation of alkali metal organic compounds is by the action of the metal on certain ethers,

$$R_2O+2Na = RNa+R\cdot ONa.$$

Potassium phenyldimethylmethyl, CMe_2PhK, for example, is prepared by treating methylphenyldimethylmethyl ether in ethereal solution with a sodium-potassium alloy, in an atmosphere of nitrogen; the solution gradually turns red owing to the formation of the potassium derivative,

$$CMe_2Ph \cdot OCH_3 + 2K = CMe_2PhK + CH_3 \cdot OK.$$

This compound combines directly with various olefinic substances, giving products which are usually highly coloured; with phenyl- and diphenyl-ethylene, for example, it gives, respectively,

$$C_6H_5 \cdot CHK \cdot CH_2 \cdot CMe_2Ph \quad \text{and} \quad C_6H_5 \cdot CHK \cdot CHPh \cdot CMe_2Ph.$$

Certain lithium alkyls and aryls may also be prepared by treating an alkyl or aryl halide with the metal in the presence of ether or benzene. The alkyl chlorides are most suitable for this purpose, as the bromides, and especially the iodides, readily undergo the Wurtz-Fittig reaction, which occurs in two stages:

$$RI + 2Na = RNa + NaI,$$
$$RNa + RI = R \cdot R + NaI.$$

A solution of *lithium butyl*, prepared from the chloride, gives additive compounds with various olefines; with unsymmetrical diphenylethylene, for example, the product is $C_4H_9 \cdot CH_2 \cdot CLi(C_6H_5)_2$, as is shown by the fact that, when treated first with carbon dioxide and then with acids, it is converted into *αα-diphenyl-n-heptylic acid*, $C_4H_9 \cdot CH_2 \cdot C(C_6H_5)_2 \cdot COOH$.

A potassium derivative of triphenylmethyl (p. 1040) is obtained by treating triphenylmethane with potassamide in liquid ammonia,

$$Ph_3CH + KNH_2 = Ph_3CK + NH_3.$$

Sodium and potassium combine with certain olefinic compounds, giving either a simple additive product or a compound formed from two molecules of the olefine:

$$Ph_2C{:}CPh_2 + 2Na = Ph_2CNa \cdot CNaPh_2,$$
$$2Ph_2C{:}CH_2 + 2Na = Ph_2CNa \cdot CH_2 \cdot CH_2 \cdot CNaPh_2.$$

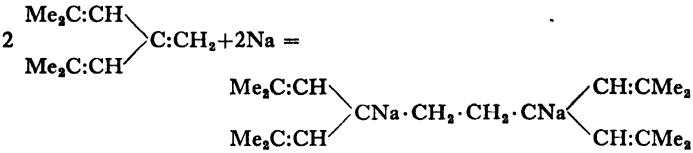
The second type of reaction occurs in two stages, as shown,

$$Ph_2CNa \cdot CH_2Na + Ph_2C{:}CH_2 = Ph_2CNa \cdot CH_2 \cdot CH_2 \cdot CNaPh_2.$$

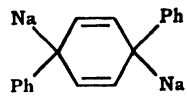
The polymerisation of olefines by sodium (p. 969) is probably due

to a reaction of this kind, which, theoretically, may be repeated indefinitely with other molecules of the olefine.

As a rule only those ethylenic compounds in which aryl groups are combined with one or both of the olefinic carbon atoms, form additive derivatives with the alkali metals ; an exception, however, occurs in the case of di-*iso*butylene-ethylene, which reacts in the following manner :



It is also noteworthy that certain purely aromatic compounds may give metallic derivatives ; 4-phenyldiphenyl (terphenyl, p. 1027), for example, gives the compound,



All these alkali metal compounds are decomposed by water, alcohol, and other substances containing a hydroxyl group, or capable of existing in an enolic form, and the metal is displaced by hydrogen. When treated with carbon dioxide, they give salts of carboxylic acids, and, as shown above, the identification of the product of such a reaction serves to establish the constitution of the metal derivative.

They react with alkyl halides in different ways according to their structure, as illustrated by the following examples :

$$Ph_2CNa \cdot CNaPh_2 + 2CH_3I = Ph_2C{:}CPh_2 + C_2H_6 + 2NaI,$$

$$Ph_2CNa \cdot CH_2 \cdot CH_2 \cdot CNaPh_2 + 2CH_3I = Ph_2C(CH_3) \cdot CH_2 \cdot CH_2 \cdot C(CH_3)Ph_2 + 2NaI.$$

The alkali metal compounds described above may be classed as follows : (1) Simple colourless alkyl or aryl metal compounds, such as potassium ethyl and sodium phenyl, insoluble in organic solvents and decomposed by ether (p. 1037). (2) Coloured compounds usually stable towards ether and soluble in organic solvents to form conducting solutions ; those compounds in which the carbon atom combined with the metal is directly united to a benzene

nucleus (or to an olefinic carbon atom) belong to this group, as for example sodium benzyl, potassium phenyldimethylmethyl, and di-sodium 1:2-diphenylethylene. (3) Colourless substances soluble in organic solvents, some of which, such as lithium ethyl, may be distilled or sublimed ; such compounds are similar to the alkyl derivatives of the metals of the second periodic group ; they are non-electrolytes, and even when mixed with zinc dialkyls are poor conductors of electricity.

Free Radicals

The fundamental assumption that carbon is quadrivalent in all its compounds is the basis of the structural formulae of organic chemistry, and the use of double and treble bonds is not only a necessary consequence of this assumption but seemed to be justified by the fact that, until 1900, it had not been possible to obtain any substance in which such quadrivalency could not be postulated. It is true that, before that time, Nef had questioned this assumption and, in a series of papers published in the *Annalen* from 1890 onwards, had argued that the molecules of hydrogen cyanide, alkyl *iso*cyanides, fulminic acid, and halogen substitution products of acetylene, contained *bivalent* carbon atoms. His experimental evidence no doubt seemed to justify his conclusions, but as it was also possible to explain his results with the aid of the orthodox formulae, his arguments did not carry conviction.

In 1900, however, Gomberg prepared triphenylmethyl, the existence of which seemed to demand a modification of the accepted views ; since then it has been shown by various workers that not only carbon, but also several other elements, give rise to compounds of greater or less stability in which the ordinary valency of the element is not shown ; a brief account of some of these cases of ' abnormal valency ' is given below.

Compounds of Tervalent Carbon

In attempting to prepare hexaphenylethane, Gomberg treated triphenylmethyl chloride, in benzene solution, with copper, silver, zinc, or mercury in the absence of air ; the product had the composition of *hexaphenylethane*, but its properties were not those of such a compound. Its solution was *yellow*, but on evaporation in an indifferent atmosphere gave a *colourless* substance, m.p. about

95°, which crystallised with benzene ; the yellow solution rapidly absorbed oxygen, giving a colourless *peroxide*, $Ph_3C \cdot O \cdot O \cdot CPh_3$, m.p. 185°, which yielded triphenyl carbinol with concentrated sulphuric acid. The solution also reacted with iodine, giving triphenylmethyl iodide, and with nitric oxide and nitrogen peroxide yielding substances, $Ph_3C \cdot NO$ and $Ph_3C \cdot NO_2$ respectively ; with sodium a red salt, *sodium triphenylmethyl*, $Ph_3C \cdot Na$, was produced, and with concentrated hydrochloric acid, p-*diphenylmethyltetraphenylmethane*, $Ph_2CH \cdot C_6H_4 \cdot CPh_3$ (p. 1045).

This new type of highly reactive compound was named *triphenylmethyl* and represented by the formula, CPh_3, because it seemed that it could not be hexaphenylethane, CPh_3—CPh_3. Cryoscopic determinations, however, gave results considerably higher than those required for triphenylmethyl. It was therefore concluded that the colourless solid (m.p. 95°) is hexaphenylethane, which partly dissociates in solution, giving two molecules of yellow triphenylmethyl,

$$Ph_3C \cdot CPh_3 \rightleftarrows 2Ph_3C ;$$

as [illegible] dissociation would take place on treatment with reagents this view would account for the additive reactions given above.

In ionising solvents, such as sulphur dioxide, colourless hexaphenylethane affords a coloured conducting solution in which it is assumed that triphenylmethyl *cations* exist, an electron having been lost to the solvent,

$$Ph_3C \cdot CPh_3 \rightleftarrows 2Ph_3C^+ + 2\epsilon,$$

or that both cations and anions have been formed,

$$Ph_3C \cdot CPh_3 \rightleftarrows Ph_3C^+ + Ph_3C^-.$$

Triphenylmethyl halides similarly give conducting solutions in sulphur dioxide, while triphenylmethyl anions are furnished by sodium triphenylmethyl,

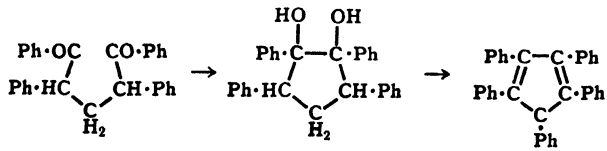
$$Ph_3CNa \rightleftarrows Ph_3C^- + Na^+.$$

The triphenylmethyl complex can thus exist as an uncharged radical, as a carbanion, or as a carbcation.

Tri-4-diphenylmethyl, $(C_6H_5 \cdot C_6H_4)_3C$, is obtained from the corresponding chloride by treatment with copper and exists in the solid form in dark green crystals ; cryoscopic determinations show that

in benzene solution almost the whole of the compound is present in the ' monomolecular ' form.

Tri-4-nitrophenylmethyl, $(NO_2 \cdot C_6H_4)_3C$, and *pentaphenylcyclopentadienyl*, (III), are respectively deep green and violet, and do not seem to associate. The latter is prepared by reducing the diketone, (I), formed from desoxybenzoin (phenylbenzyl ketone) and formaldehyde to a cyclic pinacol, (II), eliminating water (2 mol.), condensing with *p*-nitrosodimethylaniline and hydrolysing the product to 2:3:4:5-tetraphenyl*cyclo*penta-Δ-2:4-dienone ; this compound reacts with phenyl magnesium bromide giving the tertiary alcohol which is converted into the chloride and treated with silver,



I II III

Diphenyl-β-naphthylmethyl, $Ph_2(C_{10}H_7)C$, on the other hand, is ' bimolecular ' in the solid state, but dissociates to the extent of from 15 to 50% in various solvents.

Pentaphenylethyl, $Ph_3C \cdot CPh_2$, is formed by the action of sodium triphenylmethyl on benzophenone dichloride in ethereal solution in an atmosphere of nitrogen (Schlenk and Mark, *Ber.* 1922, 2285),

$$2Ph_3CNa + Ph_2CCl_2 = Ph_3C \cdot CPh_2 \cdot CPh_3 + 2NaCl ;$$

on evaporation, the solution gives a mixture of pentaphenylethyl (golden yellow crystals) and hexaphenylethane (triphenylmethyl).

Many analogous compounds containing (tervalent) carbon atoms of *abnormal valency* have been prepared, and they all show additive reactions analogous to those of triphenylmethyl. In all such cases it would seem that the normal or ' *bimolecular* ' compounds are colourless or nearly so, whereas the radicals (or ions) containing tervalent carbon atoms are highly coloured, but the changes in colour of the solutions are not always parallel to the changes in the extent of the dissociation.

Compounds of other Elements with Abnormal Valency

When a solution of diphenylsilicon dichloride, $SiPh_2Cl_2$, in toluene is heated with sodium, various compounds are formed ;

among others two crystalline substances of the composition, $(SiPh_2)_n$. One of these is relatively very stable, and gives cryoscopic results which correspond with those required for an *octaphenylcyclosilicotetrane*, Si_4Ph_8 ; the other is so sparingly soluble that its molecular weight cannot be determined cryoscopically, but as it is readily attacked by iodine in benzene solution at the ordinary temperature, giving a compound, $Si_4Ph_8I_2$, it is regarded as an *octaphenylsilicotetrane*, $SiPh_2 \cdot SiPh_2 \cdot SiPh_2 \cdot SiPh_2$, the molecule of which contains two *tervalent* silicon atoms. This compound differs from those which contain tervalent carbon atoms in being colourless, both in the solid state and in solution, but it is extraordinarily reactive, and even when it is boiled with benzyl alcohol, benzaldehyde, nitrobenzene, ethylene dibromide, etc., it undergoes change, giving oxides, $Si_4Ph_8O_2$, Si_4Ph_8O, and other products.

When *trimethylstannic bromide*, dissolved in liquid ammonia, is treated with sodium, a colourless solid, m.p. 23°, is obtained ; from the results of cryoscopic measurements, it is concluded that dilute solutions of this product contain *trimethyltin*, $(CH_3)_3Sn$, which, in more concentrated solutions, gives ' bimolecular ' *hexamethyldistannane*, $(CH_3)_3Sn \cdot Sn(CH_3)_3$. The compound combines with chlorine, giving *trimethylstannic chloride*, and with sodium, yielding *sodium trimethyltin*, $(CH_3)_3SnNa$. Organic compounds of bivalent tin are also known.

The interaction of *p*-xylyl magnesium bromide and lead dichloride yields a compound of the composition of a *hexaxylyldiplumbane*, $(C_6H_3Me_2)_3Pb \cdot Pb(C_6H_3Me_2)_3$, and cryoscopic results in benzene solution correspond with this formula. As, however, the compound gives coloured solutions and combines with bromine in pyridine solution at −40°, yielding *trixylylplumbic bromide*, it probably dissociates in solution, giving $Pb(C_6H_3Me_2)_3$. *Cyclo*hexyl magnesium bromide reacts with lead dichloride, giving a compound which in dilute solution has a molecular weight corresponding with that of *tri*cyclo*hexyllead*, $Pb(C_6H_{11})_3$; this product combines with iodine, yielding *tri*cyclo*hexylplumbic iodide*.

Wieland, in 1911, showed that *tetraphenylhydrazine*, which is colourless in the solid state, gives in boiling toluene a green solution ; as treatment with nitric oxide results in the formation of *diphenylnitrosoamine*, $NPh_2 \cdot NO$, it was concluded that the solution contained a free radical :

$$Ph_2N \cdot NPh_2 \rightleftharpoons 2Ph_2N.$$

Tetra-anisylhydrazine, $(MeO \cdot C_6H_4)_2N \cdot N(C_6H_4 \cdot OMe)_2$, and *tetra-p-dimethylaminophenylhydrazine*, $(Me_2N \cdot C_6H_4)_2N \cdot N(C_6H_4 \cdot NMe_2)_2$, also dissociate in solution but to a rather larger extent.

Hexaphenyltetrazane, $Ph_2N \cdot NPh \cdot NPh \cdot NPh_2$, gives dark blue solutions the colour of which increases when they are warmed or diluted; with nitric oxide it gives nitrosotriphenylhydrazine, $Ph_2N \cdot NPh \cdot NO$. It is inferred from these facts that the tetrazane dissociates, giving $2Ph_2N \cdot NPh$.

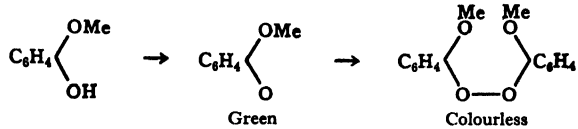
Diphenylpicrylhydrazyl, $Ph_2N \cdot N \cdot C_6H(NO_2)_3 \cdot OH$, crystallises in dark-violet prisms, which resemble potassium permanganate, and has probably the given molecular formula even in the solid state. It is reduced by quinol to the corresponding hydrazine.

Diphenyl nitric oxide was prepared by Wieland by the oxidation of diphenylhydroxylamine with silver oxide,

$$2Ph_2N \cdot OH + Ag_2O = 2Ph_2NO + H_2O + 2Ag.$$

It crystallises in deep red needles.

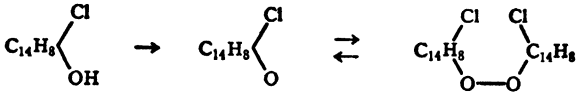
Goldschmidt, in 1922, oxidised guaiacol with lead dioxide and obtained a green solution, which was decolourised by the addition of quinol or triphenylmethyl,



Neither the green nor the colourless compound could be isolated.

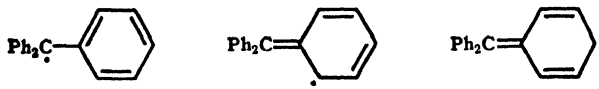
9-*Hydroxy*-10-*methoxyphenanthrene*, oxidised with ferricyanide, was converted into a colourless substance, which was isolated; this product gave a yellowish-green solution of the equilibrium mixture of the two products, analogous to those shown above.

9-*Chloro*-10-*hydroxyphenanthrene* gave on oxidation a corresponding product in which a state of equilibrium was reached so slowly that both the blue ('monomolecular') and the colourless ('bimolecular') forms could be isolated by fractional precipitation,



All the compounds of abnormal valency so far described are examples of *free radicals*, which may be defined as uncharged

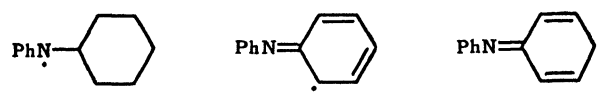
complexes showing additive properties and having an odd number of electrons. The stability of those of long life may usually be ascribed at any rate partially to a redistribution of the electrons by resonance ; triphenylmethyl, for example, might exist as a mesomeric form of the following structures, in which resonance could occur with any one of the three nuclei :



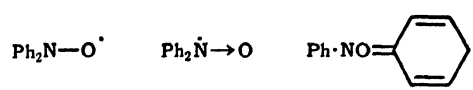
I II III

The formation of *p*-diphenylmethyltetraphenylmethane (p. 1041) might then be attributed to the union of (I) and (III), followed by isomeric change.

In the case of the hydrazine derivatives (p. 1043) there is the possibility of a complex resonance, corresponding with that of triphenylmethyl,



in which one of the forms is regarded as derived from bivalent nitrogen and the others from tervalent carbon ; similarly diphenyl nitric oxide is a mesomeric form of structures containing univalent oxygen, ' bivalent ' nitrogen, and tervalent carbon,



The ketyls (p. 1046) may also be represented as mesomeric structures.

All molecules which contain an odd number of electrons are paramagnetic and the percentage dissociation of a hexa-arylethane, for example, can be calculated from its magnetic susceptibility ; in this way it has been shown that tri-4-diphenylmethyl is almost completely dissociated both in the solid state and in solution.

Metallic Ketyls

When an ethereal or benzene solution of a ketone or an aldehyde is treated with an excess of sodium, in the absence of air and moisture, there is formed an insoluble, coloured, metallic compound which readily undergoes atmospheric oxidation, and is immediately decomposed by water (Beckmann and Paul, *Ann.*, 266, 1). The product from benzophenone, for example, with water, gives benzophenone, *benzhydrol*, $(C_6H_5)_2CH\cdot OH$, and *benzopinacol*, $(C_6H_5)_2C(OH)\cdot C(OH)(C_6H_5)_2$; when its suspension in ether is treated with dry carbon dioxide, it gives equimolecular quantities of benzophenone and the sodium salt of benzilic acid.

From these reactions it was inferred that the sodium derivative had the structure, $CPh_2Na\cdot O\cdot CPh_2\cdot ONa$. Benzaldehyde also gives a sodium compound, from the reactions of which it seemed that its structure was $NaO\cdot CHPh\cdot CHPh\cdot ONa$.

Schlenk and his colleagues (*Ber.* 1913, 2840; 1914, 486) stated that such sodium compounds are not formed from two molecules of the ketone or aldehyde, because on the addition of potassium to a boiling ethereal solution of *p*-phenylbenzophenone, $C_6H_5\cdot C_6H_4\cdot CO\cdot C_6H_5$, there is no change in the boiling-point, although the potassium derivative, $C_6H_5\cdot C_6H_4\cdot C(OK)\cdot C_6H_5$, is produced. This compound is readily soluble in ether, and its molecule, $KO\cdot CR_2$, contains a *tervalent* carbon atom, but in solution there is an equilibrium between the mono- and bi-molecular forms and the percentage dissociation varies with the conditions,

$$2Ph_2CONa \rightleftarrows Ph_2C(ONa)\cdot C(ONa)Ph_2.$$

Such substances are called *metal ketyls*.

The sodium (and potassium) ketyls obtained from *p*-phenylbenzophenone and from *pp'*-diphenylbenzophenone are highly coloured, like other compounds containing tervalent carbon; they combine avidly with oxygen, probably giving peroxides, $NaO\cdot CR_2\cdot O\cdot O\cdot CR_2\cdot ONa$, since the products, with water, give sodium peroxide and a ketone; when treated directly with water, they are probably first converted into the corresponding hydroxide, $R_2C(OH)$, because the final products are a pinacol, *or* a ketone and a secondary alcohol,

$$2R_2C(OH) = R_2C(OH)\cdot CR_2\cdot OH,$$
$$2R_2C(OH) = R_2CO + R_2CH\cdot OH.$$

They react with methyl iodide,

$$2R_2C(ONa)+CH_3I = R_2C(ONa)I+R_2C(ONa)\cdot CH_3,$$

and the subsequent addition of water gives a ketone, a tertiary alcohol, sodium iodide, and sodium hydroxide.

When an ethereal solution of the potassium ketyl of phenylbenzophenone is added to various compounds such as dimethylpyrone, xanthone, etc., highly coloured insoluble ketyls are formed by a transference of the potassium atom.

Free Radicals of Short Life

In addition to those relatively stable radicals described above, the transitory existence of other free radicals has been demonstrated, in the first instance, by Paneth and his collaborators (*Ber.* 1929, 1335 ; 1931, 2702).

When the vapour of lead tetramethyl under 1·5–2 mm. pressure is passed through a tube heated by a narrow flame, a mirror of lead is produced ; when the gas which is simultaneously formed is immediately passed over a mirror, previously deposited in the same tube a little further from the flame, this older film disappears ; it can be caused to reappear still further along by heating the tube with a second burner. These and other facts seem to establish the existence, for a short time, of *methyl radicals.*

$$Pb(CH_3)_4 \rightleftharpoons 4CH_3+Pb,$$

which are capable of forming lead tetramethyl if passed over a film of lead before they have combined to form ethane. The free methyl radical, containing a tervalent carbon atom, also attacks zinc, with the formation of zinc dimethyl. The half-life period of the methyl radical has been estimated to be 0·006 second. Similar experiments have shown the transitory existence of the ethyl radical.

Norrish and his collaborators have shown that free radicals are produced in a number of photochemical reactions. Thus, when the vapour of methylethyl ketone is exposed to ultra-violet light, it decomposes into free methyl and ethyl radicals, together with carbon monoxide ; the radicals then combine with one another to give ethane, propane, and butane.

At low temperatures acetone is decomposed, giving acetyl radicals which unite to form diacetyl. In solution in *iso-octane* at 80–100°,

the radicals from methylethyl ketone react with the solvent, giving methane and ethane, and an olefine is formed from the *iso-octane*; the formation of free radicals is thus conclusively demonstrated, and the transitory existence of free radicals is now assumed in many reactions.

Steric Hindrance

As a rule tertiary amines unite readily with methyl iodide yielding a quaternary ammonium salt; it has been found, however, that of the six isomeric *dimethylxylidines*, $C_6H_3(CH_3)_2 \cdot N(CH_3)_2$, the 2:6-compound [$NMe_2 = 1$] is incapable of forming a quaternary salt, whereas the other isomerides react with methyl iodide in a normal manner. The same difference in behaviour is observed with the corresponding *bromotoluidine* derivatives, and whereas *iso*butyltoluidine [$Me:NH_2:Bu^{\beta} = 1:2:5$] readily gives a quaternary salt, the isomeride [$Me:NH_2:Bu^{\beta} = 1:2:3$] is hardly attacked by methyl iodide at 150°.

As it is difficult to suggest any chemical effect of the alkyl groups which could account for these facts, it has been supposed that their influence is spatial or *steric*: that in the di-ortho- or 2:6-compounds, the substituents, by reason of their size, block the approach of the methyl iodide and prevent salt formation, but when the substituent radicals are further removed from the dimethylamino-group, blocking does not occur.

