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PERKIN AND KIPPING'S

ORGANIC CHEMISTRY

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ORGANIC CHEMISTRY

Part II

BY

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NEW EDITION

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PERKIN AND KIPPING'S

ORGANIC CHEMISTRY

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PREFACE TO PARTS I AND II

PERKIN and KIPPING'S *Organic Chemistry*, first published in 1