This phenomenon, in which chemical reactions appear to be hindered or entirely suppressed by the mere presence of neighbouring atoms or groups, which have no apparent chemical effect, is called *steric hindrance* or the *ortho effect* when the groups are *o*- in a benzene ring; as will be seen, however, from the examples given below, it would appear unlikely that the whole effect is due to such mechanical action, and it seems possible that the substituents have an influence on the mesomerism of the molecule, but the evidence relating to this phenomenon is very conflicting. 2:5-*Dimethylxylidine*, $C_6H_3Me_2 \cdot NMe_2$, for example, is more reactive towards methyl iodide than is *dimethyl*-o-*toluidine*, $C_6H_4Me \cdot NMe_2$, and 2:3-*dimethylxylidine* is more reactive than either, differences which cannot be due to a merely mechanical effect. It has also been found that, in the case of *o*-substituted dimethylanilines, the yield of quaternary salt obtained under comparable conditions is very roughly parallel with the yield of substituted p-*dimethylaminobenzyl*

alcohol, obtained by condensation with formaldehyde, in the presence of acids,

$$Me_2N \cdot C_6H_4X + CH_2O = Me_2N \cdot C_6H_3X \cdot CH_2 \cdot OH$$
(X = Me, Cl, Br, or OMe)

Derivative of dimethyl-aniline	*o*-Me	*o*-Cl	*o*-Br	*o*-OMe
Yield of quaternary salt	7·6	15·6	16	100
Yield of alcohol	6	36	45	60

It is not easy to see why a group in the *o*-position to the tertiary amino-radical should have a steric influence on the condensation in the *p*-position to the latter.

The hydrolysis of aromatic nitriles and amides is very greatly hindered by the presence of halogen atoms or of alkyl or nitro-groups in one or both *o*-positions to the nitrile or amide radical; thus 2:3:5:6-*tetramethylbenzonitrile* and *pentamethylbenzonitrile* resist hydrolysis by the usual methods. 2:4:6-*Trimethylbenzonitrile* is hydrolysed only with great difficulty, whereas *mono-* and *dinitro-*2:4:6-*trimethylbenzonitriles* are hydrolysed comparatively readily.

Apparent steric effects are also observed in the case of oxime formation; thus while quinone easily gives a dioxime, 2:6-*dichloro-quinone* gives a monoxime only, and *tetrachloroquinone* (chloranil, p. 509) does not react with hydroxylamine; further, although 2:4:6-*trimethylbenzaldehyde* gives an oxime, *phenylmesityl ketone*, $C_6H_5 \cdot CO \cdot C_6H_2(CH_3)_3$, [2:4:6], does not.

The most exhaustive inquiries into the effects attributed to steric hindrance have been made in the case of the esterification of acids (Meyer, V., and Sudborough, *Ber.* 1894, 510, 1580, 3146). Thus, with the substituted benzoic acids the presence of methyl, halogen, nitro- or other groups in both *o*-positions to the carboxyl radical hinders esterification by alcohol and hydrogen chloride; even with only one substituent in the *o*-position, the yield of ester under comparable conditions is substantially less than with the corresponding *m*- or *p*-acids. On the other hand, phenylacetic acid is esterified more rapidly than benzoic acid, and it is difficult to imagine that the *o*-hydrogen atoms of benzoic acid exert a steric effect.

2:4:6-*Trichloro-*, *tribromo-*, and *trinitro-benzoic acids* yield no ester with boiling alcohol and hydrogen chloride, whereas mesitylenecarboxylic acid and *pentamethylbenzoic acid* give esters slowly. It may also be noted that the rate of esterification of substituted

acetic acids diminishes with the number of substituents in the methyl group. In general the rate of hydrolysis of the esters is parallel to their speed of formation.

Although in many of the above-mentioned cases the effect *appears* to be steric, some other examples of chemical inactivity, such as the resistance to oxidation with chromic acid of the cresols (p. 487), cannot be due to a steric effect, because all three isomerides behave alike; furthermore, the protection is withdrawn when the hydroxyl group is methylated, although an increase in the size of the group occurs.

Examples of a different kind are met with in many cases in which an atom of carbon or other quadrivalent element is directly combined with radicals, the shape or volume of which seems to affect the course of a reaction, and the existence of compounds in which certain elements show abnormal valencies may, in some cases, possibly be due, at any rate in part, to such steric effects; in addition, the following examples, which are very suggestive, may be mentioned: When triphenyl carbinol is reduced catalytically under pressure it is converted into *tri*cyclo*hexyl carbinol*, $C(C_6H_{11})_3 \cdot OH$, but tetraphenylmethane, treated in the same way, does not give tetra*cyclo*hexylmethane. *Germanium tetrachloride* and phenyl magnesium bromide give *tetraphenylgermane*, $Ge(C_6H_5)_4$, but the tetrachloride and *cyclo*hexyl magnesium bromide give *tri*cyclo*hexylchlorogermane*, $Ge(C_6H_{11})_3Cl$, and the tetra*cyclo*hexyl derivative is not formed. Similarly, although tetraphenylsilicane is easily obtained from silicon tetrachloride and phenyl magnesium bromide, phenylsilicon trichloride does not give tri*cyclo*hexylphenylsilicane with *cyclo*hexyl magnesium bromide, but is converted into *di*cyclo*hexylphenylsilicane*, $SiH(C_6H_{11})_2 \cdot C_6H_5$; on the other hand, the bromide, $SiBr(C_6H_{11})_2 \cdot C_6H_5$, reacts normally with ethyl magnesium bromide, apparently because the ethyl occupies a smaller volume than the *cyclo*hexyl group.

Many examples of undoubted steric influences which hinder the free rotation of groups have already been given (pp. 731, 758), and it can also be shown with the aid of models that the existence of otherwise possible stereoisomerides is sometimes inhibited by the size of the atoms or groups (p. 720), but such purely physical effects do not seem to be related to the phenomena of steric hindrance.

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CHAPTER 62

HETEROCYCLIC COMPOUNDS AND ANTIBIOTICS

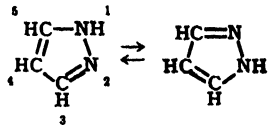
MANY different types of heterocyclic organic compounds are known, in addition to those which have already been described, because one or more atoms of various elements may take the place of the carbon atoms in many closed chain structures ; the more important of these elements are oxygen, nitrogen, and sulphur. Some heterocyclic compounds are so closely allied to certain open chain compounds, into which they may be easily converted, that they are more conveniently classed with the latter ; as, for example, the oxides of the glycols, the anhydrides and imides of dibasic acids, the lactones and lactides, and the glycosidic forms of the sugars. Other heterocyclic compounds, such as furan, thiophene, pyrrole, etc., are not related in this way to open chain compounds, but form stable nuclei, of which many derivatives are known ; such structures are usually unsaturated, but nevertheless are often of very great stability, and show the behaviour of aromatic rather than that of olefinic substances.

Of the compounds of this kind a few only are described and one or two of the many methods for the preparation of each type ; it will be seen that various unsaturated five-membered rings are formed with great facility, a fact which seems to show that the valencies of the nitrogen, oxygen, and sulphur atoms are directed in space similarly to those of the carbon atom.

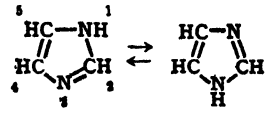
Azoles

The term *azole* is used to denote those five-membered heterocyclic structures containing two double bonds and more than one nitrogen atom, or nitrogen atoms together with those of oxygen (oxazoles) or sulphur (thiazoles) ; the atoms of the ring are numbered in a conventional manner, always starting with one of the hetero-atoms, for the usual purpose.

The substances of this kind containing two nitrogen atoms are classed as *pyrazoles* or *gyloxalines* (iminazoles) according to the relative positions of the two nitrogen atoms :

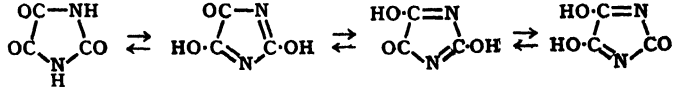


Pyrazole



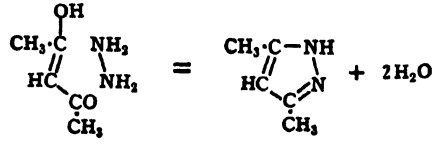
Glyoxaline (iminazole)

Now although in the pyrazoles the 3- and 5-positions are apparently different, this is not so, as 1-phenyl-3-methyl- and 1-phenyl-5-methyl-pyrazoles yield the same methylpyrazole when the phenyl group is displaced by hydrogen (p. 1053); the given structures are therefore tautomeric. The same phenomenon occurs in the glyoxalines in which the 4- and 5-positions are identical. Another kind of tautomerism is observed in these structures, as the hydroxy-derivatives are tautomeric with the keto-compounds: owing to this complex tautomerism, the formula of oxalylurea (parabanic acid, p. 633), for example, can be written in any one of several ways,

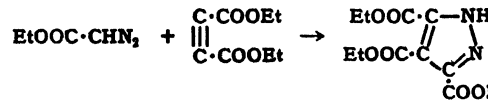


Similar changes are observed in analogous six-membered ring compounds and in those with condensed rings, as, for example, the purines (p. 637).

Pyrazoles are formed by the condensation of 1:3-diketones or β-ketonic esters with hydrazines; thus acetylacetone and hydrazine give 3:5-*dimethylpyrazole*,



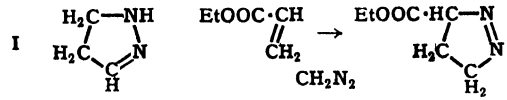
whereas a keto-pyrazoline (below) or *pyrazolone* derivative (1-phenyl-3-methylpyrazolone) is formed from ethyl acetoacetate and phenylhydrazine (p. 591). An ester of a pyrazoletricarboxylic acid results from the interaction of ethyl diazoacetate (p. 468) and diethyl acetylenedicarboxylate,



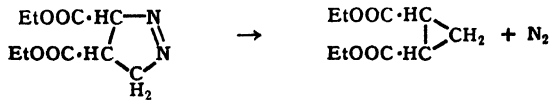
Similarly acetylene and diazomethane yield *pyrazole*, m.p. 70°.

Pyrazoles are weakly basic and those with an unsubstituted imino group give metallic derivatives and can be acetylated ; they have a benzenoid character in that they can be halogenated, nitrated and sulphonated. Alkylpyrazoles can be oxidised to carboxylic acids, and even phenylpyrazoles on oxidation yield pyrazolecarboxylic acids ; the acids lose carbon dioxide when they are heated. Aminopyrazoles can be diazotised and the resulting diazonium compounds couple with amines and phenols.

Derivatives of *pyrazoline*, (I), can be obtained by reducing the pyrazoles with sodium and alcohol or by condensing unsaturated esters, etc., with aliphatic diazo-compounds,



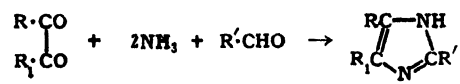
they are much less stable than the pyrazoles and have an aliphatic character. Many pyrazoline derivatives decompose when they are heated, giving nitrogen and *cyclo*propane derivatives (p. 781),



Glyoxaline, (II), is formed by the condensation of glyoxal with formaldehyde and ammonia,

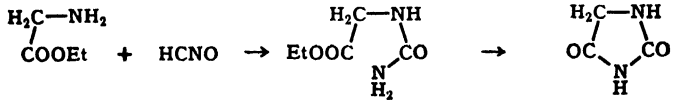


in a similar manner 1:2-diketones give substituted glyoxalines,



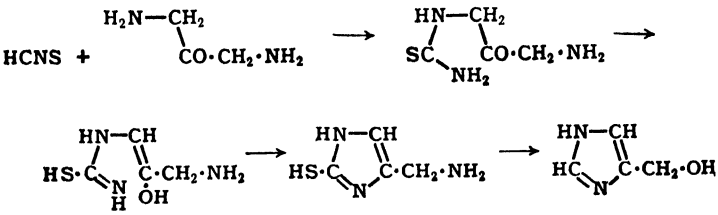
Glyoxalines are more strongly basic than the pyrazoles, but the hydrogen atom of the imino-group can be displaced by metals; they can be halogenated and nitrated.

Hydantoin (2:4-*diketotetrahydroglyoxaline* or 2:4-*dihydroxyglyoxaline*) is prepared by the electrolytic reduction of parabanic acid, or by converting ethyl glycine into the substituted urea with potassium cyanate and heating the latter with hydrochloric acid,

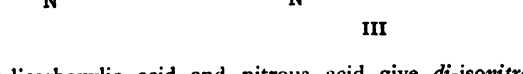


Such cyclic urea derivatives are readily hydrolysed, giving open chain compounds, and are therefore usually classed with the latter.

l-*Histidine* (p. 626) has been synthesised as follows: Diaminoacetone hydrochloride [1] is heated with potassium thiocyanate, and the resulting compound, (I), is treated with dilute nitric acid [2]:



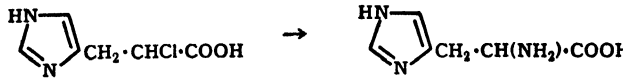
The hydroxymethyl derivative, (II), which is thus formed, is converted into the chloro-compound and condensed with diethyl sodiochloromalonate to give (III); the 4- (or 5-) glyoxalinechloropropionic acid, (IV), formed by the hydrolysis of (III), is converted by ammonia into *dl*-histidine, (V), which is resolved with tartaric acid:



III

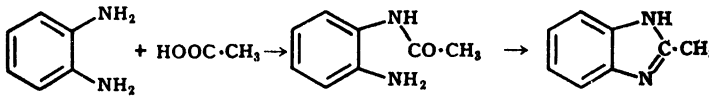
[1] Acetonedicarboxylic acid and nitrous acid give *di*-iso*nitrosoacetone*, with the elimination of carbon dioxide, and the product is reduced to diaminoacetone.

[2] The amino- is converted into the hydroxy-group by nitrous acid which is produced during the reaction.



IV V

Benzoglyoxalines or *benziminazoles* are produced from *o*-phenylenediamines and acids,



Benzoglyoxaline is oxidised to glyoxaline-4:5-dicarboxylic acid with permanganate.

Triazoles. When three nitrogen atoms and two carbon atoms form a five-membered ring, four different arrangements would appear to be possible :

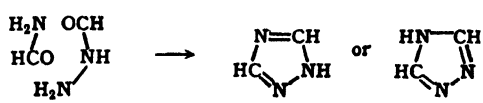


I II III IV

But (I) and (II), and also (III) and (IV), are tautomeric and so the triazoles are usually divided into two classes only, namely *triazoles* (I and II) and *osotriazoles* (III and IV). When, however, the imino-hydrogen atom in either class is displaced by some radical tautomerism is no longer possible, and two derivatives of each type can be obtained.

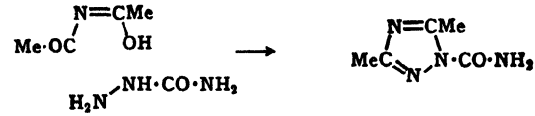
Both triazoles and osotriazoles are very weakly basic and the imino-hydrogen atom can be displaced by metals ; the *C*-alkyl compounds can be oxidised to the corresponding acids.

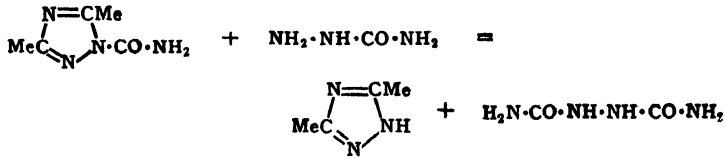
Triazoles are produced by heating amides with hydrazides, which are themselves prepared by the action of hydrazine hydrate on esters :



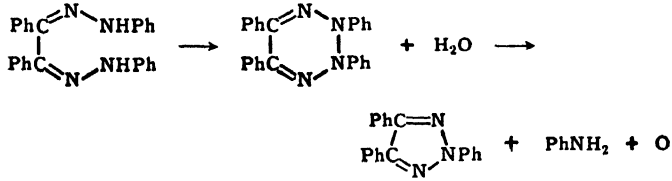
Also by the interaction of diacetamide or one of its homologues (in

the enolic form), and semicarbazide hydrochloride, in the presence of sodium acetate,



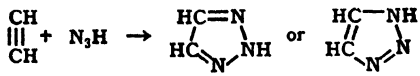


Osotriazoles are produced by oxidising the osazones of (1:2-) diketones and heating the products with dilute acid,

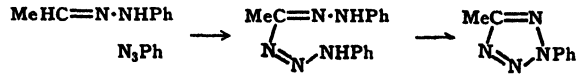


Some of the osotriazole is oxidised by the liberated oxygen.

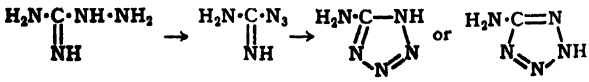
Osotriazole may be obtained by the condensation of acetylene and hydrazoic acid,



Tetrazoles may be obtained by the condensation of phenyl azide (p. 470), with the phenylhydrazones of aldehydes in the presence of alcoholic sodium ethoxide, aniline being eliminated,



Aminotetrazole is formed from aminoguanidine and nitrous acid, in nitric acid solution, the azide which is first produced, undergoing isomeric change,

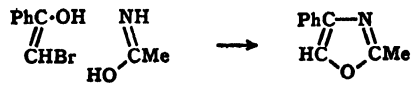


As with the triazoles, tautomerism occurs in those tetrazoles in which there is an unsubstituted imino-group.

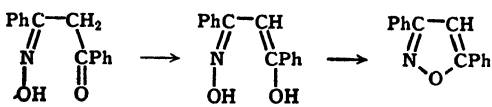
Tetrazole and its derivatives are not basic, and in fact the imino-hydrogen atom is strongly acidic. The nucleus exhibits benzenoid characteristics, and aminotetrazoles can be diazotised.

As examples of heterocyclic rings containing two elements other than carbon, the following may be mentioned :

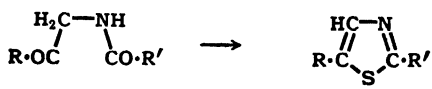
Oxazoles are formed from (the enolic forms of) α-halogen ketones and amides,

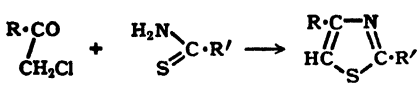


Isoxazoles are produced from the monoximes of β-diketones,



Thiazoles are formed by the action of phosphorus pentasulphide on the acyl derivatives of α-aminoketones or by condensing thio-amides with α-halogen ketones, etc.,

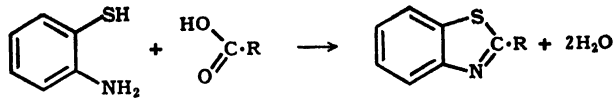




2-Aminothiazole is prepared from thiourea and αβ-dichloro-diethyl ether (which gives chloroacetaldehyde).

Various thiazole derivatives, such as sulphathiazole (p. 477), penicillin (p. 1061) and vitamin B_1 (p. 1066), are very important.

Benzothiazoles are formed from *o*-aminothiophenols and acids,

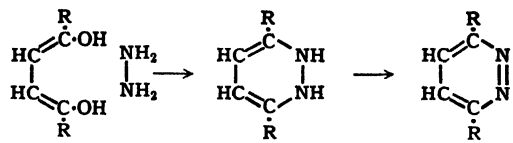


Primuline (p. 680) is an example of a complex which contains two benzothiazole rings.

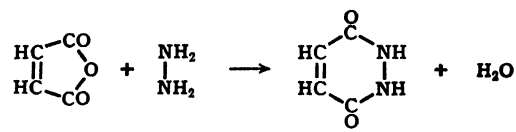
Diazines

The *diazines* are six-membered heterocyclic compounds of the structures shown below.

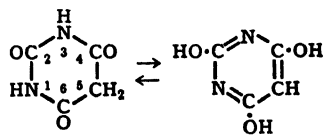
Ortho-**diazines**, or *pyridazines*, are produced from enolic 1:4-diketones and hydrazine, the dihydrodiazines which are formed intermediately undergoing atmospheric oxidation,



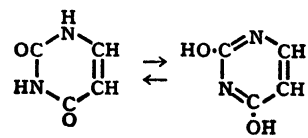
Maleic anhydride and hydrazine yield *diketotetrahydropyridazine*,



Meta-**diazines**, or **pyrimidines**, are the most important diazines; many, usually hydroxypyrimidines, such as alloxan, barbituric acid, uracil, thymine, cytosine (2-hydroxy-6-aminopyrimidine), etc., occur naturally, some of them as constituents of nucleic acids (p. 1075). Such hydroxypyrimidines show lactam-lactim tautomerism (p. 838) and the method of writing their formulae is arbitrary :

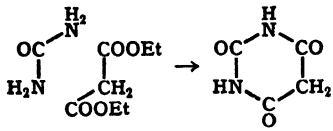


(2:4:6-Triketohexahydropyrimidine)

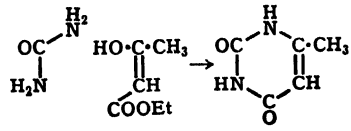


Uracil
(2:6-Dihydroxypyrimidine)

Syntheses of barbituric acid and 4-methyluracil have already been given (pp. 634, 635) as examples of a general method, which consists in the condensation of urea with an ester of the malonic or acetoacetic type or with a β-diketone (in the enolic form),

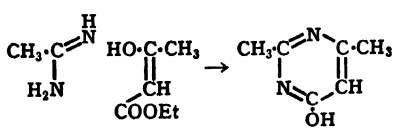


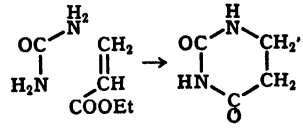
Barbituric acid



4-Methyluracil

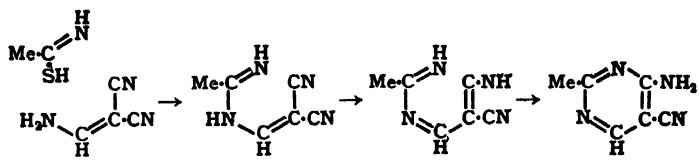
These reactions may be extended by condensing amidines (and other amino-compounds) instead of urea with the esters mentioned above or with certain unsaturated esters ; acetamidine, for example, with ethyl acetoacetate gives 6-*hydroxy*-2:4-***dimethylpyrimidine***, while urea and ethyl acrylate give dihydrouracil,





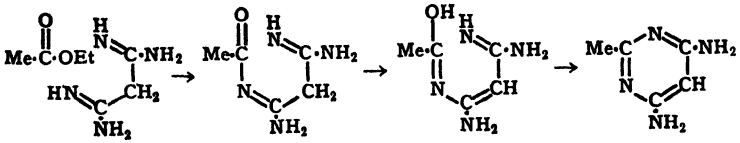
Dihydrouracil, treated with bromine and pyridine successively, gives uracil (p. 1058).

Aminopyrimidines may be prepared by various reactions of a similar type of which the following may serve as examples : thioacetamide and aminomethylenemalononitrile [1] give a cyanoaminomethylpyrimidine,



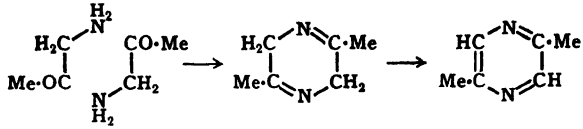
[1] Ethyl orthoformate condenses with malononitrile in the presence of acetic anhydride to give ethoxymethylenemalononitrile which is treated with ammonia.

while ethyl acetate and malonodiamidine give 4:6-*diamino*-2-*methyl-pyrimidine* (Todd and co-workers) :



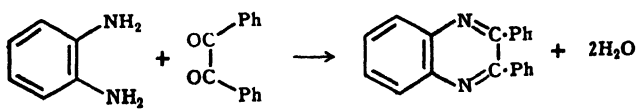
Pyrimidine, m.p. 20–22°, b.p. 124°, may be prepared by the reduction of the trichloro-compound obtained from barbituric acid and phosphorus oxychloride ; it gives a neutral solution in water, but combines with acids giving salts. Homologous pyrimidines can be oxidised to carboxylic acids. Hydroxypyrimidines are phenolic and basic and with phosphorus oxychloride give chloro-pyrimidines. Purine and its derivatives contain a pyrimidine condensed with a glyoxaline ring.

Para-**diazines**, or *pyrazines*, are formed spontaneously from α-aminoketones, with the intermediate production of dihydro-pyrazines, which are very easily oxidised,



On reduction with sodium and alcohol, pyrazines yield hexahydro-pyrazines or piperazines.

Benzo*para***diazines**, or *quinoxalines*, result from the condensation of *o*-phenylenediamines and 1:2-diketones, 1:2-dialdehydes,



α-ketoacids, etc. *o*-Quinones condense similarly with 1:2-diamines (cf. p. 1071); mauveine (p. 679) is a derivative of dibenzo*para*diazine.

Antibiotics

During recent years a number of organic compounds which are tormed by micro-organisms and which have the power of inhibiting

the growth or activity of other micro-organisms have been isolated; such substances are known as *antibiotics* and their use has opened new vistas in the treatment of disease. Probably penicillin, of which a short description has already been given (p. 654), is the best known and most important compound of this type, but the field is very fertile and it is possible that even more useful substances may be discovered in the future.

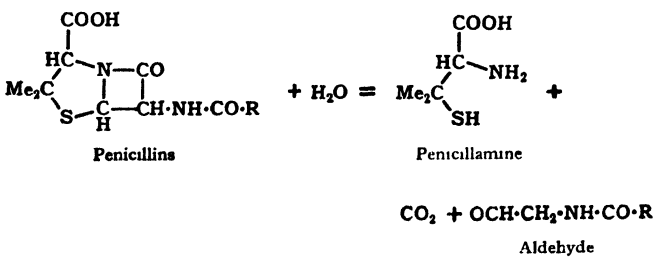
A short account of some of the work which led to the determination of the structure of penicillin follows, together with a mention of two other antibiotics, *chloromycetin* and *streptomycin*.

Penicillin. This name has been given to a mixture of closely related acids, $C_9H_{11}O_4N_2SR$, which differ only in the nature of the group R, and three of which are mentioned here:

British Name	*American Name*	*R*
Penicillin-I	F-penicillin	$-CH_2 \cdot CH{:}CH \cdot CH_2 \cdot CH_3$
Penicillin-II	G-penicillin	$-CH_2 \cdot C_6H_5$
Penicillin-III	X-penicillin	$-CH_2 \cdot C_6H_4 \cdot OH$ (1:4)

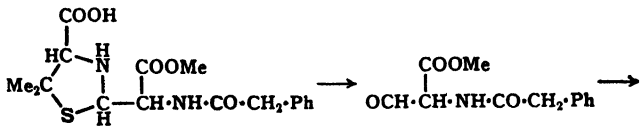
Their structures have been established by the combined and sustained efforts of many workers both here and in the U.S.A. and many of their important decomposition products have been synthesised; they are generally used medicinally in the form of their sodium salts.

The penicillins are hydrolysed by hot dilute mineral acids giving equimolecular quantities of *penicillamine* (d-*ββ-dimethylcystein*), carbon dioxide and an aldehyde which contains the group R:

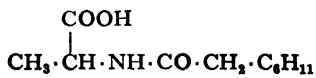


When they are treated with methyl alcohol methyl esters are produced and biological inactivation occurs; the methyl ester

from penicillin-II undergoes hydrolysis giving penicillamine and *methyl penaldate* which by catalytic reduction and hydrolysis yields cyclo*hexylacetylalanine* (synthesised); the structure of methyl penaldate is thus established and R, in penicillin-II, is $—CH_2 \cdot C_6H_5$:

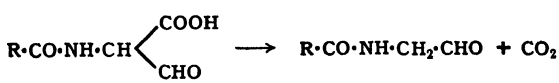


Methyl penaldate-II

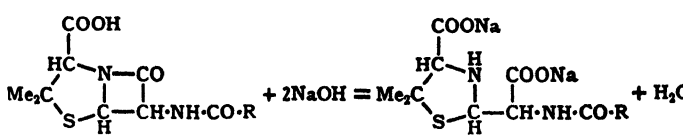


*Cyclo*hexylacetylalanine

With diazomethane, the penicillins give monomethyl esters which with mercuric chloride solution yield the methyl ester of penicillamine : this proves that the acidic group in the penicillins is the carboxyl radical of penicillamine and the formation of methyl penaldate shows that a new carboxyl group, esterified by methyl alcohol, is produced by the gentle hydrolysis of the penicillins. It also proves that the carbon dioxide evolved when the penicillins are hydrolysed with mineral acids is formed from this new carboxyl group by the decomposition of a penaldic acid :



When the penicillins are treated with alkali, salts of dicarboxylic acids, *penicilloic acids*, are formed ; these dicarboxylic acids have been synthesised,

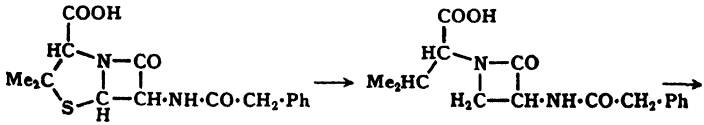


Penicillins

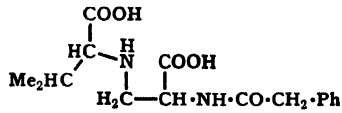
Penicilloic acids (sodium salt)

Finally the sodium salt of penicillin-II, treated with hydrogen and Raney nickel in aqueous solution, gives *desthiopenicillin*-II, $C_{16}H_{20}O_4N_2$, in which the sulphur has been exchanged for two

hydrogen atoms ; a part of this product undergoes hydrolysis giving *phenylacetyl*-l-*alanyl*-d-*valine* :



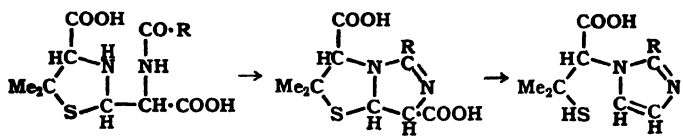
Penicillin-II Desthiopenicillin-II



Phenylacetyl-*l*-alanyl-*d*-valine

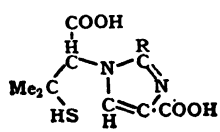
The formation of the last-named compound, which has been synthesised, affords very strong evidence of the structure of the penicillins (including that of R in penicillin-II), since it contains all the atoms of the penicillin molecule except that of sulphur. The results also show that the molecules of the penicillins contain certain complex groups which are present in some well-known protein amino-acids (alanine and valine).

In the presence of dilute mineral acids at 30°, the penicillins show mutarotation and give crystalline isomerides, *penillic acids* ; these products with cold aqueous mercuric chloride evolve carbon dioxide and give *penillamines*, which resist hydrolysis :



Penillic acids Penillamines

Penillic acids with hot dilute acids give penicillamine, carbon dioxide and an aldehyde in the same way as the penicillins, but with baryta water they are isomerised to iso*penillic acids* :



Chloromycetin (*chloroamphenicol*) was first isolated from *Streptomyces venezuelae* and has proved of value in the treatment of some forms of typhus. It is laevorotatory, melts at 150°, and its structure,

$$p\text{-}NO_2\cdot C_6H_4\cdot CH(OH)\cdot CH(NH\cdot CO\cdot CHCl_2)\cdot CH_2\cdot OH,$$

has been proved by synthesis : the presence of an aromatic nitro-group in the molecule is noteworthy.

Streptomycin, $C_{21}H_{39}O_{12}N_7$, is isolated from cultures of *Streptomyces griseus* ; it is a complex glycoside of known structure and has given promising results in cases of tuberculous meningitis.

CHAPTER 63

VITAMINS AND CONJUGATED PROTEINS

Vitamins

THE immense amount of work which has been done since the existence and importance of vitamins was proved has led to the discovery of many new vitamins and a better understanding of their function in the living organism : our knowledge of the chemistry of the vitamins has also made rapid progress and many of them have been synthesised. Some of these developments are described in this chapter, but vitamins A, C and D are found elsewhere (pp. 978, 881, 1099) owing to their close relationship to other compounds of outstanding importance.

Vitamin B. The active substance, originally called vitamin B, proved to be a complex mixture, which contains a vitamin now known as B_1, and various other components, referred to collectively as the vitamin B_2 complex.

Vitamin B_1, or *aneurin*, called *thiamin* in the U.S.A., is the anti-beri-beri factor (p. 653), and is destroyed by heat.

The vitamin B_2 complex is much more stable towards heat, and from it the following components have been isolated ; the names in parentheses were formerly used :

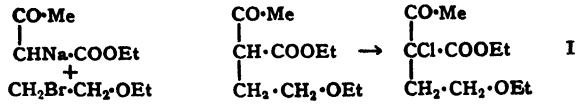
Riboflavin (lactoflavin, vitamin G)	Nicotinamide
Pyridoxin (vitamin B_6, adermin)	*Meso*inositol (p. 798)
Pantothenic acid	*p*-Aminobenzoic acid
Biotin (vitamin H)	Folic acid (vitamin B_c ?)

Of these riboflavin is a growth factor for rats, pyridoxin prevents dermatitis in rats and pantothenic acid in chicks, etc. ; nicotinamide is the anti-pellagra component. It should be noted, however, that in these and other cases the effects mentioned are those by which the compounds are usually most easily recognised, but doubtless do not cover the whole activity. Many of these substances are also *bios factors*, in that they promote the growth of yeast and other micro-organisms, but it is not yet known whether or not they are true vitamins, that is to say are necessary for the growth and health of human organisms; possibly they would be better called *biotics* rather than vitamins (cf. antibiotics, p. 1060).

Most, if not all, of these substances, are present in living matter as more complex molecules, combined with one another and often also with phosphoric acid and a sugar ; they then form the prosthetic groups of conjugated proteins. Such proteins are often enzymes or co-enzymes, and it may well be that vitamin activity is due to some simple chemical change brought about by enzyme action. Co-carboxylase (aneurin pyrophosphate) and co-zymase have already been mentioned (p. 903) in this connection.

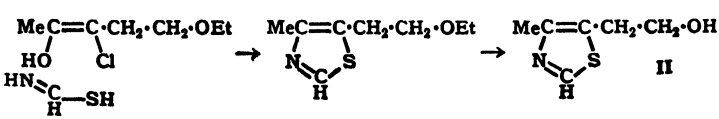
Aneurin, vitamin B_1, was first isolated in the crystalline state in 1926 in the form of its ' hydrochloride ' (Jansen and Donath), to which the formula, $C_6H_{10}ON_2,HCl$, was assigned ; six years later it was shown that the vitamin contained sulphur, but it was not until about 1934 that much progress was made with the determination of its structure. It was then found (R. R. Williams and co-workers) that the chloride, of which the correct formula was $C_{12}H_{18}ON_4Cl_2S$, could be quantitatively converted by sodium sulphite containing sulphurous acid into an oily base, C_6H_9ONS, and a sulphonic acid, $C_6H_9O_3N_3S$. The structures of both these compounds were then determined by physical methods and degradations and established by synthesis ; the synthesis of aneurin itself was then accomplished.

The basic decomposition product of aneurin was obtained as follows : The sodium derivative of ethyl acetoacetate is treated with β-bromodiethyl ether and the product is converted into the compound, (I), with the aid of sulphuryl chloride,



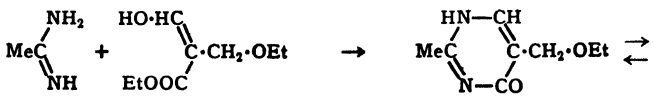
I

The carbethoxy-group of (I) is then displaced by hydrogen (ketonic hydrolysis), and the product (in its enolic form) is condensed with thioformamide, to give the thiazole ether, which is converted into the alcohol, with hydrochloric acid ; the hydrochloride of the resulting base, *4-methyl-5-β-hydroxyethylthiazole*, (II), is identical with that of the base obtained from aneurin :

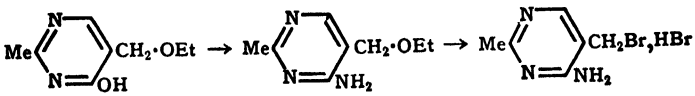


II

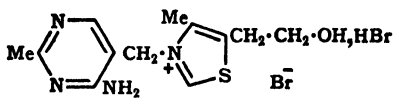
The vitamin itself was synthesised by R. R. Williams and Cline in the following manner: Ethyl β-ethoxypropionate is converted into its hydroxymethylene derivative with the aid of ethyl formate and this product, (III), is condensed with acetamidine. The resulting compound, (IV), in its lactim form, (V), gives with phosphorus oxychloride a chloro-derivative, which on treatment with alcoholic ammonia is converted into an amine, (VI); the ethoxy-group of this base is then displaced by bromine, with the aid of hydrogen bromide, and finally the salt of the bromo-derivative, (VII), which is thus formed, is combined with the thiazole, (II). The final product, (VIII), gives a corresponding chloride, which is identical with that of the naturally occurring vitamin B_1 in antineuritic action.



III IV



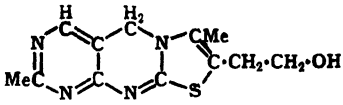
V VI VII



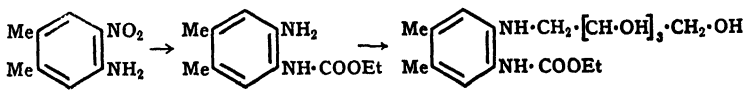
VIII

Co-*carboxylase*, the co-enzyme of carboxylase which plays such an important role in alcoholic fermentation (p. 905), is the pyrophosphoric ester of aneurin.

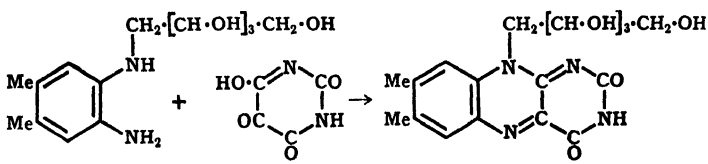
Thiochrome, $C_{12}H_{14}ON_4S$, was isolated from yeast by Kuhn and his co-workers in 1935; it is a yellow basic compound, the solutions of which show an intense blue fluorescence. It is also obtained when aneurin is oxidised in alkaline solution, and is probably formed by such a reaction during its extraction from natural sources. Thiochrome has the structure shown (p. 1068) and has been synthesised by Todd; this synthesis, and the relation between thiochrome and aneurin, confirm the structural formula assigned to the latter.



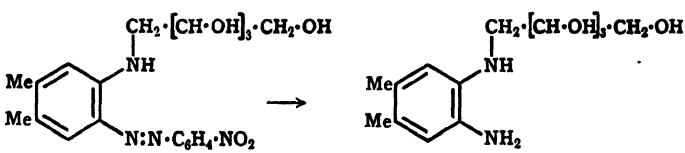
Riboflavin has been isolated from whey, and forms orange-brown crystals which show a yellowish-green fluorescence. Its structure is proved by various syntheses, of which those of Karrer and of Kuhn appeared almost simultaneously. In one method, nitroxylidine is converted into its carbethoxy-derivative, which is reduced catalytically; the resulting amino-compound is then condensed with *d*-ribose in the presence of hydrogen and palladium, which reduce the —N=CH-group :



The amine produced by the alkaline hydrolysis of this ribose derivative condenses with alloxan, in the presence of boric acid, and gives riboflavin :



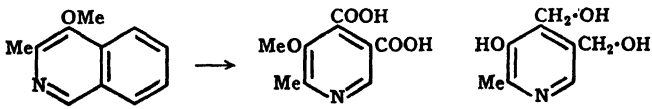
In another synthesis the reduced condensation product of *d*-ribose and 4-amino-*o*-xylene is coupled with a *p*-nitrophenyldiazonium salt and the resulting compound is catalytically reduced with hydrogen and nickel under pressure ; the amine is then condensed with alloxan as before :



Pyridoxin, (II), previously called vitamin B_6 or *adermin*, is the component of the vitamin B_2 complex which prevents dermatitis in rats.

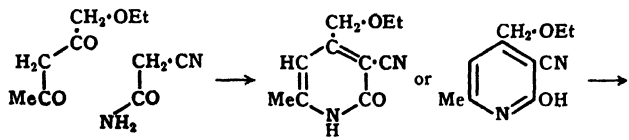
It is usually prepared from rice bran and is obtained as (the hydrochloride of) a weak tertiary base, $C_8H_{11}O_3N$. One of its oxygen atoms is phenolic and the other two form primary alcoholic groups; its absorption spectrum is very similar to that of 3-hydroxypyridine and different from those of the 2- and 4-isomerides. Its phenolic methyl ether is oxidised by alkaline permanganate to a *methoxypyridinetricarboxylic acid*, which gives a red colour with ferrous sulphate and readily loses carbon dioxide (1 mol.), two characteristics of pyridine-2-carboxylic acids (p. 575).

Under slightly different conditions pyridoxin methyl ether is oxidised to a *methoxymethylpyridinedicarboxylic acid*, (I), which does not give a reaction with ferrous sulphate ; this acid is also obtained by the oxidation of 4-methoxy-3-methyl*iso*quinoline, a synthetic compound of known structure,

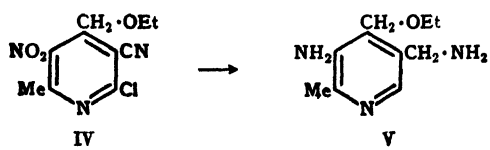


I II

The constitution of pyridoxin, established by these and other facts, is therefore represented by (II), and confirmed by the following synthesis :- Cyanoacetamide is condensed with ethoxyacetylacetone in the presence of piperidine and the product, (III), after having been nitrated in the free β-position, is converted into (IV) with the aid of phosphorus pentachloride ; this chloride is then reduced to (V), which, treated successively with nitrous acid and hydrobromic acid, gives the (hydrobromide of) pyridoxin (II),

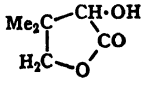


III



IV V

Pantothenic acid is the chick anti-dermatitis factor of the vitamin B_2 complex and its usual source is liver, from which it is extracted only with very great difficulty ; its investigation is mainly due to R. J. Williams and his collaborators. On hydrolysis with alkali it gives β-alanine and an $\alpha\gamma$-dihydroxy-acid (as a salt) ; the latter passes into a hydroxy-γ-lactone, (I), $C_6H_{10}O_3$, m.p. 91–92°, $[\alpha]_D^{26°} -49{\cdot}8°$. The structure of this lactone was proved by converting it into the trihydric alcohol, (II), with methyl magnesium iodide, oxidising this alcohol to the hydroxyaldehyde, (III), with lead tetra-acetate, and then into $\alpha\alpha$-dimethyl-β-hydroxypropionic acid, (IV), by further oxidation :



I

$$\longrightarrow \underset{\text{II}}{CH_2(OH)\cdot CMe_2\cdot CH(OH)\cdot C(OH)Me_2} \longrightarrow$$

$$\underset{\text{III}}{CH_2(OH)\cdot CMe_2\cdot CHO} \longrightarrow \underset{\text{IV}}{CH_2(OH)\cdot CMe_2\cdot COOH}$$

Pantothenic acid has been synthesised by the following method : *iso*butyraldehyde is condensed with formalin in the presence of potassium carbonate and the bisulphite compound of the resulting hydroxyaldehyde is converted into the cyanohydrin,

$$CH_2O+CHMe_2\cdot CHO \longrightarrow CH_2(OH)\cdot CMe_2\cdot CHO \longrightarrow CH_2(OH)\cdot CMe_2\cdot CH(OH)\cdot CN;$$

this product, hydrolysed with concentrated hydrochloric acid, gives the *dl*-lactone, (I, above), from which by resolution with quinine, a *l*-lactone, identical with that from pantothenic acid is obtained. After condensation with β-alanine ethyl ester and hydrolysis of the ester with cold baryta, *d*-pantothenic acid, (V), identical chemically and physiologically with the natural substance is obtained,

$$\underset{\text{V}}{CH_2(OH)\cdot CMe_2\cdot CH(OH)\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot COOH}$$

Biotin prevents injury to rats caused by the ingestion of large quantities of egg-white ; it is also one of the bios substances which promotes the growth of yeast, etc., and for this it is effective at a dilution of one in 5×10^{11}. It was first isolated as its methyl ester

from egg-yolk and subsequently from liver extracts : 1 million eggs would be required to obtain 1 g. It has recently been shown that the sources mentioned above furnish two isomeric biotins, α-biotin from egg-yolk and β-biotin from liver.

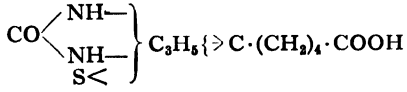
The structure of β-biotin was determined mainly by the work of du Vigneaud. β-Biotin methyl ester, $C_{11}H_{18}O_3N_2S$, is readily hydrolysed to the acid, biotin, $C_{10}H_{16}O_3N_2S$, m.p. 230–231°, $[\alpha]_D^{22°} = +92°$ in 0·1 *N*. sodium hydroxide solution; the acid is reconverted into the ester by diazomethane. With baryta or concentrated hydrochloric acid biotin gives carbon dioxide and a diamino-acid, $C_9H_{18}O_2N_2S$, m.p. 186–190°, which is reconverted into biotin by phosgene. Biotin, therefore, is a cyclic ureide :

$$\begin{matrix} >C\cdot NH_2 \\ >C\cdot NH_2 \end{matrix} + COCl_2 \longrightarrow \begin{matrix} >C\cdot NH \\ >C\cdot NH \end{matrix} \!\!\rangle CO$$

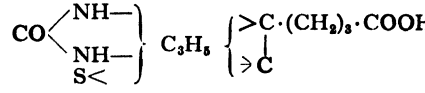
On oxidation it gives a sulphone, and biotin methyl ester, with methyl iodide, gives a sulphonium salt; the sulphur atom is therefore present as a thio-ether group.

The diamino-acid, on oxidation, gives adipic acid and that its carboxyl group remains as such in the adipic acid is proved by the fact that when the carboxyl group of biotin methyl ester is displaced by $—NH_2$ by the Curtius method and the product is hydrolysed, the resulting triamine does not give adipic acid on oxidation.

Partial formulae, (I) or (II), for β-biotin may therefore be written : [1]



I

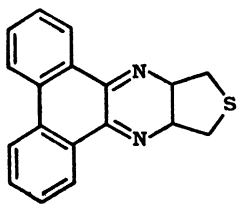


II

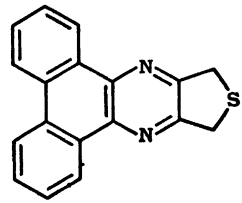
Now the diamino-acid combines with phenanthraquinone to give a substituted quinoxaline (p. 1060), so that the $—NH_2$ groups are combined with adjacent carbon atoms; further, the ultraviolet absorption spectrum of this quinoxaline is very similar to

[1] In the case of (II) adipic acid would be formed from a substituted malonic acid or β-keto-acid.

that of the quinoxaline, (IV), from $\beta\beta'$-diaminotetrahydrothiophene, and different from that of the intermediate *dihydro*quinoxaline, (III, which gave IV when heated in the air) :

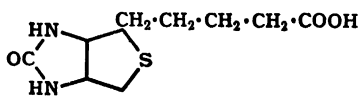


III

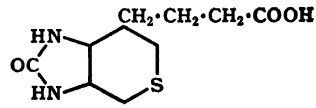


IV

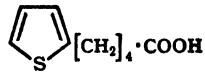
The carbon atoms attached to the amino-groups in the diamino-acid, therefore, are also directly united to hydrogen atoms ; possible formulae (V) and (VI) follow for biotin :



V



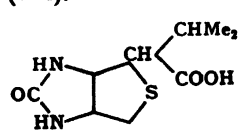
VI



VII

Finally, when the nitrogen atoms of the diamino-acid are displaced by exhaustive methylation, the product (which was synthesised later) is α[ω-carboxy-*n*-butyl]thiophene, (VII) ; these results prove that the structure of β-biotin is expressed by the formula (V), which has been confirmed by the synthesis of the *dl*-compound.

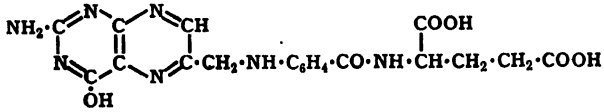
α-Biotin is shown at (VIII).



VIII

Folic acid. The chemistry of this component of the vitamin B mixture has not yet been clearly elucidated and confusion has arisen

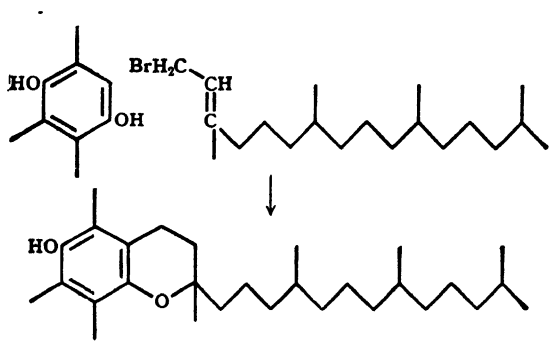
because the name folic acid has been used for several different, but closely related, compounds. One of these, vitamin B_C, is probably identical with the synthetic product, *pteroylglutamic acid*, shown below :



Pteroylglutamic acid is beneficial in cases of pernicious anaemia.

Vitamin B_{12}, also effective against pernicious anaemia, forms red crystals and is remarkable in that it contains cobalt : its structure has been elucidated by Todd and his co-workers (*Nature*, 1955, **176**, 329).

Vitamin E, which occurs in wheat germ oil (p. 654), is also found in other seed oils, such as cotton seed and its absence from a diet brings about sterility. It is now known that there are at least two and possibly more naturally occurring compounds which possess vitamin E activity, and these have been called *tocopherols* (Gr. *tokos*, childbirth ; *phero*, to bear). α-Tocopherol has been synthesised by the interaction of 2:3:5-trimethylquinol and phytyl bromide (cf. p. 973) and its structure is shown below ; it is a derivative of dihydrobenzopyran or chroman,

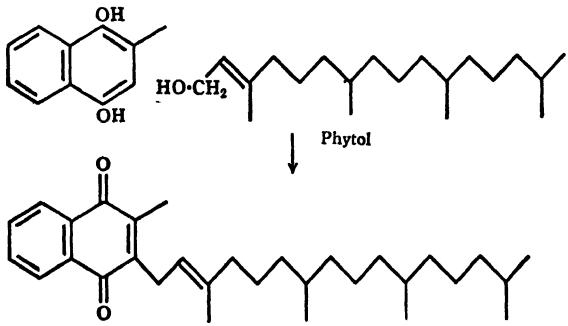


α-Tocopherol

β-Tocopherol is a lower homologue of the α-compound.

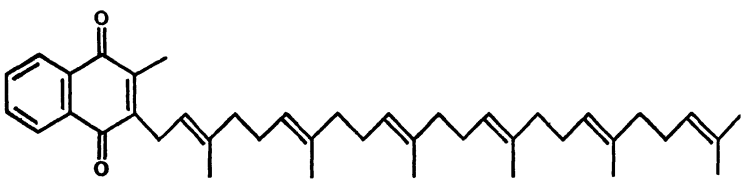
Vitamin K occurs in hog's liver fat, and green vegetables, such as spinach and alfalfa ; it is concerned in the clotting of blood and its absence from a diet lengthens the time of blood clotting. Vitamin

K_1 has been synthesised: Phytol reacts with 2-methyl-1:4-dihydroxynaphthalene in the presence of oxalic acid and the resulting methylphytylnaphthoquinol is oxidised to the corresponding quinone with silver oxide in the presence of magnesium sulphate:



Vitamin K_1

Vitamin K_2 is a related compound of the structure:



Conjugated Proteins

Conjugated proteins (p. 645) contain, in addition to the protein matter, a small proportion of some relatively simple substance known as the *prosthetic group*, which may be separated from the protein by gentle hydrolysis or even in some cases by dialysis. The chief types of conjugated proteins and their prosthetic groups are the following:

Conjugated proteins	*Prosthetic groups*
Nucleoproteins	Nucleic acids
Chromoproteins	Haem, chlorophyll
Glycoproteins	Carbohydrates or carbohydrate derivatives

In addition, many, if not all, the B vitamins and the lecithins probably constitute the prosthetic group of proteins; many prosthetic groups, such as that of caseinogen, have not yet been identified.

The nucleoproteins form the chief constituents of the cell nucleus in both plants and animals, and it seems very probable that many of the viruses, responsible for so many diseases, are nucleoproteins. The chromoproteins, haemoglobin and chlorophyll,[1] have already been briefly described; the glycoproteins or mucins occur in the mucous membrane of animals.

In the sequel a brief account is given of the prosthetic groups of the nucleoproteins and chromoproteins and allied compounds.

Nucleic Acids

The nucleoproteins are weak acids as their molecules contain phosphoric acid residues, and they undergo progressive hydrolysis with various reagents as indicated below:

Nucleoprotein
↓
Nucleic acids+Protein
↓
Nucleotides
↓
Nucleosides+Phosphoric acid
↓
Base+Sugar

In considering the structure of the nucleic acids it will be convenient to start with the nucleosides.

Nucleosides. Many nucleosides are very readily hydrolysed by dilute acids to a base (purine or pyrimidine) and a sugar and are thus shown to be glycosides; others are resistant to such reagents, and when hydrolysed with concentrated acids give a product from which a sugar cannot be isolated. The glycosidic nature of such nucleosides has, however, been shown in other ways; uridine (p. 1076), for example, can be hydrogenated to dihydrouridine, which hydrolyses normally giving a base and a sugar.

The identification of the basic decomposition product of the

[1] The term chlorophyll is often applied either to the chromoprotein or to the prosthetic group.

molecule (aglycone) is a fairly simple matter and the bases which are thus obtained are either :

(*a*) Purine derivatives (adenine, guanine, p. 639).

(*b*) Pyrimidine derivatives (uracil, cytosine, p. 1058, thymine or 5-methyluracil).

The sugar component is isolated with more difficulty, but it is now known that it is either *d*-ribose or *d*-2-deoxyribose, two sugars which are not known to occur elsewhere in nature. Nucleosides are therefore *d*-ribosides or *d*-deoxyribosides, and some of the more important are shown below :

d-Ribonucleosides

9-Guanine *d*-ribofuranoside, guanosine
9-Adenine *d*-ribofuranoside, adenosine
3-Cytosine *d*-ribofuranoside, cytidine
3-Uracil *d*-ribofuranoside, uridine

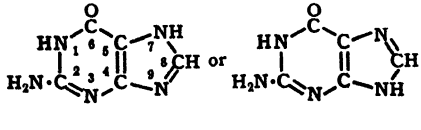
d-Deoxyribonucleosides

9-Guanine *d*-deoxyribofuranoside
9-Adenine *d*-deoxyribofuranoside
3-Cytosine *d*-deoxyribofuranoside
3-[5-methyluracil] *d*-deoxyribofuranoside

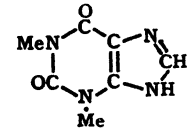
Now, before a structure and configuration can be assigned to a nucleoside the following points have to be settled :

(*a*) To which atom of the base the sugar is united, (*b*) whether the sugar is pyranose or furanose, (*c*) the nature, α- or β-, of the glycoside link.

(*a*) As an example guanosine may be considered ; when this substance is treated with nitrous acid, an amino-group is displaced and xanthosine (9-xanthine *d*-ribofuranoside) is formed ; this compound, with diazomethane, gives a dimethyl derivative, which on hydrolysis yields theophylline (1:3-dimethylxanthine, p. 638),



Guanine



Theophylline

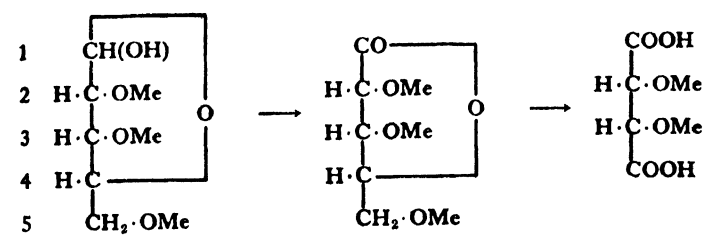
This result proves that in xanthosine, positions 1 and 3 were free and that, probably, 7 (or 9) was occupied by the sugar residue: had the sugar residue been at 8, leaving 7 (or 9) free, a trimethyl derivative, caffeine (1:3:7-) or 1:3:9-trimethylxanthine would have been expected.

But since the 7 and 9 positions in unsubstituted purines are tautomeric, the ribose residue might be attached to either of these nitrogen atoms. A comparison of the ultra-violet absorption spectrum of guanosine with those of 7-methyl- and 9-methyl-guanine shows, however, a close resemblance to that of the 9-derivative; guanosine, therefore, is 9-guanine riboside (p. 1078). It has been shown in a similar manner that in all nucleosides derived from *purine* bases, the sugar residue is in the 9-position (Gulland), and this physical evidence has been confirmed in other ways (p. 1078).

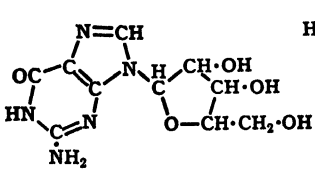
On the other hand, cytidine, with nitrous acid gives uridine, the methyl derivative of which yields 1-methyluracil on hydrolysis; the ribose residue must therefore be in the 3-position of the *pyrimidine* base.

Inconclusive spectroscopic evidence has shown that the sugar residue in the 2-deoxyribosides is also probably in the 9- or the 3-position according to the type of base.

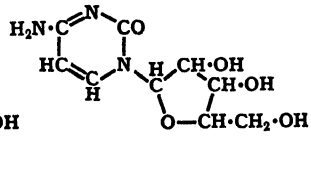
(*b*) The glycosidic structure of a nucleoside is determined as follows: The compound is completely methylated and the product is hydrolysed with dilute acid: the 2:3:5-trimethyl-*d*-ribose thus produced is oxidised to a γ-lactone, which is proved on further oxidation to afford *meso*dimethyltartaric acid:



The sugar, therefore, is a furanoside (as shown) and similar sugar residues are assumed to be present in all nucleosides; the structures of guanosine and cytidine, which represent the two types of nucleosides, are therefore as shown (p. 1078). In the deoxyribonucleosides there is a hydrogen atom instead of the hydroxyl group at the 2-position in the sugar molecule.



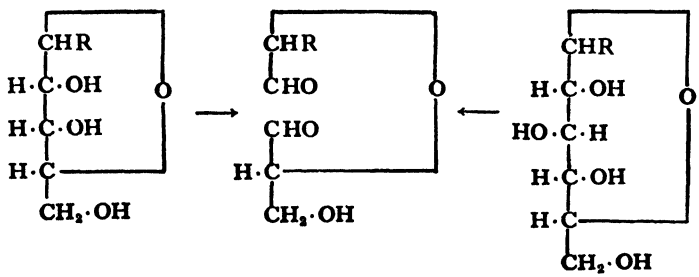
Guanosine



Cytidine

(*c*) Todd and his co-workers have shown that when adenosine, (I), is oxidised with sodium periodate, a dialdehyde, (II), is formed. This confirms the furanose structure of the ribose : a pyranose sugar would have been oxidised with the elimination of one carbon atom (p. 895). Further, adenine *d*-glucopyranoside, (III), synthesised by a method which proves conclusively that the sugar residue is in the 9-position, gives the same dialdehyde, (II), with the loss of one carbon atom, when it is oxidised with periodate ; the 9-position of the ribose in adenosine is thereby proved conclusively (p. 1077).

Another synthesis of (III) starts from 2:3:4:6-tetra-acetyl-1-bromoglucose which gives [illegible] (p. 895) ; assuming this to be so in the present instance, (III), is a β-glucopyranoside. The configuration of carbon atom 1 of the sugar molecules in (I) and (III) must be the same as they both yield (II) on oxidation ; adenosine is therefore a β-riboside and the other ribonucleosides have been shown to have the same configuration.



I II III

R = $C_5H_4N_5$

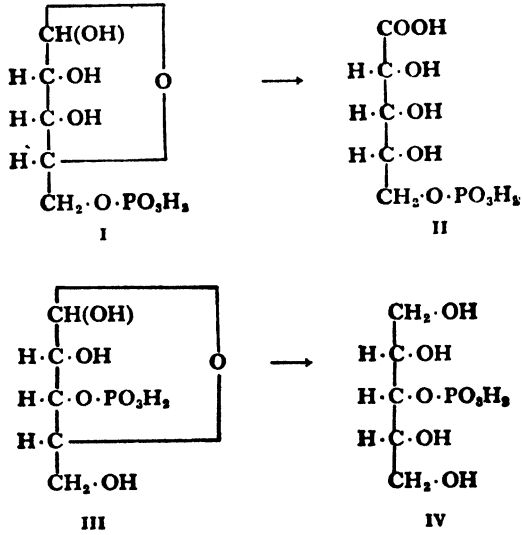
The structures of the ribonucleosides have been finally confirmed by their syntheses (Todd and co-workers, *J.* 1947-48).

Nucleotides are phosphoric esters (hydrogen phosphates) of nucleosides, and as the structures of the nucleosides are known the

only matter to settle concerning the nucleotides is the point of attachment of the phosphoric acid residue. In the case of the typical nucleotides, the adenylic acids, this has been done as follows:

The nucleotide is treated with nitrous acid and the product is carefully hydrolysed; a base and a ribose phosphate are thus obtained. The latter is then oxidised to a ribonic acid phosphate, or reduced to a ribitol (adonitol) phosphate, from the nature of which the structure, *i.e.* the position of the phosphate residue, may be determined. Thus the *d*-ribose phosphate, (I), of the nucleotide, adenylic acid obtained from muscle, gives a *d*-ribonic acid phosphate, (II), on oxidation and *d*-ribitol phosphate on reduction, so that the phosphate residue must be at 5: had it been at 2 or 3, *d*-ribotrihydroxyglutaric acid phosphate would have been formed.

On the other hand, the *d*-ribose phosphate, (III), obtained from the adenylic acid of yeast, gives on reduction an (inactive) *meso*-ribitol phosphate, (IV), in which the phosphate group must be at 3, the only position which could give a *meso*-compound.



The position of the phosphate groups is also shown by the action of sodium periodate on the nucleotides. A glycoside derived from ribose 5-phosphate, (I), has free hydroxyl groups

at 2 and 3, whereas one derived from the 3-phosphate, (III), has no —CH(OH)·CH(OH)— group; only the former, therefore, should be attacked by periodate, and experiments show that this is so. The final proof of the structures of the adenylic acids is furnished by their synthesis (Todd and co-workers, *J.* 1947, 648: 1949, 2746).

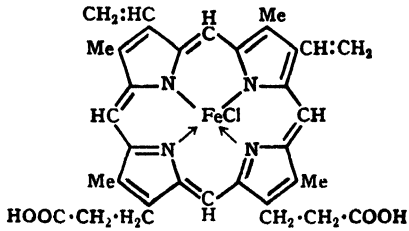
In other nucleotides the phosphate group is also either at 5 or 3.

Nucleic acids (polynucleotides) are hydrolysed by enzymes or very gentle treatment with acids or alkalis, giving equimolecular quantities of four different nucleotides, each of which may then undergo further hydrolysis as already described: yeast ribonucleic acid, for example, gives finally approximately equimolecular proportions of guanine, adenine, cytosine and uracil, together with *d*-ribose. The molecular weights of nucleic acids have been determined by many methods, such as viscosity, X-rays, etc., and minimum values corresponding with at least 30 nucleotide residues have been obtained, but it is not yet known how such residues are united in the nucleic acids.

Haemin and Chlorophyll

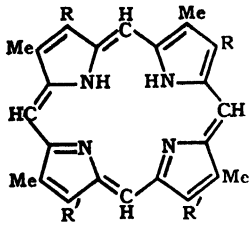
The structures of haemin and of the closely related chlorophylls have been established mainly by the work of Hans Fischer, Küster, Neucki, Piloty and Willstätter, which extended over nearly forty years; the following very brief summary of this work may give some idea of the immense difficulties which were overcome and the epoch-making results which were achieved.

Perhaps the best thing to do in order to understand these results is to start with a study of haemin, (I), and some of its degradation products, (II), referred to later; it will then be seen that after the elimination of the FeCl group, while the framework of the haemin molecule remains intact (in II), the groups R and R′ undergo various simple changes which result in the formation of the different porphyrins.



Haemin, I

II

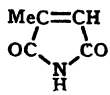


Protoporphyrin
(R = —CH:CH$_2$; R′ = —CH$_2$·CH$_2$ COOH)
Haematoporphyrin
(R = —CH(OH)·CH$_3$; R′ = —CH$_2$·CH$_2$ COOH)
Mesoporphyrin
(R = —CH$_2$ CH$_3$; R′ = —CH$_2$·CH$_2$·COOH)
Aetioporphyrin
(R = R′ = —CH$_2$ CH$_3$)
Porphin
(R = R′ = H ; Me = H)
Deuteroporphyrin
(R = H ; R′ = —CH$_2$ CH$_2$ COOH)

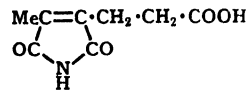
When haemin (p. 647) is treated with dilute acids the iron is eliminated and protoporphyrin is produced ; with concentrated hydrobromic and acetic acids, the two vinyl groups are converted into —CH(OH)·CH$_3$ groups and haematoporphyrin is formed, whereas with hydriodic acid they are both reduced to —CH$_2$·CH$_3$, giving mesoporphyrin. The last-named compound can also be produced from protoporphyrin by direct reduction ; when it is decarboxylated it gives aetioporphyrin. These compounds are all derivatives of the parent structure porphin shown on p. 1084.

The presence of two carboxyl groups in haemin and (some of) the above-mentioned porphyrins is shown by the formation in each case of a dimethyl ester (the melting-point of which serves for its identification), and the presence of two olefinic groups in haemin is shown by its absorption of four atoms of hydrogen on its reduction with palladium and hydrogen.

Under the prolonged action of bacteria in alkaline solution, the vinyl groups of haemin are displaced by hydrogen (and the FeCl group eliminated) with the formation of deuteroporphyrin, which can be oxidised to a mixture of two molecules of citraconimide (III, methyl maleimide) and two molecules of haematic acid, (IV),

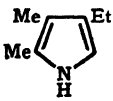


III

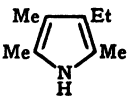


IV

When haemin is reduced vigorously with hydriodic acid it gives a mixture of four pyrroles,



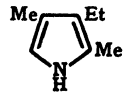
Haemopyrrole



Phyllopyrrole



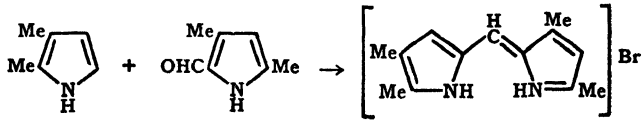
Opsopyrrole



Cryptopyrrole

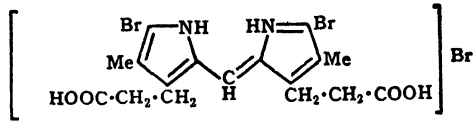
and the four corresponding carboxylic acids (—$CH_2 \cdot CH_2 \cdot COOH$ instead of —$CH_2 \cdot CH_3$ in the above formulae). During this reaction the vinyl are reduced to ethyl groups and the —CH= uniting the pyrrole nuclei remain attached to one or other of those nuclei and are at the same time reduced to —CH_3.

From these and many other facts the structure of haemin, (I, p. 1080), was deduced and then fully established by the following synthesis (H. Fischer and collaborators): (*a*) 2:3-Dimethylpyrrole is condensed with 2:4-dimethylpyrrole-5-aldehyde in the presence of alcoholic hydrobromic acid to give 4:5:3′:5′-tetramethylpyrro-2:2′-methene hydrobromide, (V),



V

(*b*) 2:4-Dimethylpyrrole-β-propionic acid (cryptopyrrolecarboxylic acid) treated with bromine gives 5:5′-dibromo-3:3′-di-β-carboxy-ethyl-4:4′-dimethylpyrro-2:2′-methene hydrobromide, (VI), with the loss of one carbon atom,



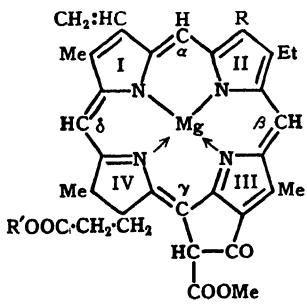
VI

The compounds (V) and (VI) heated together with succinic acid at 180–190° give a mixture from which deuteroporphyrin (p. 1081) is isolated; in this reaction (V) forms the top and (VI) the bottom of the structure (as printed) and the two methyl groups in the α-positions in (V) supply the carbon atoms of the —CH= groups uniting the nuclei in (II, p. 1081).

Deuteroporphyrin, treated in acetic acid solution with ferrous acetate, sodium chloride and hydrochloric acid, takes up FeCl and gives deuterohaemin (I, —$CH{:}CH_2$ = H) which, unlike deuteroporphyrin, is converted into a diacetyl derivative by acetic anhydride and stannic chloride; this compound, reduced with alcoholic potash, gives haematoporphyrin, the FeCl group being eliminated. Finally haematoporphyrin, distilled at 105° in a vacuum, loses two molecules

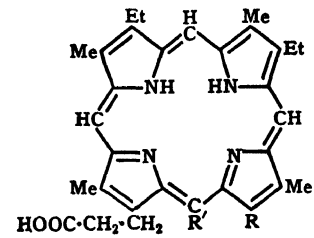
of water giving protoporphyrin, from which haemin is obtained by the reintroduction of the FeCl group.

Chlorophyll *a*, $C_{55}H_{72}O_5N_4Mg$, is hydrolysed by alkali, giving a green magnesium compound, *chlorophyllin a*, together with equimolecular proportions of methyl alcohol and phytol; it is therefore an ester of a dibasic acid. With acids chlorophyll *a* loses magnesium affording *phaeophytin a* from which chlorophyll *a* can be regenerated with methoxy magnesium bromide (from methyl alcohol and methyl magnesium bromide). When hydrolysed with acids and then heated strongly with alkalis phaeophytin *a* gives three porphyrins, closely related to those obtained from haemin under various conditions, namely rhodoporphyrin, phylloporphyrin and pyrroporphyrin.



VII

(R' = $-C_{20}H_{39}$)
Chlorophyll *a* (R = —Me)
Chlorophyll *b* (R = —CHO)



VIII

R' [illegible] (R = —COOH; R' = —H)
[illegible] (R = —H; R' = —Me)
Pyrroporphyrin (R = —H; R' = —H)

Rhodoporphyrin gives pyrroporphyrin when it is heated with alkali and on being heated with soda-lime both pyrroporphyrin and phylloporphyrin lose the carboxyl group of the propionic acid residue to give pyrroaetioporphyrin and phylloaetioporphyrin respectively.

By the following series of reactions:

$$R\cdot H \xrightarrow[SnCl_4]{MeO\cdot CH_2\cdot Cl} R\cdot CH_2\cdot OMe \xrightarrow{HBr} R\cdot CH_2Br \xrightarrow{KCH(COOEt)_2} R\cdot CH_2\cdot CH(COOEt)_2 \longrightarrow R\cdot CH_2\cdot CH_2\cdot COOH$$

a second propionic acid residue can be introduced into pyrroporphyrin (in place of R, VIII) giving mesoporphyrin, thus supplying a link with the haemin series.

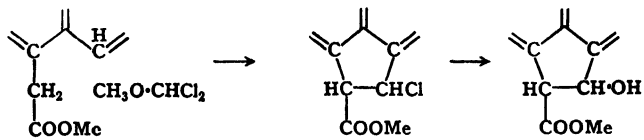
Pyrroporphyrin, obtained from rhodoporphyrin by decarboxylation, has been synthesised by a method similar to that for deutero-

porphyrin (p. 1082): its structure is thus proved and therefore also that of rhodoporphyrin ; phylloporphyrin has also been synthesised.

From the above and much other evidence the structure, (VII), has been assigned to chlorophyll *a* (R = Me) and a similar structure (R = CHO) to chlorophyll *b*. The chief differences between these structures and that of haemin are the presence of an extra carbon ring containing a carbonyl group and the partial reduction of the pyrrole ring IV.

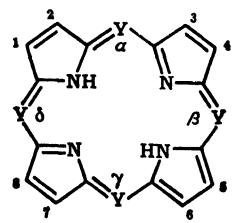
The presence of the extra carbon ring is proved by the following : (*a*) By careful hydrolysis it is possible to remove the phytyl group and the magnesium atom from chlorophyll *a* giving phaeophorbide *a* ; this last compound with hydrogen iodide yields an isomeric compound phaeoporphyrin a_5,[1] the two hydrogen atoms in ring IV being lost and the vinyl group reduced.

(*b*) Phaeoporphyrin a_5 is obtained from phylloporphyrin methyl ester, already synthesised (above), by oxidising the latter with iodine and sodium acetate, thus converting the methyl group at γ (VIII, R′) into —CHO ; the —CHO was then converted through the cyanohydrin, etc., to —CH_2·COOMe, which condensed with dichlorodimethyl ether in the presence of ferric chloride,



oxidation finally gives phaeoporphyrin a_5 dimethyl ester.

It will be seen that the structures given to haemin, the porphyrins, the chlorophylls and the phthalocyanines (p. 683) may all



IX

[1] The numeral used in this and similar cases signifies the number of oxygen atoms in the compound in question.

be regarded as being derived from the fundamental structure, (IX). In the case of the porphyrins and allied compounds, Y is CH throughout and various substituents are attached at the numbered positions. The parent compound of this group is porphin (IX, Y = CH). In the phthalocyanines the group Y is N in all cases and benzene nuclei are fused to the pyrrole rings in the 1,2 ; 3,4 ; 5,6 ; and 7,8 positions. Other compounds are known, as, for example, phthalocyanine without the benzene rings and substances in which some of the Y groups are CH and some are N.

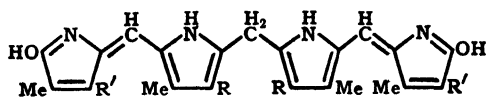
Now the degradation results and the various syntheses do not completely prove the structures of the naturally occurring derivatives of type (IX) : many of the syntheses, for example, are carried out at a high temperature at which isomeric changes, etc. might occur. Direct evidence for the given structures of the phthalocyanines has however been furnished by X-ray examinations and molecular weight determinations, and it has been shown that the compounds consist of flat molecules with the four pyrrole residues and the four Y groups all in one plane and arranged as shown in (IX). It will be seen that such molecules contain an inner heterocyclic ring of sixteen atoms, similar to those suggested by Drew for the higher cycloparaffins (p. 796), and a system of completely conjugated double and single bonds of the same type as that in aromatic hydrocarbons, etc. ; thus although the double bonds are of necessity shown in a particular position in (IX), others are equally possible and the conditions necessary for resonance are satisfied. The actual state therefore may be that of a mesomeric form, which may account for the strong colours exhibited by all such substances and also for their great stability, ease of formation, and chemical behaviour in general : the porphyrins, for example, like aromatic compounds, can be halogenated, nitrated and sulphonated and show none of the instability of the pyrroles. The indicated positions of the hydrogen atoms on the nitrogen atoms are also arbitrary, as it may be assumed that each hydrogen atom is held also by a hydrogen bond to another nitrogen atom : no porphyrin has been found to exist in the two forms which would be possible if the hydrogen atoms were attached to opposite nitrogen atoms in one form (as in IX) and to adjacent nitrogen atoms in the other (as in II, p. 1081, and VIII, p. 1083). In the case of the metallic derivatives, haemin, the chlorophylls and the metallic phthalocyanines also, different modes of union of the nitrogen atoms to the metal are apparently possible, but do not in fact exist

as each bivalent metal is shared equally by all four nitrogen atoms; when the metal or metallic radical takes the place of the two hydrogen atoms of the NH groups it does so without changing the shape or size of the structure as a whole.

Many porphyrins occur naturally in, for example, yeast, pearl-oysters, mussels, feathers, etc., and even in minerals: many of these compounds were synthesised during the investigation of haemin.

Treibs has shown that certain porphyrins occur in various petroleums, shales and coals: a bituminous marl from Switzerland, for example, contained 0·4% of total porphyrins, which contain vanadium (as >VO) as the central atom. It appears very probable that these porphyrins have originated from chlorophyll or haemin, and Treibs concludes that plants were the main source of petroleum as the quantity of chlorophyll- is greater than that of haemin-derivatives; since mesoporphyrin, which is found in such substances, is decarboxylated slowly at about 200° he infers that this is the maximum temperature to which the oil has been subjected.

As might be expected various degradation products of haemoglobin and of chlorophyll have been found to occur *in vivo*, the latter particularly in various parts of the body, and especially in the faeces of ruminants and herbivora such as cattle, elephants, sheep and silk-worms. An interesting example of a degradation product of haemoglobin is *bilirubin*, $C_{33}H_{36}O_6N_4$, which is best obtained from ox gall-stones. It has a very different absorption spectrum from that of haemin and hence does not contain the porphyrin ring system; its structure has not yet been completely determined, but is probably as shown:



R = $-CH_2 \cdot CH_2 \cdot COOH$ R′ = $-CH{:}CH_2$

CHAPTER 64

STEROIDS

THE sterols are alcohols derived from a complex hydrocarbon, cyclo*pentanoperhydrophenanthrene*. They occur in nature in association with fats, carbohydrates and proteins, partly in the free state, and partly as esters of the higher fatty acids ; about 20 such compounds are known, and like so many products of living organisms they are optically active.

They may be divided into three classes :

Zoosterols, which occur in animals ; cholesterol in bile, gall-stones, etc.

Phytosterols, which occur in plants ; stigmasterol in calabar bean, soya bean, etc.

Mycosterols, which occur in fungi ; ergosterol in ergot, yeast, etc.

As, however, some are found in both animals and plants, this classification cannot be rigidly applied.

Closely related to the sterols, and doubtless formed from them in the animal organism, are the important bile acids, some of which have long been known and which are now classed with the sterols, as *steroids*, because they are derived from the same hydrocarbon framework as the former.

The group of steroids also includes the sex hormones, comparatively recently discovered compounds of very great interest and physiological importance ; other naturally occurring substances such as the adrenal hormones, saponins and cardiac poisons of the same fundamental structure are also included in the steroid group.

Sterols

Cholesterol, $C_{27}H_{45}\cdot OH$ (Gr. *cholē*, fat ; *stereos*, solid), occurs in bile, in the brain, and in considerable proportions (up to 98%) in certain gall-stones and cancerous and tubercular deposits ; it is also found in the yolk of egg and in some vegetable oils. The fat (lanoline) obtained from wool is a mixture of cholesteryl palmitate, stearate, and oleate.

Cholesterol is very easily prepared by extracting common gall-

stones with alcohol, boiling the extract with a little potassium hydroxide, and precipitating the product from the concentrated solution with water; it is washed with water and crystallised from a mixture of ether and alcohol.

It separates from ether in plates, melts at 148°, and distils at about 360° without appreciable decomposition; it is laevorotatory and insoluble in water. In the lower intestine it is reduced to *coprostanol*, $C_{27}H_{47}\cdot OH$.

A cold saturated solution of cholesterol in acetic anhydride, to which is added concentrated sulphuric acid, turns red and then blue and finally green. Concentrated sulphuric acid, containing a little iodine, colours cholesterol violet, then blue, then green, and lastly red. Warmed with dilute (20%) sulphuric acid, cholesterol crystals are coloured red at the edges.

Stigmasterol, $C_{29}H_{47}\cdot OH$, m.p. 170°, occurs in the soya and calabar bean; it is laevorotatory.

Ergosterol, $C_{28}H_{43}\cdot OH$, is probably widely diffused in animals and plants and occurs particularly in ergot and yeast, from the latter of which it is usually extracted; it melts at 154° and is laevorotatory.

On exposure to ultra-violet light, it is partly converted into a resinous or waxy product, which is a mixture of various isomerides of the sterol (produced successively) and from which *calciferol* was isolated in 1931.

Coprostanol (*coprosterol*), $C_{27}H_{47}\cdot OH$, occurs in faeces; it melts at 102° and is dextrorotatory.

The investigation of cholesterol and the bile acids was a task of exceptional difficulty, not only because of the great complexity of the compounds but for many other reasons. Although the sterols crystallise readily, traces of impurities may prevent them from doing so and different sterols often form mixed crystals or molecular compounds, so that their isolation was particularly troublesome.[1] They also proved to be compounds of an entirely novel type and new processes had to be devised for their degradation to substances of known structure. Thus although cholesterol was first analysed by Chevreul as long ago as 1823, it was only in 1859 that it was proved to be a monohydric alcohol, and a secondary alcohol in 1903.

[1] It is interesting to note that Pregl developed his method of micro-analysis to deal with a bile acid product which was only available in minute quantities.

During the years immediately following, mainly as the result of the work of Wieland and Windaus, many new facts concerning the structures of the steroids were established, but the data were disconnected and progress was still comparatively slow ; it was not until about 1932 that notable advances were made. In that year, after it had been shown by Diels that cholesterol could be partly converted into chrysene (p. 1022) and Diels' hydrocarbon (p. 1090), and Bernal's X-ray measurements of ergosterol had been published, it was suggested by Rosenheim and King, and also by Wieland and Dane, that cholesterol and other sterols were derivatives of a cyclo*pentanoperhydrophenanthrene*. This view, fully confirmed by further evidence, threw a flood of light on the chemistry of these and other natural products and rendered possible the striking advances which immediately ensued.

The following is a brief account of the methods and reactions by which the structures of the sterols and more particularly that of cholesterol were determined, and the synthesis of many important steroids, including that of the fundamental framework, was accomplished.

Structures of the Sterols

The catalytic reduction of the olefinic binding of cholesterol yields *cholestanol*, $C_{27}H_{47}\cdot OH$; this alcohol cannot be reduced further by ordinary direct methods, but when it is *oxidised* to the corresponding ketone, the latter can be reduced to a saturated hydrocarbon, *cholestane*, $C_{27}H_{48}$, by Clemmensen's method; cholesterol, therefore, is tetracyclic, for, had it been an open chain compound, it would have given a hydrocarbon, $C_{27}H_{56}$.

The procedure just given, by means of which a secondary alcohol group, $>CH\cdot OH$, is converted into $>CH_2$ by oxidation, followed by reduction, is of great importance in the investigation of the steroids.

The *size of the rings* in the cholesterol molecule was decided in early investigations mainly by the Blanc rule (cf. p. 779), according to which 1:4- and 1:5-dicarboxylic acids, when heated with acetic anhydride and then distilled, yield anhydrides, whereas 1:6- (and 1:7-) acids give cyclic ketones. *Cyclo*hexanone, for example, on oxidation yields adipic acid (1:6), which gives *cyclo*pentanone, whereas the latter gives glutaric acid (1:5), which yields its anhydride

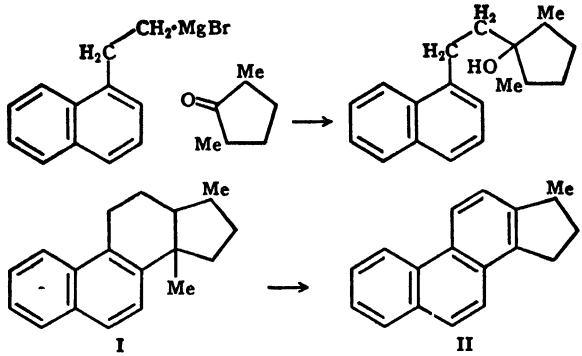
and not *cyclo*butanone. It is therefore possible to distinguish a six- from a five-membered ring, provided that the ring contains a —CH_2·CO— or —CH_2·CH(OH)— group and can therefore be oxidised to the desired dicarboxylic acid. Fortunately various compounds (the bile acids), derived from cholesterol and containing hydroxyl groups in different rings, are known, so that this procedure is of fairly general application. Blanc's method, however, is unreliable when the carboxyl groups of the acid are attached to different rings, as they would be, for example, in the acid obtained by the oxidation of ring C of cholesterol at 11 or 12;[1] in such cases a 1:6-acid may give an anhydride instead of a ketone.

The structural *framework* of cholesterol was finally decided by the results of oxidation experiments on the sterol and on the bile acids, but more particularly by the study of the *Diels' hydrocarbon.*

This most important compound, $C_{18}H_{16}$, was obtained by the dehydrogenation of cholesterol with selenium (p. 944) at 320°, a very complex reaction during which chrysene and picene (p. 1023) are also formed. In such dehydrogenations a methyl group attached to a carbon atom common to two rings (*angular* methyl group) must of necessity be eliminated (as selenide) when the *cyclo*paraffin or *cyclo*-olefine rings become aromatic (except in certain cases where ring enlargement can occur or where the methyl group migrates to a new position, cf. p. 1104). The production of chrysene here does not prove, as might have been expected, the existence of four six-membered closed chains in cholesterol; only three are originally present as the fourth is formed from the *cyclo*pentane ring and the angular methyl group at 13.

The results of oxidation experiments, X-ray crystal analysis, etc., showed that Diels' hydrocarbon was probably *methyl*cyclo*penteno-phenanthrene*, (II), and it was then synthesised by Harper, Kon, and Ruzicka: β-[α-Naphthyl]ethyl magnesium bromide was treated with 2:5-dimethyl*cyclo*pentanone and the hydrolysed product was distilled with phosphorus pentoxide under reduced pressure; ring closure occurred, giving (I), which was then dehydrogenated to the Diels' hydrocarbon, (II), with selenium:

[1] The numerals used in this chapter to show the positions of substituents and the capital letters by which the rings are distinguished refer throughout to those in the formula on p. 1095.



I II

The **di**-methyl derivative of *cyclo*pentanone is used here to ensure the presence of a methyl group in the position shown in the final product; the other methyl group being in an angular position is eliminated when the group $>$CMe— is converted into $>$C=.

The X-ray examination of the Diels' hydrocarbon and the synthetic compound proved their identity;[1] the two preparations also gave the same nitroso- and tribromo-derivatives. When the Diels' hydrocarbon is formed from cholesterol it seems likely that the methyl group at 13 passes to 17 and the long side chain is eliminated.

The structure of the long *side chain* in the molecule of cholesterol (at position 17) is proved by the production of methyl*iso*hexyl ketone, $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CHMe_2$, from cholesteryl acetate or cholesterol on oxidation; the formation of this compound also shows that the side chain is saturated and that it is united to the *cyclo*pentane ring by that carbon atom which forms the carbonyl group in the oxidation product.

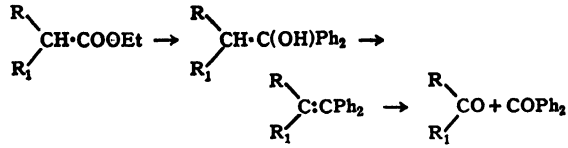
The structure of the side chain of cholesterol and of many other compounds has also been determined by an important method due to Wieland (cf. p. 975): when an ester is treated with an excess of phenyl magnesium bromide it gives a tertiary alcohol, which can be dehydrated in one way only,

$$R \cdot CH_2 \cdot COOEt \longrightarrow R \cdot CH_2 \cdot C(OH)Ph_2 \longrightarrow R \cdot CH{:}CPh_2 \longrightarrow R \cdot COOH + COPh_2$$

The oxidation of the resulting olefine then yields, as shown, benzophenone and an acid containing one carbon atom less than that of

[1] The mixed melting-point method is useless, because here, as in many other cases, related substances do not depress each other's melting-point.

the original ester. If, however, there is a branch in the chain in the α-position of the acid, the oxidation products of the olefine obtained from the tertiary alcohol will be benzophenone and another ketone instead of an acid :



The branching of the side chain having thus been established, the new ketone can then be oxidised further and the process of degradation continued.

When cholestane (p. 1089) is oxidised with chromic acid the $-CHMe_2$ group is attacked, acetone and *allo*cholanic acid [1] being produced. The latter can be degraded by Wieland's method and then gives successively, *norallo*cholanic acid, bis*norallo*cholanic acid, and finally aetio*allo*cholylmethyl ketone. This ketone is oxidised with the loss of one carbon atom to aetio*allo*cholanic acid :

>—$CHMe \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CHMe_2$	Cholestane
>—$CHMe \cdot CH_2 \cdot CH_2 \cdot COOH$	*Allo*cholanic acid
>—$CHMe \cdot CH_2 \cdot COOH$	*Norallo*cholanic acid
>—$CHMe \cdot COOH$	Bis*norallo*cholanic acid
>—$CO \cdot Me$	Aetio*allo*cholylmethyl ketone
>—$COOH$	Aetio*allo*cholanic acid

These results show that the side chain in cholestane and, therefore, that in cholesterol has the given constitution.

Aetio*allo*cholanic acid, further degraded by Wieland's method, gives a cyclic ketone which on oxidation affords a dibasic acid ; as this product gives an anhydride with acetic anhydride, the ring to which the side chain is attached is probably five-membered (p. 1089),

[1] The prefix *allo* denotes the stereochemical nature of the compound only (p. 1097).

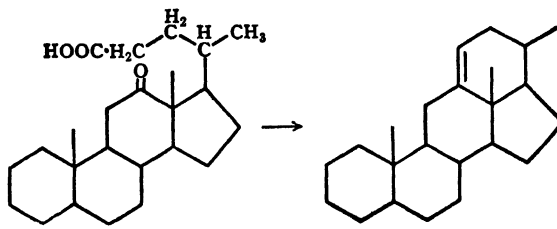
an inference which is established by the synthesis of the Diels' hydrocarbon already described.

The *position* of the side chain in the five-membered ring, first suggested by X-ray and surface film measurements, has been determined in the following manner: Cholesterol is oxidised by copper oxide to a ketone, *cholestenone*,[1] $C_{27}H_{44}O$ (I, p. 1094), which is then converted into *coprostanol*, $C_{27}H_{47}\cdot OH$ (a stereoisomeride of cholestanol, p. 1097), by the reduction of the carbonyl group (to $>CH\cdot OH$) and the ethylenic binding. The oxidation of coprostanol to the ketone, followed by a Clemmensen reduction of the latter, gives *coprostane*, $C_{27}H_{48}$, a stereoisomeride of cholestane, which yields cholanic acid on oxidation.

Now deoxycholic acid, a bile dihydroxy-acid (p. 1098), also affords cholanic acid when its two $>CH(OH)$ groups are both converted into $>CH_2$ in the usual way; the side chains of deoxycholic acid and cholesterol are therefore in the same position.

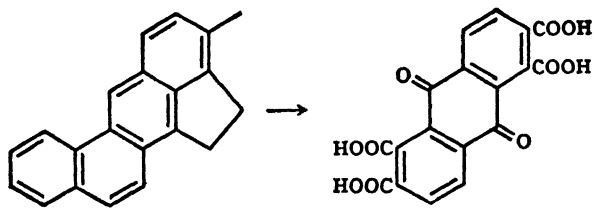
Cholesterol ⟶ Coprostanol ⟶ Coprostane ⟶ Cholanic acid.
Deoxycholic acid ⟶

When the two $>CH\cdot OH$ groups of deoxycholic acid are both oxidised to $>CO$, and only the carbonyl radical at 3 is reduced by the Clemmensen method, the product is 12-*ketocholanic acid* (below); this compound undergoes internal condensation at 330° with the loss of carbon dioxide, giving *dehydronorcholene*, which on dehydrogenation with selenium loses two angular groups and yields *methylcholanthrene*. The structure of this hydrocarbon was proved by its oxidation to anthraquinone-1:2:5:6-tetracarboxylic acid, and subsequently by its synthesis.



Ketocholanic acid Dehydro*nor*cholene

[1] It will be seen that the 5:6-olefinic binding of cholesterol takes up a different position in cholestenone: such changes are common in compounds of this type, but as the double bond is finally reduced, its position is immaterial in the present instance.

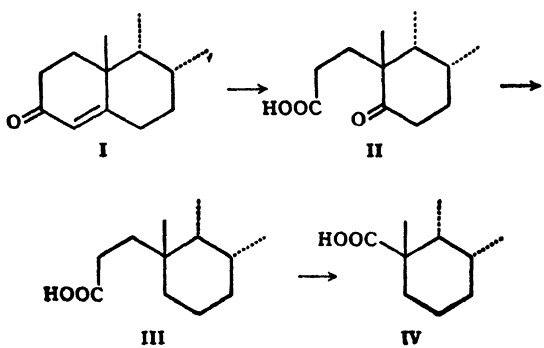


Methylcholanthrene — Anthraquinone-tetracarboxylic acid

These results can be explained only if the position of the side chain in ketocholanic acid, and therefore in cholesterol, is, as shown, at 17 (p. 1095).

The synthesis of methylcholanthrene also confirms the presence of the *cyclo*pentanophenanthrene skeleton in cholesterol, a fact of great importance in view of the very poor yield of the Diels' hydrocarbon when the sterol is dehydrogenated.

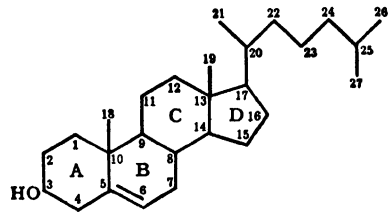
The position of the *hydroxyl* group in cholesterol is fixed in the following manner: *Cholestenone*, (I), formed by the oxidation of cholesterol, can be proved to be an $\alpha\beta$-unsaturated ketone; further oxidation yields a ketonic acid, (II), which can be reduced to a saturated acid, (III). The degradation of the latter by the Wieland method to give (IV) shows that the newly formed side chain has the constitution $-CH_2 \cdot CH_2 \cdot COOH$; the partial structure of cholestenone, which accounts for these results, is shown below, and the fact that the final acidic product is esterified only with difficulty (steric hindrance) confirms the presence of the methyl group in the α-position.



I II III IV

Kon has proved the position of the hydroxyl group in a very simple way: cholestanol (below) is oxidised to cholestanone which is treated with methyl magnesium iodide. When the resulting tertiary alcohol is heated with selenium at 350°, 7-methyl-1:2-*cyclo*pentenophenanthrene, which has been synthesised, is one of the products: the methyl group in this phenanthrene derivative obviously occupies the same position as the hydroxyl group of cholestanol.

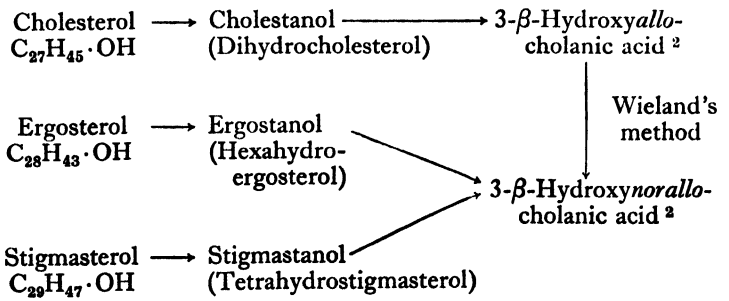
The above is an outline of the way in which the main features of the structure of cholesterol have been decided; the position of the double bond and those of the methyl groups at 10 and 13 can only be proved by very difficult methods which illustrate no new important principles.



Cholesterol [1]

It may be noted in conclusion that the structural formula of cholesterol is based, not only on the results of experiments with the sterol itself, but also, of course, as usual, on a consideration of all relevant evidence obtained in the study of allied compounds.

The relationship of cholesterol, ergosterol, and stigmasterol is shown below:

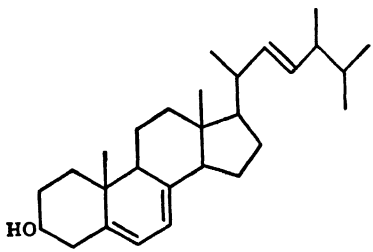


[1] Sometimes the numbering of positions 18 and 19 is reversed.
[2] The letter β refers to the configuration of the acid (p. 1097).

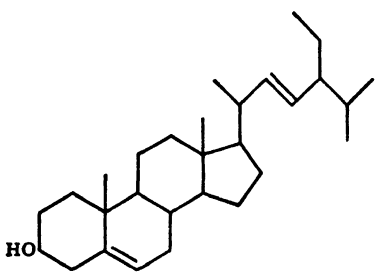
Each sterol can be reduced catalytically to the corresponding saturated alcohol, which is acetylated ; the acetyl derivative is then oxidised and the acetyl group displaced by hydrolysis. The product is a hydroxy-acid : when that from cholesterol is degraded one stage by Wieland's method, the same compound as that obtained directly from the other two sterols is produced.

All three sterols, therefore, have the hydroxyl group in the same position and the same configurations about atoms 3, 9, 10, 13, 14, 17 and 20 ; their catalytic reduction products differ solely as regards the structure of the side chain.

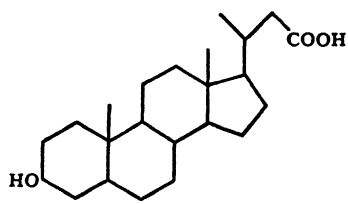
On ozonolysis ergosterol yields $\alpha\beta$-dimethylbutyraldehyde, whilst stigmasterol gives α-ethyl-β-methylbutyraldehyde ; the nature of the side chains and the position of the double bonds in these sterols are therefore as shown. Ergosterol combines with maleic anhydride and on oxidation yields a benzene derivative : these facts show that there are conjugated double bonds in one ring of the sterol molecule. From all the evidence the following structures are assigned to the two sterols and the related hydroxy*norallo*cholanic acid respectively.



Ergosterol



Stigmasterol

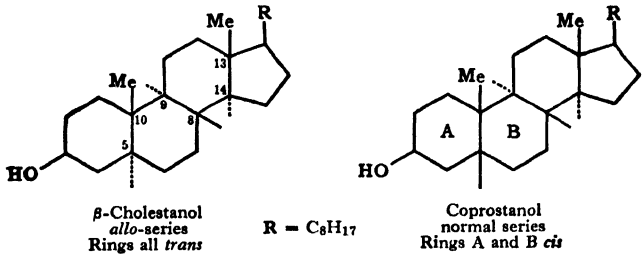


3-Hydroxy*norallo*cholanic acid

An examination of the formula of cholesterol (p. 1095) reveals the presence of eight asymmetric groups in the molecule, namely those at 3, 8, 9, 10, 13, 14, 17, 20 ; there are, therefore, 256 possible stereoisomerides. The chief point to decide, however, is the *cis*- or *trans*-relationship of the four rings. Now sterols can be degraded in a suitable manner to a *trans*-acid, derived from *cyclo*pentane ; the rings C and D are therefore *trans*- to one another. X-ray measurements reveal a flat molecule, which is only possible if the rings B and C are *trans*-. A comparison of the physical properties of cholestane and coprostane with those of *cis*- and *trans*-decalane shows that rings A and B are *trans*- in cholestane (the *allo*-series) and *cis*- in coprostane. Thus cholestane is *trans-trans-trans*- and coprostane is *cis-trans-trans*-.

It has also been shown that the hydroxyl group of cholesterol (at position 3) is in the *cis*-position relatively to the methyl radical at 10. A similar stereochemical arrangement is found in all the naturally occurring sterols, and this configuration is denoted when necessary by the prefix β, the *trans*-form by α or *epi*.

The stereochemical relationships of the steroids are usually indicated in formulae by showing atoms or groups projecting in one direction from the rings by continuous, and in the other by dotted, lines ; two groups *cis* to one another will therefore *both* be shown *either* by continuous *or* by dotted lines.



β-Cholestanol
allo-series
Rings all *trans*

R = C_8H_{17}

Coprostanol
normal series
Rings A and B *cis*

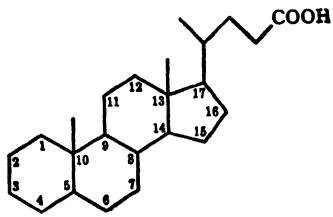
As it is necessary to consider the stereochemical arrangement at 5, 8, 9 and 14, where no substituents occur, the hydrogen symbols cannot be omitted as usual from the formula : in such cases lines or dots are therefore used to represent hydrogen atoms and methyl groups are then shown by Me. Compounds of the *epi*- or α-series, such as *epi*cholestanol, would have the hydroxyl group at 3 attached by a dotted line.

Digitonin (p. 1109) forms a very stable insoluble complex with β-steroids, a fact which is extensively employed in stereochemical studies and also for effecting the separation of stereoisomerides.

Bile Acids

A brief description of some of the compounds found in the bile, including the bile acids, has been given (p. 629). Cholic acid and all the related bile acids are hydroxy-acids and, when heated, they yield the corresponding olefinic compounds, all of which can be reduced to cholanic or *allo*cholanic acid ; they can also be converted into cholanic acid by oxidation to ketones followed by a Clemmensen reduction.

The structure of cholanic acid being known from its relationship to cholesterol, and the positions of their hydroxyl groups having been determined in much the same way as in the case of that sterol, the bile acids may now be represented :

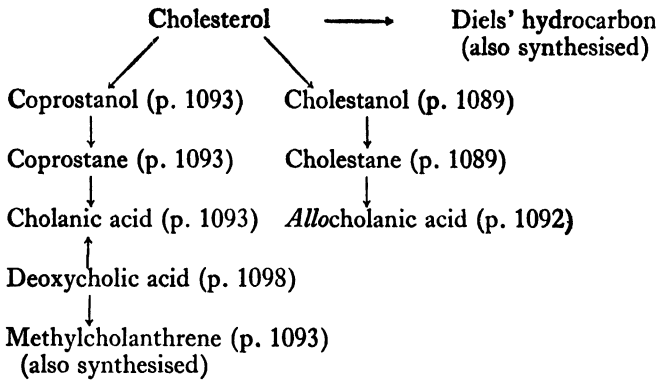


Cholanic acid or *allo*cholanic acid

Cholic acid, 3:7:12-trihydroxycholanic acid
Deoxycholic acid, 3:12-dihydroxycholanic acid
Hyodeoxycholic acid, 3:6-dihydroxycholanic acid
Chenodeoxycholic acid, 3:7-dihydroxycholanic acid
Lithocholic acid, 3-hydroxycholanic acid

The first two acids, and the last, occur notably in human bile ; hyodeoxycholic acid in that of swine ; chenodeoxycholic acid in that of geese and fowls ; lithocholic acid is also found in the bile of cattle. It is thought that all these compounds may be formed in the animal by the oxidation of cholesterol.

Some important relationships between cholesterol and its derivatives and the bile acids may be seen from the following table :



It will be observed that these interrelationships demonstrate clearly a common framework, the structure of which is proved by the syntheses indicated. Coprostane and cholestane, and also cholanic and *allo*cholanic acids, are stereoisomerides, differing only in the *cis* or *trans* arrangement of the rings A and B (p. 1097).

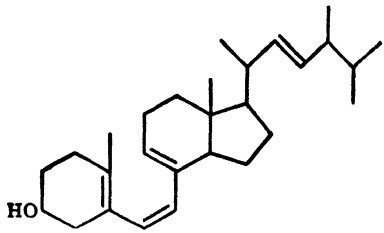
Vitamin D

A short account of this vitamin has already been given (p. 653). Crystalline vitamin D_2, now known as *calciferol*, was first isolated from irradiated ergosterol in 1931 and it is now clear that there are several compounds with vitamin D activity; a numerical suffix is therefore used to distinguish them.

When ergosterol is irradiated with ultra-violet light various isomeric compounds are successively produced, but of these only calciferol shows antirachitic activity:

Ergosterol ⟶ Lumisterol ⟶ Tachysterol ⟶ Calciferol ⟶ Suprasterols.

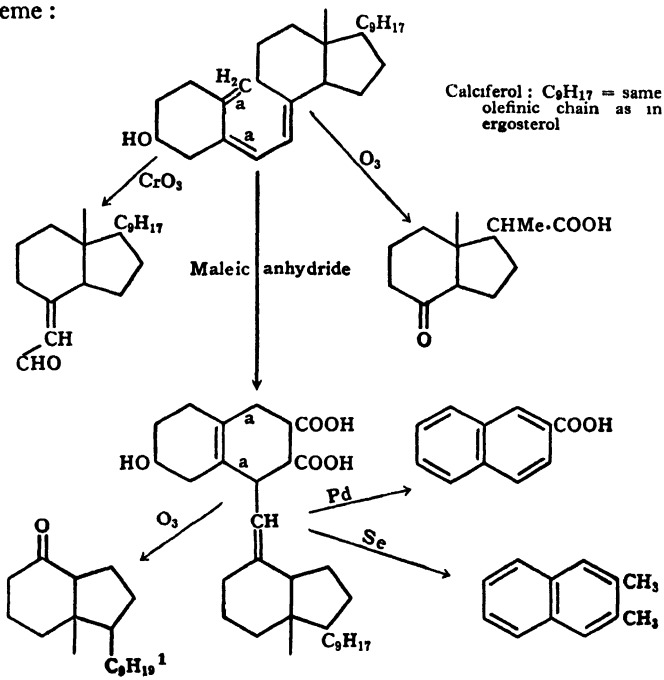
All have the same side chain, which gives $\alpha\beta$-dimethylbutyraldehyde on ozonolysis. Ergosterol and lumisterol have almost identical absorption spectra and both give the Diels' hydrocarbon on dehydrogenation; they are stereoisomeric, the configuration at C_{10} undergoing inversion during the transformation. The other isomerides have absorption spectra different from those of ergosterol and lumisterol and do not yield the Diels' hydrocarbon. During the change of lumisterol into tachysterol ring B is broken and the double bonds take up new positions in calciferol.



Tachysterol

Calciferol combines with four molecules of hydrogen in the presence of a catalyst giving a saturated compound, $C_{28}H_{51}\cdot OH$, and is therefore tricyclic; its structure is based mainly on its relationship to ergosterol. On ozonolysis it yields formaldehyde (evidence of the presence of a $=CH_2$ group in the vitamin), and the keto-acid shown below.

Other important decompositions are summarised in the following scheme :

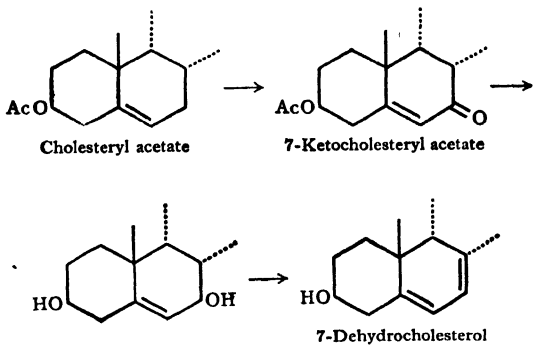


[1] The side chain is reduced before ozonolysis is carried out.

In the reaction with maleic anhydride addition occurs to the conjugated system (a, a,) with the formation of the *cyclo*hexene ring and, in the formula of the (hydrolysed) product, the —CH== group attached to this ring is shown below it for the sake of convenience. The reduction of carboxyl groups to methyl radicals, which occurs in the selenium reaction, also takes place in other compounds.

Sodium and alcohol reduce calciferol and tachysterol to the same product so that their skeletons are identical, but the positions of the double bindings in tachysterol have not been decided.

An antirachitic product distinguished as vitamin D_3 (isolated by chromatographic analysis from tunny-liver oil) has been prepared by irradiating 7-dehydrocholesterol with ultra-violet light; the last-named compound can be obtained from cholesterol as indicated below:



Cholesteryl acetate — 7-Ketocholesteryl acetate

7-Dehydrocholesterol

The oxidation of the $>CH_2$ group (7) of cholesteryl acetate to $>CO$ by chromic acid in the manner shown is a type of reaction which often occurs in the sterol series (cf. p. 809); the ketone is then reduced by aluminium *iso*propoxide, and the dibenzoate of the resulting diol is heated. 7-Dehydrocholesterol benzoate is produced (with the loss of benzoic acid) and the remaining (3) benzoyl group is displaced by hydrolysis.

Sex Hormones

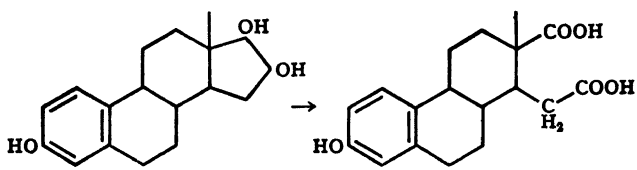
Oestrogenic (female) *hormones.* In 1929 Doisy and Butenandt, independently, prepared in the pure state from pregnancy urine a substance, *oestrone*, $C_{18}H_{22}O_2$, which has the property of producing oestrus in castrated female rodents. This discovery led to the

isolation of other sex hormones, and in the short space of ten years the structures of many of these most important and interesting compounds were determined, and pure materials became available for clinical use.

Oestriol, $C_{18}H_{24}O_3$, was isolated in 1930 (Marrian), also from the urine of pregnancy, and later *oestradiol*, *equilin*, and *equilenin* were discovered, all of which had physiological properties similar to those of oestrone.[1] As an illustration of the great difficulties involved in such work, it may be mentioned that only 25 mg. of oestradiol (p. 1103) were obtained from 4 tons of swine ovaries.

Oestriol contains in its molecule one phenolic hydroxyl radical (and therefore an aromatic nucleus) and two secondary alcohol groups; with potassium hydrogen sulphate it yields oestrone, the complex —CH(OH)·CH(OH)— becoming —CO·CH_2—, and this phenolic ketone gives chrysene on distillation with zinc-dust. From this fact, X-ray data, and other physical measurements, it was concluded that these sex hormones were structurally related to the sterols.

When oestriol is fused with potash the ring containing the alcoholic hydroxyl groups undergoes fission and oxidation, and the dibasic acid thus formed gives a dimethylhydroxyphenanthrene on dehydrogenation; in the last reaction both the carboxyl radicals are eliminated as carbon dioxide.

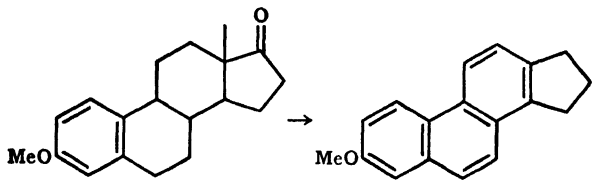


Oestriol — Marrianolic acid

Dimethylhydroxyphenanthrene

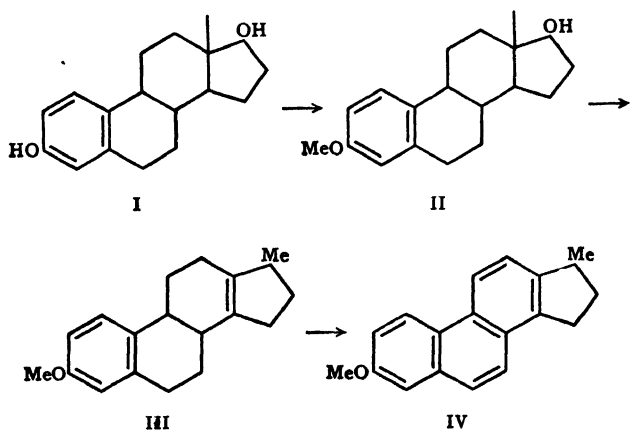
[1] It will be seen that some of these sex hormones have names which indicate the presence of carbonyl or more than one hydroxyl group in the molecule.

The methyl ether of this dimethylhydroxyphenanthrene has been synthesised by Cook, and the structure of oestriol is thus established ; further evidence, moreover, is provided by Cook's synthesis of the methoxy*cyclo*pentenophenanthrene, which is formed by the reduction and dehydrogenation of methylated oestrone.



Methyloestrone Methoxy*cyclo*pentenophenanthrene

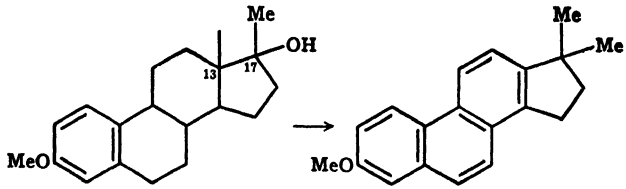
Oestradiol, (I), is formed by the reduction of oestrone, and when its phenolic monomethyl derivative, (II), is heated with zinc chloride an olefinic binding is produced, accompanied by the migration of the angular methyl group ; on dehydrogenation with selenium this *cyclo*pentene derivative, (III), yields methylmethoxy-*cyclo*pentenophenanthrene, (IV), which has been synthesised.



I II

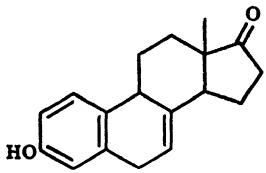
III IV

Similarly methyloestrone gives with methyl magnesium iodide a tertiary carbinol, which, heated with selenium, yields a dimethyl-methoxy*cyclo*pentenophenanthrene ; this product has also been synthesised.

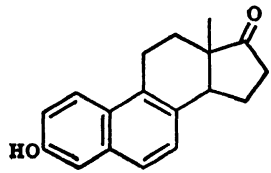


These changes can be explained only by assuming the presence at C_{13} of an angular methyl group (which migrates) and a carbonyl group at C_{17} in oestrone.

The structures of equilin and equilenin shown below have been proved by similar methods; like oestrone and its derivatives, to which they are closely related, these substances are phenols.



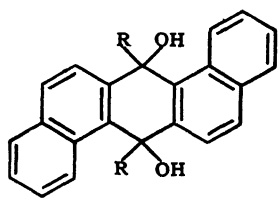
Equilin



Equilenin

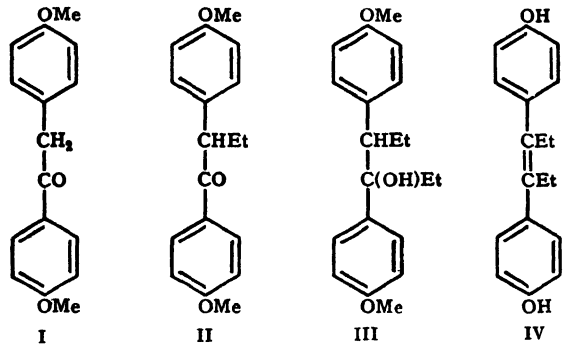
A complete synthesis of equilenin, identical in all respects with the natural product, was accomplished by Bachmann in 1940.

Many synthetic oestrogenic compounds have been prepared. The first substances of this type (Cook and Dodds) were derivatives of *ang*-dibenzanthracene, in which R = Me, Et, Pr^{α}, Pr^{β}, etc.:



The most active compound is that in which R is Pr^{α}, and this shows a biological activity nearly as great as that of oestriol, as does also (*trans*)stilboestrol (diethylstilboestrol, IV), a very important simpler compound, which is now synthesised for clinical use as follows: Anisaldehyde is converted into anisoin, which is reduced to 4-methoxyphenyl-4′-methoxybenzyl ketone, (I), and then ethylated with sodium ethoxide and ethyl iodide; the product, (II), when

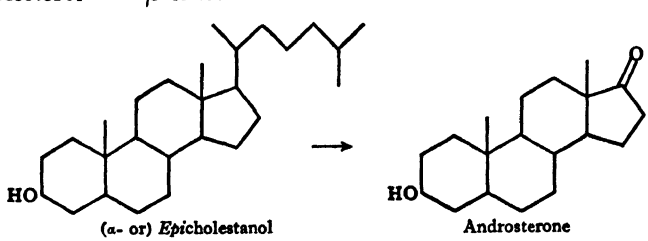
converted into the tertiary alcohol, (III), dehydrated and finally demethylated, gives stilboestrol, (IV):



Androgenic (male) *hormones.* *Androsterone*, $C_{19}H_{30}O_2$, was isolated by Butenandt in 1931, from male urine of which 100,000 litres were required; it is a male hormone and it can be detected and estimated by the increase in the area of the combs of capons which is brought about by its administration. Later, *dehydroiso-androsterone*[1] and *androstenedione* were discovered, and in 1935 Lacqueur isolated *testosterone* (10 mg. from 100 kilos of testes). These substances have important effects on certain male characterstics, such as the pitch of the voice, hair on the body, and the sex glands.

The structures of the androgenic hormones have been determined mainly by the preparation of the compounds from known sterols; androsterone, for example, can be obtained from cholesterol (overall yield up to 0·2 per cent.) by converting it into *epi*cholestanol and oxidising (the acetate of) this alcohol with chromic acid (Ruzicka):

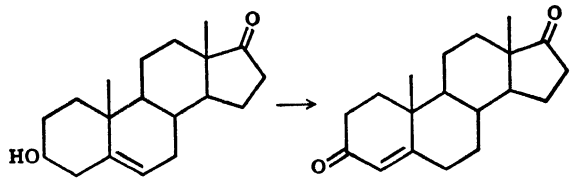
Cholesterol ⟶ β-cholestanol ⟶ cholestanone ⟶ α-cholestanol



[1] Whereas androsterone belongs to the α- or *epi*-series, dehydro*iso*-androsterone has the β-configuration at position 3.

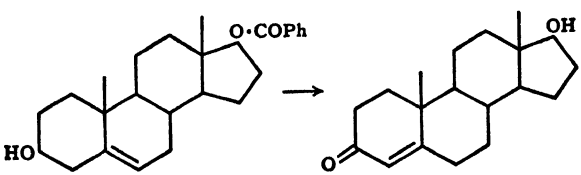
*Dehydroiso**androsterone*** is obtained by the oxidation of the acetyl derivative of cholesterol dibromide followed by debromination and hydrolysis; the overall yield is about 2·8%. The dibromide is used to prevent the oxidation of the double bond in ring B and the group $>CBr \cdot CHBr-$ is subsequently reconverted into $>C{=}CH-$ with the aid of zinc.

The oxidation of dehydro*iso*androsterone then yields androstenedione, the double bond changing its position, as in other cases (footnote, p. 1093, and p. 1094):



Dehydro*iso*androsterone Androstenedione

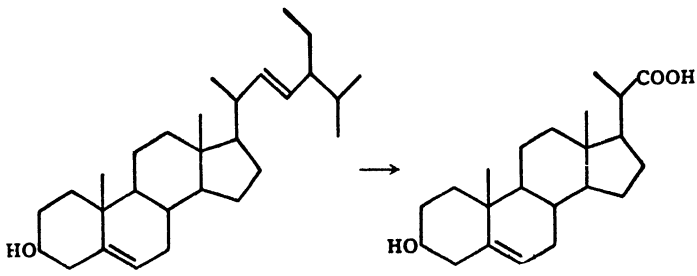
Testosterone can be obtained from the acetate of dehydro*iso*androsterone, which is reduced to an alcohol and then benzoylated; the product is partially hydrolysed to eliminate the acetyl group (giving I) and then oxidised to the benzoylated ketonic alcohol, which yields testosterone on hydrolysis:



I Testosterone

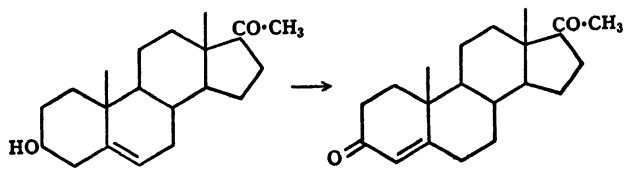
Testosterone is usually used clinically in the form of one of its esters.

Progesterone, the *corpus luteum* hormone, which prepares the uterus for the implantation of the fertilised ovum, was isolated by Butenandt in 1934; 50 mg. were obtained from 10 kilos of swine ovaries. Its structure is shown by its preparation from stigmasterol (and other compounds); the dibromo-additive product of the acetylated sterol is oxidised to an acid, which is debrominated (above) and the acetyl group is then displaced by hydrogen.



Stigmasterol II

The acid, (II), so formed is degraded by the Wieland method (after protecting the nuclear double bond by bromination), and the resulting ketonic alcohol (pregnenolone, III), in the form of its dibromide, is oxidised to a diketone, which is finally debrominated :



III Progesterone

Pregnenolone is more easily oxidised to progesterone by heating it with acetone and aluminium *iso*propoxide (Oppenauer). This is an important general method for the oxidation of alcohols and is the reverse of the Ponndorf reaction (p. 156) : it depends on the use of a large excess of acetone.

Progesterone is now manufactured by this method for clinical use.

Although the steroids so briefly described above are directly responsible for the regulation of the various sexual processes, their formation in its turn is controlled from the pituitary (brain) gland by certain other hormones, which pass in the blood to the testes and ovary and stimulate the functions of these organs. It is interesting to note that androstenediol which has high male activity is also oestrogenic ; most of these compounds, in fact, have certain bi-sexual characteristics.

Adrenal Hormones

When the adrenal glands are removed from an animal death ensues, but life may be prolonged by the administration of extracts from the cortex of the gland ; the hormone which produces this effect was originally called *cortin*, but it is now known to be a complex mixture of at least 20 steroids, only some of which are physiologically active. These active compounds, hormones of the adrenal cortex, were investigated mainly by Reichstein, Kendall and Wintersteiner and shown to be derivatives of progesterone :

Corticosterone or 11:21-dihydroxyprogesterone
Dehydrocorticosterone or 11-keto-21-hydroxyprogesterone
Deoxycorticosterone or 21-hydroxyprogesterone

In addition, a 17-hydroxy-derivative of each steroid also occurs in the gland.

The isolation of such substances from the complex natural mixture is accomplished only with very great difficulty and the so-called Girard reagents proved of great value for this purpose.

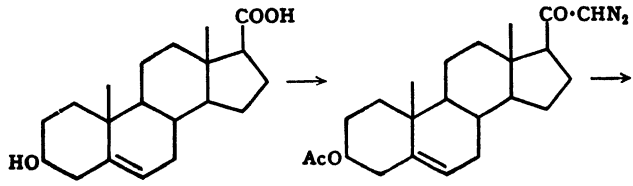
The Girard reagent-T is prepared by mixing trimethylamine and ethyl chloroacetate and then adding hydrazine,[1]

$$Me_3N + Cl\cdot CH_2\cdot COOEt + H_2N\cdot NH_2 = [Me_3N\cdot CH_2\cdot CO\cdot NH\cdot NH_2]Cl + EtOH.$$

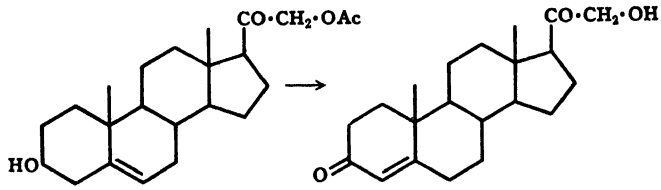
The resulting hydrazide combines readily with *ketones* giving products which are *soluble* in water ; non-ketonic compounds may then be extracted from the aqueous solution with a solvent, after which the hydrazide is hydrolysed and the required ketone extracted.

The structures of the cortical hormones have been proved by their partial synthesis from steroids of known structure. Deoxycorticosterone, for example, has been prepared as follows : The hydroxyketone (III, p. 1107), prepared from stigmasterol, is further degraded to (I) and the acid chloride of the acetyl derivative of this compound is treated with diazomethane ; the product, (II), is hydrolysed with alkali and treated with acetic acid, whereon the acetate, (III), is produced : this compound is then converted into deoxycorticosterone, (IV), by the Oppenauer oxidation (p. 1107), followed by the hydrolysis of the acetyl group :

[1] The Girard reagent-P is made with pyridine instead of trimethylamine.



I II



III IV

The synthesis of cortical hormones with a hydroxyl group at 11 proved much more difficult as the few known steroids substituted in this position are unsuitable as starting materials.

17-Hydroxydehydrocorticosterone (*cortisone*, *compound* E) has proved of value in the treatment of rheumatoid arthritis.

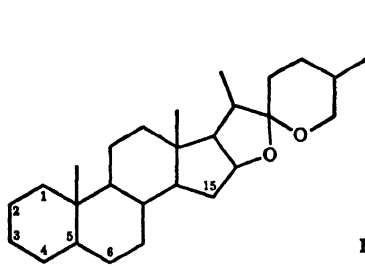
Saponins

Saponins and sapogenins. The saponins are vegetable glycosides, which act as emulsifiers of oils and produce stable foams when their aqueous solutions are shaken ; they also dissolve the red corpuscles, poison fish and the lower animals, and irritate the eyes and organs of taste. On hydrolysis they yield a *sapogenin* and a sugar or sugars.

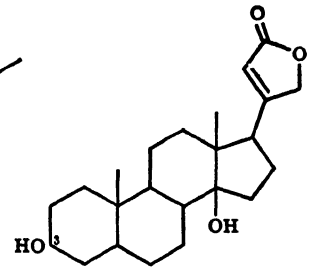
The sapogenins are all closely related structurally, and like the sterols they give the Diels' hydrocarbon on dehydrogenation ; they are hydroxy-derivatives of the framework shown (p. 1110).

Digitonin is a saponin which occurs in *Digitalis purpurea*, the purple foxglove ; on hydrolysis it yields the sapogenin digitogenin (1 mol.), glucose (2 mol.), galactose (2 mol.) and xylose (1 mol.). *Digitonin*, is a 2:3:15 (?)-trihydroxy-derivative of the first structure shown below. In the same plant occur *gitonin* and *tigonin*, which are

respectively glycosides of the 2:3- and the 3-hydroxy-derivatives of this same structure.



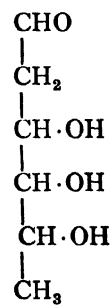
Framework of Sapogenins



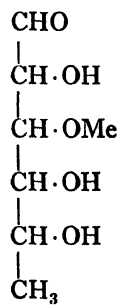
Digitoxigenin

Cardiac poisons. Since very early times certain plant extracts have been used as arrow-poisons and are now employed medicinally to revive the action of the heart. The potent principles of such extracts have been isolated and their structures have been determined by Jacobs, Tschesche and Windaus.

Digoxin, *digitoxin* and *gitoxin*, for example, are isolated from *Digitalis purpurea*, and *Digitalis lanata*; these substances are glycosides, and on hydrolysis yield aglycones (or *genins*) and sugars.



Digitoxose



Digitalose

The sugar obtained from these glycosides is *digitoxose*, and from others *digitalose* has been isolated. As will be seen, these aldoses are of a novel type; they do not occur except in these cardiac poisons. The aglycones yield cholanic acid derivatives on degradation and have a structure similar to that shown for *digitoxigenin*, the aglycone of digitoxin (above); the sugar residues are

attached to the hydroxyl group at 3. In the plant these glycosides are present as still more complex compounds combined with other sugars.

The unsaturated 5-membered ring is very important from a physiological standpoint; when the olefinic bond is saturated little activity remains, and a fission of the lactone ring also causes a loss of activity. The steroid part of the molecule of the so-called toad poisons, such as *bufotoxin*, is probably structurally similar to that of the genins.

APPENDIX

Some Examination Questions

MANY examination questions on organic chemistry relate to general methods of preparation, general reactions, and general properties of important types of compounds, and can be answered if the student is able to reproduce the facts which he has studied in his text-books. Others, however, are of a different character, and are set with the object of testing the ability of the student to apply his text-book knowledge in an intelligent manner ; those of the latter type only are considered below.

1. Methods for the preparation of di-substitution derivatives of benzene are often required, as, for example : ' Suggest methods for the preparation of m-*nitroaniline*, p-*sulphobenzoic acid*, and m-*dibromobenzene*.'

In answering such questions, it is of course essential to bear in mind the rules of aromatic substitution (pp. 433, 1004) and to remember that many di-derivatives, C_6H_4XY, cannot be obtained directly from certain mono-substitution products, C_6H_5X, owing to the orientating effect of X.

m-*Nitroaniline* cannot be obtained by the nitration of aniline except under very particular conditions (p. 1013), because the amino- or NHAc-group is *op*-orientating. It may, however, be prepared from nitrobenzene because the nitro-group is *m*-orientating, and one of the nitro-groups in the dinitro-compound can be reduced without changing the other.

p-*Sulphobenzoic acid* cannot be obtained by sulphonating benzoic acid, and the carboxyl group cannot be introduced into the molecule of benzenesulphonic acid in the *p*-position by the general method, $NO_2 \longrightarrow NH_2 \longrightarrow N_2X \longrightarrow CN \longrightarrow COOH$, because both the carboxyl radical and the sulphonic group are *m*-orientating. On the other hand, the methyl radical is *op*-orientating and can then be converted into —COOH ; the suggested method therefore might be :

$$C_6H_5 \cdot CH_3 \longrightarrow C_6H_4\begin{cases} CH_3 \\ SO_3H \end{cases} \longrightarrow C_6H_4\begin{cases} COOH \\ SO_3H \end{cases}$$

When, as in this case, it is known that the product would probably be a mixture, a method for the separation of the two or more components at one or other stage of the operations should be suggested, if possible. If, as would commonly be the case, the actual process could not be given, it would be known, nevertheless, that for volatile liquids, fractional distillation, and for soluble solids, fractional crystallisation of the actual components of the mixture, or of some simple derivatives, are generally employed, and a statement to that effect should be made. As a rule, details of the isolation of a product need not be given (except in the case of ordinary ' preparations ') but are sometimes required.

m-*Dibromobenzene* cannot be prepared by the direct bromination of benzene or of bromobenzene, or by nitrating bromobenzene and then displacing the NO_2— group by bromine by the usual series of reactions, because bromine is *op*-orientating. It might, however, be obtained by brominating nitrobenzene and then substituting Br for NO_2 by reducing the compound to *m*-bromoaniline with stannous chloride and hydrochloric acid and then displacing the amino-group by bromine.

How could (*a*) m-*aminophenol* and (*b*) p-*hydroxybenzoic* acid be obtained ? m-*Aminophenol* cannot be obtained by nitrating phenol and then reducing the nitro-compound, or by sulphonating aniline and then displacing the sulphonic group by hydroxyl, since both the HO— and the NH_2— groups are *op*-orientating ; its preparation by the following series of reactions might therefore be suggested :

$$C_6H_6 \longrightarrow C_6H_4(NO_2)_2 \longrightarrow C_6H_4\begin{matrix}NO_2\\NH_2\end{matrix} \longrightarrow C_6H_4\begin{matrix}NO_2\\OH\end{matrix} \longrightarrow C_6H_4\begin{matrix}NH_2\\OH\end{matrix}$$

p-*Hydroxybenzoic acid* cannot be obtained by first nitrating or sulphonating benzoic acid and then displacing the nitro- or sulphonic group by the usual methods ; it might, however, be prepared by nitrating toluene and then submitting the product, a *mixture* of isomerides, to the following changes :

$$C_6H_4\begin{matrix}CH_3\\NO_2\end{matrix} \longrightarrow C_6H_4\begin{matrix}COOH\\NO_2\end{matrix} \longrightarrow$$

$$C_6H_4\begin{matrix}COOH\\NH_2\end{matrix} \longrightarrow C_6H_4\begin{matrix}COOH\\N_2X\end{matrix} \longrightarrow C_6H_4\begin{matrix}COOH\\OH\end{matrix}$$

The isomerides would probably be separated most easily as nitrobenzoic acids.

2. Methods for the synthesis, or the *complete* synthesis[1] of compounds of a given structure, other than simple substitution products of benzene, have often to be suggested. To do so successfully a knowledge of the important general reactions is of course essential, particularly of those which bring about the union of carbon atoms ; among the latter the following may be mentioned, but there are many others : The uses of hydrogen cyanide and its salts ; simple condensations of aldehydes and ketones with one another and with acids, including the aldol condensation (pp. 141, 148, 158) and the Perkin reaction (p. 526) ; the uses of Grignard reagents (pp. 236, 431, 497), and of diethyl malonate and ethyl acetoacetate (pp. 200-210) ; the Tiemann-Reimer reaction (p. 502) ; the Claisen condensation (p. 827) ; the Michael reaction (p. 807) ; the Reformatsky reaction (p. 286).

The first step in answering such questions is to set out the structural formula of the required substance, possibly in the various ways in which it might be written and then to examine it carefully. A relationship to some better-known compound may then be seen, and a method of preparation may suggest itself. If not, the formula is resolved into various imaginary fragments or residues, which occur in certain simpler, commonly available, compounds and methods for bringing about their union, and for the subsequent modification, if necessary, of the resulting structure, are then considered.

This procedure may be illustrated by the following examples :

' Suggest a method for the synthesis of each of the following compounds : (*a*) $CHMe_2 \cdot N{:}CHPh$, (*b*) $CPhMe(O \cdot COPh) \cdot COOEt$, (*c*) $N(CH_2 \cdot CH_2 \cdot OH)_3$, (*d*) $CMe_3 \cdot COOH$.'

The molecule of (*a*) is related to that of benzylideneaniline (p. 499); it contains an *iso*propyl residue and also a benzal group, which is present in benzaldehyde. Since aldehydes condense with primary amines, *iso*propylamine might be prepared from acetoxime (obtained from acetone), and could then be condensed with benzaldehyde to give the desired product.

[1] The word ' synthesis ' is often used to denote any method of preparation, except from some natural source; the words ' complete synthesis ' usually imply the production of the compound from its elements.

The molecule of (*b*) is that of a benzoyl derivative of the ester of an α-hydroxy-acid. Now α-hydroxy-acids are obtained from aldehydes or ketones, with the aid of hydrogen cyanide, followed by the hydrolysis of the hydroxycyanide. In this case a ketone, acetophenone, might be the starting-point; the hydroxy-acid, prepared from it, is then benzoylated and esterified, or esterified and then benzoylated.

(*c*) The molecule of this compound is closely related to that of triethylamine, obtained from ethyl bromide and alcoholic ammonia, but instead of the ethyl radicals it contains three hydroxyethyl groups. If, therefore, instead of ethyl bromide, ethylene bromohydrin, obtained from ethylene and hypobromous acid, were used, the desired compound might be obtained, since alcoholic ammonia does not react with alcoholic hydroxyl groups. It is probable, of course, that the primary and secondary hydroxyamino-compounds, as well as the quaternary salt, might be produced at the same time; it is also conceivable that the bromohydrin might be converted into ethylene oxide. Such considerations, however, do not necessarily invalidate the suggested method, which is based on reasonable assumptions. On the other hand, to suggest that the hydroxyamine, (*c*), might be obtained by chlorinating triethylamine, and hydrolysing the product, would be most unsatisfactory, since it should be known that a hydrogen atom of a $CH_2<$group would be displaced rather than that of a CH_3— group. What is required in such answers is not necessarily a method which *must* give the desired product, but one which is based on sound analogies: if the process involves improbable (or unknown) reactions, or if it is more likely that at any stage the reaction will take a course different from that which is assumed, then the suggested method is of course unsatisfactory.

(*d*) As this compound is trimethylacetic acid, a possibility which might suggest itself would be to start with acetic acid, convert it into trichloroacetic acid, and then to treat an ester of this compound with methyl magnesium iodide; or to treat ethyl αα-dichloropropionate with methyl magnesium iodide. Neither project, however, would be satisfactory as the carbethoxy-group might also react with the Grignard compound.

Now the required acid is related to trimethyl carbinol, $CMe_3 \cdot OH$, which could be obtained from acetone and methyl magnesium iodide, or from ethyl acetate and the same Grignard reagent; the

displacement of hydroxyl by —COOH might then be accomplished by the usual series of changes, but the displacement of a tertiary bromine by the CN— radical is likely to prove very difficult :

$$OH \longrightarrow Br \longrightarrow CN \longrightarrow COOH \quad \text{or}$$
$$OH \longrightarrow Br \longrightarrow MgBr \longrightarrow COOMgBr \longrightarrow COOH$$

If perchance the formula of trimethylacetic acid recalls that of pinacolone, which can be prepared from acetone, it might also be remembered that this ketone can be oxidised to trimethylacetic acid. Such a method, however, would not be arrived at by deduction and would not be based on a general reaction, since, from the usual behaviour of ketones on oxidation, it might be expected that pinacolone would give acetic acid, acetone, and carbon dioxide.

' Suggest methods for the preparation of (*a*) $Ph \cdot CH_2 \cdot CH_2 \cdot CO \cdot Me$ and (*b*) $CMe_2{:}CH \cdot CH_2 \cdot CH_3$, and for a *complete* synthesis of (*c*) $CHMe_2 \cdot CH_2 \cdot CH_2 \cdot CHEt \cdot COOH$.'

(*a*) This molecule contains an acetone residue and a benzyl group and is that of a mixed ketone. It might be obtained by the destructive distillation of a mixture of the calcium salts of acetic acid and β-phenylpropionic acid (hydrocinnamic acid) ; destructive distillations, however, generally give very poor results, and, in addition, three products might be obtained, of which the desired compound might form only a very small proportion. Now the ketone (*a*) is closely related to benzylideneacetone, which is easily prepared ; it might possibly be obtained from this unsaturated compound by treating the latter with a suitable reducing agent, which would saturate the olefinic binding without affecting the carbonyl group ; alternatively, by treating the olefinic compound with hydrogen bromide and reducing the additive product. But many ketones containing the group, $—CH_2 \cdot CO \cdot CH_3$, are obtainable from ethyl acetoacetate, and such reactions generally give good results ; the desired compound might therefore be prepared from that ester and benzyl chloride by the usual procedure.

(*b*) An important fragment of this molecule is an acetone or *iso*propyl residue, but it should be known that the substance could not be obtained by the condensation of acetone with propane or by the condensation of propane with propaldehyde. The compound is related to mesityl oxide, which is easily prepared from acetone, but to obtain it from the unsaturated ketone the carbonyl group

must be reduced to $>CH_2$. Various processes for bringing about such a change are known, but as the reduction of the carbonyl radical might involve the saturation of the olefinic binding, the use of mesityl oxide would not be very promising. Further consideration might then suggest that the olefinic compound (*b*) might be obtained from the alcohol, $CMe_2(OH)\cdot CH_2\cdot CH_2\cdot CH_3$, or from the corresponding halogen derivative, by the elimination of the elements of water or of halogen acid ; in such operations it is not likely that an isomeride, $CH_2{:}CMe\cdot CH_2\cdot CH_2\cdot CH_3$, would be formed in large proportions owing to the general inactivity of the CH_3— in comparison with that of a $CH_2<$ group. Now many tertiary alcohols can be easily prepared from ketones or esters with the aid of Grignard reagents. It is therefore suggested that (*b*) might be obtained by treating acetone with propyl magnesium bromide, decomposing the additive compound, and then heating the alcohol with, say, zinc chloride or potassium hydrogen sulphate (or alone) to bring about the elimination of the elements of water ; or the tertiary alcohol might be treated with hydrobromic acid and the product heated with quinoline or alcoholic potash. The tertiary alcohol might also be prepared from ethyl butyrate and methyl magnesium iodide.

Very many other secondary and tertiary alcohols, such as $CHMe_2\cdot CH_2\cdot CH(OH)\cdot CH_3$, $C_2H_5\cdot CH(OH)\cdot CH_2\cdot CH_2\cdot CH_3$, $C_6H_5\cdot CH(OH)\cdot CH_2\cdot CH_3$, $C_6H_5\cdot CH_2\cdot CMe_2\cdot OH$, $CMe_2Ph\cdot OH$, might of course be obtained by corresponding methods, and then converted into olefines and subsequently into paraffins by reduction.

(*c*) It will be seen that this compound may be regarded as ethyl-*iso*amylacetic acid. It might therefore be prepared (as an ester) from diethyl malonate with the aid of *iso*amyl bromide and then ethyl bromide, in two separate operations as usual (p. 207). Since a complete synthesis of (*c*) is required, it would also be necessary to give methods for the synthesis of diethyl malonate and of the two alkyl halides from their elements. The *iso*amyl iodide might be obtained from synthetic acetone by converting it into *iso*propyl alcohol, and then into *iso*butyl alcohol by the usual series of reactions,

$$—OH,\quad —Br,\quad —CN,\quad —CH_2\cdot NH_2,\quad —CH_2\cdot OH,$$

for passing up a series, repeating these operations in order to convert the *iso*butyl into *iso*amyl alcohol ; or more shortly from *iso*propyl magnesium bromide and ethylene oxide, etc. (p. 225).

'How might the compound $CMe_2(CH_2 \cdot COOH)_2$ be obtained?'

This molecule contains an acetone or *iso*propyl residue and two radicals derived from acetic acid, but it does not seem possible to unite such residues by general reactions. A group, $-CH_2 \cdot COOH$, however, is easily formed from $-CH(COOH)_2$, a residue of malonic acid, and the $CH_2<$ group of the latter is very reactive. The required compound might therefore be obtained from acetone by converting it into CMe_2Br_2 and then treating the dibromide with diethyl sodiomalonate (2 mol.); the resulting ester would then be hydrolysed and the tetracarboxylic acid decomposed in the ordinary way:

$$CMe_2Br_2 \longrightarrow CMe_2\begin{matrix}\nearrow CH(COOEt)_2 \\ \searrow CH(COOEt)_2\end{matrix} \longrightarrow CMe_2\begin{matrix}\nearrow CH(COOH)_2 \\ \searrow CH(COOH)_2\end{matrix} \longrightarrow CMe_2\begin{matrix}\nearrow CH_2 \cdot COOH \\ \searrow CH_2 \cdot COOH\end{matrix}$$

A further examination of the formula of the acid shows that the molecule contains a residue of *iso*valeric acid united to a $-CH_2 \cdot COOH$ group, and that of *iso*valeric acid, residues of acetone and acetic acid. Now *iso*valeric acid could be synthesised from ethyl acetoacetate or diethyl malonate, but a saturated acid such as this does not lend itself to further synthetical operations. It might be transformed into an unsaturated acid, $CMe_2{:}CH \cdot COOH$, however, by bromination and subsequent elimination of the elements of halogen acid, and the *ester* of this product would be expected to give the compound, $(COOEt)_2CH \cdot CMe_2 \cdot CH_2 \cdot COOEt$, by direct combination with diethyl sodiomalonate (Michael reaction). The unsaturated acid might also be prepared from the condensation product of acetone and diethyl malonate (but not by the condensation of acetone and acetic acid). It might also be possible to convert the unsaturated acid into $CMe_2Br \cdot CH_2 \cdot COOH$ with the aid of hydrobromic acid and then to treat the ester of this compound with diethyl sodiomalonate; if the ester of the tricarboxylic acid were thus obtained it could be easily converted into the desired compound.

It will be seen from the examples given above that every stage of a suggested method must be carefully considered in order to avoid the use of operations which, although they may bring about the desired change, may also cause others which would defeat the end in view.

3. Another type of question is that which deals partly or mainly with isomerism and which often causes unnecessary trouble owing to the haphazard manner in which it is treated; some simple examples may serve to show the best procedure.

'Write the structural formulae of the alcohols, $C_5H_{11}\cdot OH$, and of the amines, $C_5H_{13}N$.'

In answering all such questions the formulae should be deduced systematically, otherwise some of the possible isomerides may be omitted, or two formulae, which are merely set out differently, may be returned as those of two isomerides, when they are in fact identical.

Now the alcohols, $C_5H_{11}\cdot OH$, are derived from the pentanes, C_5H_{12}, and the first step, therefore, is to write the formulae of these hydrocarbons; in this, and similar cases, skeleton formulae of carbon atoms alone might suffice.

I $\overset{a}{\underset{a'}{CH_3}}\cdot\overset{b}{\underset{b'}{CH_2}}\cdot\overset{c}{\underset{b'}{CH_2}}\cdot\overset{b}{\underset{a'}{CH_2}}\cdot\overset{a}{CH_3}$ II $\begin{matrix}{}^{a}CH_3\\ {}^{a}CH_3\end{matrix}\!\!>\!\overset{b}{\underset{a'}{CH}}\cdot\overset{c}{\underset{b'}{CH_2}}\cdot\overset{d}{\underset{c'}{CH_3}}$

III $C(CH_3)_4$

It is then obvious that from (I), three isomerides, *a*, *b*, *c*, and from (II), four isomerides, *a*, *b*, *c*, *d*, are derived by substitution of HO— for hydrogen, whereas (III) gives one alcohol only.

Of the amines, $C_5H_{13}N$, there will be eight primary bases, each of which corresponds with one of the alcohols; in addition, there are secondary and tertiary amines to be considered. The structures of the former are obtained by introducing an $>NH$ group between two carbon atoms in the various possible ways; from (I) two such bases are obtained, since there are two different positions *a'* and *b'*; from (II) there are derived three isomerides by introducing the $>NH$ group at *a'*, *b'*, or *c'*; from (III) only one secondary base could be formed. The structures of the tertiary amines are easily found because the group, C_5H_{13}, must consist of three radicals which can only be CH_3, CH_3 and C_3H_7 or CH_3, C_2H_5 and C_2H_5; the group C_3H_7, however, may be either the normal or *iso*propyl group, so that there would be three tertiary bases. Altogether, therefore, 17 compounds, $C_5H_{13}N$, are theoretically possible.

'Write the structural formulae of the benzene derivatives, $C_8H_{10}O$.'

If the compound is a mono-substitution product of the hydrocarbon, it may be represented by the formula, $C_6H_5—(C_2H_5O)$, and the various isomerides of this class are first obtained by considering the possible arrangements of the group, $—C_2H_5O$. These would be :

$—CH_2·CH_2·OH$ $—CH(OH)·CH_3$ $—CH_2·O·CH_3$ $—O·CH_2·CH_3$

If the compound is a di-substitution product, its molecule may contain one side chain of two carbon atoms, or two side chains, each containing one carbon atom ; in other words, the di-substituted derivatives are isomerides obtained from *A*, $C_6H_5·C_2H_5$, by displacing a nuclear hydrogen atom by hydroxyl, or from *B*, $C_6H_4(CH_3)_2$, by displacing side chain hydrogen by hydroxyl, or by interposing an oxygen atom.

Now from *A*, *o*-, *m*-, and *p*-ethylphenols, $C_6H_4Et·OH$ would be obtained. From *B*, which may be either *o*-, *m*-, or *p*-xylene, the three corresponding xylenols, $CH_3·C_6H_4·CH_2·OH$, may be derived and also the three isomeric, *o*-, *m*-, and *p*-ethers, $CH_3·C_6H_4·OMe$.

Lastly, if the compound is a tri-substitution product of benzene, it must be represented by $C_6H_3(CH_3)_2·OH$, and of such phenols there are six isomerides, two derived from *o*-, three from *m*-, and one from *p*-xylene.

An alternative procedure would be to start from the possible hydrocarbon structures, $C_6H_4·CH_2·CH_3$ and $C_6H_4(CH_3)_2$, and then to derive the isomerides by (*a*) [illegible] an oxygen atom between two carbon atoms, and (*b*) displacing a hydrogen atom by hydroxyl, in all the possible ways. From ethylbenzene two ethers, two alcohols, and three phenols are thus obtained, whereas *each* of the xylenes gives rise to one ether and one alcohol, and in addition *o*-xylene gives two phenols, *m*-xylene three, and *p*-xylene one.

A systematic procedure thus gives the possible structural formulae without difficulty, and there is no need to compare any two of them to see whether or not they are identical

'What possible structures can be assigned to a compound of the molecular formula, $C_9H_8O_3$, which gives terephthalic acid on oxidation ?'

As the substance must be a di-derivative of benzene containing the group, $C_6H_4<$, the residue, $C_3H_4O_3$, must form two side chains in the *p*-position, of which, obviously, one carbon atom in each case must be directly combined with the benzene nucleus. Further, one of these side chains, *A*, must contain one and the other, *B*, must contain two carbon atoms.

If *A* is —COOH, *B* is C_2H_3O, namely —$CO \cdot CH_3$ or —$CH_2 \cdot CHO$.

If *A* is —CHO, *B* is $C_2H_3O_2$, namely —$CH_2 \cdot COOH$,
—$CH(OH) \cdot CHO$, —$CO \cdot CH_2 \cdot OH$, or —$COOCH_3$.

If *A* is —$CH_2 \cdot OH$, *B* is C_2HO_2, namely —$CO \cdot CHO$.

If *A* is —CH_3, *B* is C_2HO_3, namely —$CO \cdot COOH$.

By thus proceeding from the highest to the lowest stage of oxidation of *A*, the required isomerides are easily obtained.

In answering such questions it may be possible to write one or more formulae in which the valency of each atom is correctly shown, but which represent compounds, the existence of which is improbable; thus, in the above example, when *B* is $C_2H_3O_2$ it might be written $-CH_2 \cdot O \cdot CHO$. In such case the improbable formula should be given with suitable comments.

4. A few examples of questions on research problems may now be considered.

'A substance, neutral to litmus, of the empirical formula, $C_7H_7O_2N$, boiled with alkalis, gave a solution from which acids liberated a compound, **A**, free from nitrogen. 0·207 g. of **A** gave 0·462 g. CO_2 and 0·081 g. of H_2O; 0·25 g. of **A** in 25 g. of acetic acid gave $\Delta = 0{\cdot}35°$ (K for acetic acid is 39). From these data find the molecular formula of **A** and that of the original substance, and give the possible structural formulae of the compound **A**.'

As the original compound is neutral, and loses nitrogen when it is boiled with alkalis, giving apparently an acid, it is probably an ammonium salt, an amide, or a nitrile. From the combustion data, the composition of **A** is found to be C = 60·9, H = 4·35, and O = 34·8%, corresponding with the empirical formula, $C_7H_6O_3$, which requires C, 60·85, H, 4·35, O, 34·8%. From the experimental data the molecular weight of **A** is 111, and $C_7H_6O_3$ requires 138; as, however, the observed value for an acid would probably be low owing to the ionisation of the compound in acetic acid solution, the cryoscopic result may be taken to show clearly that the molecular formula of the acid is $C_7H_6O_3$ or $C_6H_4(OH) \cdot COOH$. The acid, **A**,

therefore is *o*-, *m*-, or *p*-hydroxybenzoic acid and the original compound, $C_7H_7O_2N$, is the corresponding amide.

It should be noted that as the results of cryoscopic determinations, apart from other experimental errors (which may be more than, say, 10%) are influenced by ionisation or association, they only serve to show the value of n in the expression $(E.F.)_n = M.F.$

'A hydrocarbon containing C = 85·7 and H = 14·3% combines directly with bromine, giving an oil, which contains 74·1% of bromine. This bromo-derivative is boiled with a solution of sodium carbonate and the product is oxidised with potassium permanganate solution. Acetic acid is formed. Give the possible formulae of the hydrocarbon and of the substance formed by the hydrolysis of the bromo-derivative.'

From the percentage composition, the empirical formula, CH_2, is obtained; the compound is therefore an olefine or possibly a *cyclo*paraffin. In either case, since the hydrocarbon combines directly with bromine, 74·1 : 160 : : 25·9 : x, where x is the equivalent weight of the $(CH_2)_n$ radical; as x is 56 the M.F. of the radical is $(CH_2)_4$. Alternatively the molecular weight of the hydrocarbon radical may be found by calculating that of the dibromide, which is 74·1 : 160 : : 100 : x, and then subtracting 160 for Br_2. The molecular formula of the hydrocarbon, therefore, is C_4H_8, and, if an olefine, its structure may be represented by one of the following formulae:

$CH_2{:}CH\cdot CH_2\cdot CH_3$ (I) $\quad CH_3\cdot CH{:}CH\cdot CH_3$ (II) or $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{:}CH_2$ (III)

Now the dibromide would probably give the corresponding glycol when it is boiled with sodium carbonate solution; if so, since the product gives acetic acid on oxidation it could hardly be derived from (I), as such a derivative would be expected to give propionic and carbonic acids; on the other hand, a glycol, $CH_3\cdot CH(OH)\cdot CH(OH)\cdot CH_3$, from (II) would probably give acetic acid only, and a glycol, $(CH_3)_2C(OH)\cdot CH_2\cdot OH$, from (III), acetone and carbonic acid, the former of which might then be oxidised further to acetic and carbonic acids.

The hydrocarbon, therefore, is probably (II) or (III); it could not be *cyclo*butane, but it might be methyl*cyclo*propane from which

a glycol, $CH_3 \cdot CH(OH) \cdot CH_2 \cdot CH_2 \cdot OH$ or $CH_3 \cdot CH(CH_2 \cdot OH)_2$, might be obtained and oxidised to acetic acid.

' 0·2 g. of a neutral compound gave 0·3521 g. CO_2 and 0·072 g. H_2O. When the compound was boiled with ammonium hydroxide solution and the concentrated neutral solution was treated with silver nitrate solution, there was formed a colourless silver salt which contained 65·06% of metal (Ag = 107·9). From these data assign a formula to the neutral compound and to the substance which forms a silver salt.'

The combustion results give C = 48·0, H = 4·0, and O = 48·0% (by difference); the E.F. is therefore $C_4H_4O_3$. Obviously the compound is converted directly or indirectly into an ammonium salt, and from the percentage of metal in the silver salt the equivalent of the radical (combined with one atom of silver) is 65·06 : 107·9 : : 34·94 : x, or 58. This radical must contain —CO·O—, E = 44, which apparently is combined with one atom of carbon and two atoms of hydrogen, giving $C_2H_2O_2$, E = 58; its molecular formula therefore is $(C_2H_2O_2)_n$ and that of the acid is $(C_2H_3O_2)_n$. As the original compound is $(C_4H_4O_3)_n$ the molecular formula of the acid is probably $(C_2H_3O_2)_2$ or $C_4H_6O_4$, unless some fission of the molecule has occurred; this molecule would contain two —COOH groups and may be written $C_2H_4(COOH)_2$.

The acid is therefore either succinic or *iso*succinic acid, and since it is obtained from a compound, $(C_4H_4O_3)_n$, by hydrolysis, the latter must be an anhydride and the acid is succinic acid. It will be seen that the acid cannot have the molecular formula, $(C_2H_3O_2)_n$, where n is greater than 2, but the original compound might possibly have been $(C_4H_4O_3)_n$ where n is 2, 3, or more.

' 0·2 g. of a compound containing carbon, hydrogen, and oxygen, gave 0·2933 g. of CO_2 and 0·1200 g. of H_2O. When boiled with acetic anhydride it gave a derivative which afforded the following data: 0·1741 g. gave 0·3080 g. CO_2 and 0·0902 g. H_2O: 0·25 g. dissolved in 10 g. of acetic acid gave $\Delta = 0{\cdot}56°$ (K = 39): 0·261 g. on hydrolysis neutralised 30 c.c. of N/10 alkali.

Find the empirical and molecular formulae of the derivative and of the original compound, and assign a possible constitution to the latter.'

The combustion results for the original compound give C = 40·0,

H = 6·7, and O = 53·3%, from which the E.F., CH_2O, is immediately deduced. As this compound is changed by acetic anhydride, the product might be an acetyl derivative or an anhydride. This product contains C = 48·25, H = 5·75, and O = 46·0% and seems to have the empirical formula, $C_7H_{10}O_5$. The cryoscopic value for its M.W. is 174, a result which is probably not influenced by ionisation or association and which agrees with that required for $C_7H_{10}O_5$. On the assumption that the product is an acetyl derivative, the weight of the substance which gives one equivalent of acetic acid on hydrolysis would be 3 : 1000 : : 0·261 : x = 87. As this value should be free from any considerable error, the M.W. may be taken as 174, which agrees with the cryoscopic result. The compound, $C_7H_{10}O_5$, is therefore a diacetyl derivative. Now $C_7H_{10}O_5 - 2(O \cdot CO \cdot CH_3) = C_3H_4O$, which may be written

$$—CH_2 \cdot CO \cdot CH_2—, \quad —CH_2 \cdot \overset{|}{C}H \cdot CHO, \text{ or } —CH_2 \cdot CH_2 \cdot CO—,$$

and the molecule of the original compound will contain one of these groups combined with two hydroxyl radicals. The acetyl derivative is therefore that of dihydroxyacetone or of glyceraldehyde, $C_3H_6O_3$; it cannot be derived from the group $—CH_2 \cdot CH_2 \cdot CO—$ because an acetyl derivative, $AcO \cdot CH_2 \cdot CH_2 \cdot CO \cdot OAc$, if obtainable, would neutralise three and not two equivalents of alkali.

The deduction of an E.F., not always a very easy matter, is of course very much simplified if the (approximate) M.W. is known; it is often better, therefore, to calculate the molecular weight before attempting to find the E.F.

'An optically active compound, **A**, containing C = 44·1, H = 8·8, and O = 47·1%, heated with acetic anhydride and sodium acetate gave a crystalline derivative the M.W. of which, determined cryoscopically, was found to be 300. When hydrolysed with alkali, 1·064 g. of this derivative neutralised 28 c.c. of N/2 caustic soda. On oxidation, **A** gave malonic acid as one of the products. What is the probable structure of **A**?'

The E.F. of **A** is found to be $C_5H_{12}O_4$. Since 1·064 g. of its derivative neutralises 14 c.c. of N. alkali, the weight which gives one equivalent of acetic acid is 14 : 1000 : : 1·064 : x, and x is 76. As the molecular weight is (approximately) 300, the molecule of the acetyl derivative must contain 4 acetyl groups, and that of A, which

is $C_5H_{12}O_4$, 4 hydroxyl groups; the latter, therefore, is a tetrahydroxypentane, $C_5H_8(OH)_4$, in the molecule of which, presumably, no two hydroxyl groups can be combined with the same carbon atom.

Now from the three isomeric pentanes, 8 isomeric tetrahydroxy-compounds can be derived; this will be seen by writing the structural formulae of the three isomeric hydrocarbons (p. 1119), imagining that each is converted into a pentahydroxy-derivative and that one hydroxyl group is then displaced by hydrogen in all the possible ways. Three isomeric tetrahydroxy-compounds are thus obtained from normal pentane, four from *iso*pentane, and one from tetramethylmethane. Of these, only those compounds which contain in their molecules a group, C—CH_2—C, could give malonic acid on oxidation, that is to say, the isomerides,

$$CH_2(OH)\cdot CH_2\cdot CH(OH)\cdot CH(OH)\cdot CH_2\cdot OH$$
$$CH_2(OH)\cdot CH(OH)\cdot CH_2\cdot CH(OH)\cdot CH_2OH$$
$$\left.\begin{matrix}HO\cdot CH_2\\HO\cdot CH_2\end{matrix}\right\rangle C(OH)\cdot CH_2\cdot CH_2\cdot OH$$

But as only the first two of these isomerides could show optical activity the structure of **A** must be represented by one of those formulae.

NOTE ON CONSULTING THE LITERATURE

IT is often necessary, especially for those engaged in research, to consult dictionaries, works of reference and various chemical journals to find out whether some particular compound (A) has or has not been described, and if it can be traced, to read all that has been published about it. This may be a very troublesome task and the procedure will vary according to circumstances.

When (A) is known by name a preliminary search may be made in the alphabetical indexes of the following :

Dictionary of Organic Chemistry, Heilbron and Bunbury.
Dictionary of Applied Chemistry, Thorpe.

The first of these, published in 1943, and revised ten years later, lists a large number of organic compounds and gives their physical characteristics, together with some literature references. Thorpe's dictionary (1937-54) is especially useful for commercial products, methods, etc.

A compound may be indexed alphabetically under a trivial or a systematic name, and in the latter case especially, there may be various ways of doing so. Thus, even ethyl chloride might be indexed as such, or as chloroethane [1] or monochloroethane, and hydroxyaminopropionic acid as aminohydroxypropionic acid ; the compound $C_6H_2(COOH)(NH_2)(OH)_2[1:2:4:5]$[2] might be indexed as dihydroxyaminobenzoic acid, as aminoprotocatechuic acid, or as dihydroxyanthranilic acid, and $Ph \cdot NH \cdot CH_2 \cdot NH \cdot Ph$ as diphenylmethylenediamine, dianilinomethane, and so on.

Usually, however, the substituent elements or groups contained in recorded compounds are named in a given order, and if so the sequence should be carefully noted ; in Heilbron's dictionary, for example, this order is set out at the beginning.

Very often (A) is some apparently new (unnamed) compound, the structure of which is known from its method of formation in the course of research or it may be a compound which it is desired to

[1] Ethyl is aethyl or äthyl, ethane is aethan or äthan and hydroxy is oxy in German; as a rule the systematic English and German names of a compound are practically the same.

[2] All such numbers are often omitted in an index (as are also salts in general).

synthesise, if it has not already been described. In either case it may be given one or more systematic names and looked for under each.

Another important work of reference is *Traité de Chimie Organique, Grignard*, in 23 vols. The main subjects dealt with therein are shown on the cover of each volume, to which there is also an alphabetical, formula and author index; very comprehensive lists of the literature references to the matter described in the various sections are also included. The treatise is not meant to be an encyclopaedia of organic compounds; it deals systematically and critically with facts, methods and theories and is especially useful when information is required on some particular *subject*.

Elsevier's Encyclopaedia of Organic Chemistry is useful for finding information concerning condensed carbocyclic ring compounds; this is the only part of this work published to date.

As the above-named works do not claim to be exhaustive the search should always be continued elsewhere, and *Beilstein's Handbuch der Organischen Chemie* (4th edition) may next be consulted. This work covers the literature to the end of 1909, but has two addenda, one (E I) from 1910 to the end of 1919 and the other (E II) from 1920 to the end of 1929; there are 4 volumes concerned with aliphatic, and 23 volumes with aromatic and other cyclic compounds, in the main work and in each addendum. The number of each volume of the addenda corresponds with that of the main work: that is to say a compound found for example in vol. vi of the main work will be described in the same volume of each addendum. On the cover of each volume of the main work there is a summary of the types of compounds therein described and all volumes contain an alphabetical index; there is also a general alphabetical index (vol. E II, xxviii) and formula index (vol. E II, xxix) covering the main work and the two addenda and covering also vols. xxx and xxxi which deal with rubber, carotenoids and carbohydrates to the end of 1938. A list of the abbreviations used will be found in vol. i.

When (A) is unknown by name, or it seems likely that it might be indexed under many headings, a formula index must be consulted, and time may often be saved by doing so in the first place. Also, when the name of any author associated with (A) is known, a literature search may sometimes be shortened by consulting any author indexes which may be available, but this should not take the place of the formula index search.

In a formula index compounds are arranged according to the number and nature of the atoms in their molecules, starting with the number of carbon atoms, followed immediately by the number of hydrogen atoms (if any) and then any other elements which are present arranged alphabetically.

All compounds containing one carbon atom are first given, then those with two atoms of carbon, and so on. Indexes constructed on this plan, which should be consulted in the given order, are :

Beilstein (vol. E II, xxix).

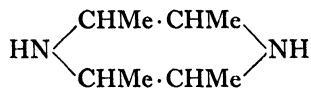
Formula indexes of the *American Chemical Abstracts*, 1920-46, and thereafter one for each year. Similar indexes will be found in *Chemisches Zentralblatt*, 1922-24, 1925-29, and for later years, at the end of each annual volume.[1]

Most of the books of reference mentioned above are generally to be found only in the libraries of large institutions such as the Patent Office, Colleges (technical and otherwise) and Universities ; here also more or less complete sets of many of the important journals may be consulted.

A common reason for consulting the literature is to find the best method for the *preparation* of some required compound ; this may often be found in Beilstein or one of the other quoted works, but it is always advisable to consult *Organic Syntheses*, in which the best-known method for the preparation of each of a large number of compounds is given in great detail.

The following two examples may serve to illustrate the general procedure suggested above :

(1) It is desired to find out whether or not a compound (A) of the following structure has been described:



It is obviously likely be called tetramethylpiperazine, and it will in fact be found in the alphabetical index to Beilstein (vol. E II, xxviii) under that name ; the page references here given are **23**, 23 ; I, 8 ;

[1] These are arranged rather differently from those of Beilstein and the American Chemical Abstracts, but a few moments study of them will afford all necessary guidance.

II, 19, 22, 23, 24. The figure **23** refers to the volume of the main work and 23 to the page. I and II refer respectively to the first and second addenda and the page figures to the same volume, i.e. **23**, of these addenda as before. The reference **23**, 23, will be found to describe all that was known about the compound (A) up to the end of 1909. The reference I (**23**), 8, will be found to describe an isomeric tetramethylpiperazine, as also will II, 19 ; further information on the required substance, complete up to the end of 1929, is found in references II, 22, 23, 24. Later references must be sought in the American Chemical Abstracts formula index where the compound will be found listed as piperazine, tetramethyl and reference must be made to each entry; these, of course, are abstracts only, but at the beginning the title of the original paper and the name of its author are given.

(2) Information is required about a substance (A) which is thought to be *p*-$CH_3 \cdot C_6H_4 \cdot SO_2 \cdot CH_2 \cdot SO_2 \cdot C_6H_5$, but for which a probable name may not suggest itself.

Under $C_{14}H_{14}O_4S_2$, in the formula index to Beilstein (vol. E II, xxix) there will be found the following five compounds named as shown :

$\alpha\beta$-Bis-phenylsulfon-äthan, $C_6H_5 \cdot SO_2 \cdot CH_2 \cdot CH_2 \cdot SO_2 \cdot C_6H_5$.
$\alpha\alpha$-Bis-phenylsulfon-äthan, $(C_6H_5 \cdot SO_2)_2CH \cdot CH_3$.
4:4′-Dimethyl-diphenyldisulfon, $CH_3 \cdot C_6H_4 \cdot SO_2 \cdot SO_2 \cdot C_6H_4 \cdot CH_3$.
Phenylsulfon-benzylsulfon-methan, $PhSO_2 \cdot CH_2 \cdot SO_2 \cdot CH_2Ph$.
pp-Diphenylen-bis-methylsulfon, $CH_3 \cdot SO_2 \cdot C_6H_4 \cdot C_6H_4 \cdot SO_2 \cdot CH_3$.

From these names formulae can be written as indicated. It is clear that the desired compound had not been described up to the end of 1929.

A further search is made in later formula indexes and it will be found under the name Methane (phenylsulfonyl) (*p*-tolylsulfonyl), in the collective index of American Chemical Abstracts, 1920-46. Further search will then be made in the annual indexes of the same work.

ABBREVIATIONS USED IN THE REFERENCES TO JOURNALS

Amer. Chem. J.	American Chemical Journal.
Ann.	Justus Liebig's Annalen der Chemie.
Ber.	Berichte der deutschen chemischen Gesellschaft.
Compt. Rend.	Comptes rendus hebdomadaires des Séances de l'Académie des Sciences.
Helv.	Helvetica Chimica Acta.
J.	Journal of the Chemical Society.
J. Am. Chem. Soc.	Journal of the American Chemical Society.
J. pr. Chem.	Journal für praktische Chemie.
J. Soc. Chem. Ind.	Journal of the Society of Chemical Industry.
Proc. Chem. Soc.	Proceedings of the Chemical Society.
Proc. R.S.	Proceedings of the Royal Society.

OXIDISING AGENTS

Acetone and aluminium *iso*propoxide, 1107, 1108.
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Benzoyl peroxide, 812.
Bromide water, 862, 872, 886.
Chromic acid, 797, 809, 921, 930, 940, 951, 972, 1026, 1027, 1089, 1092, 1100, 1101, 1105.
Ferric chloride, 923, 992.
Hydrogen peroxide, 764, 808.
Hypoiodites, 881.
Iodine, 881, 1084.
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Lead tetra-acetate, 808, 809, 975, 1070.
Mercuric oxide, 935.
Monoperphthalic acid, 895, 1078, 1079.
Nitric acid, 797, 862, 928, 933, 948, 1025.
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Hydrogen and platinum, 781, 804, 945, 967, 972, 976.
Hydrogen sulphide, 881.
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Sodium amalgam and water, 798, 801, 802, 803, 804, 813, 814, 929, 982.
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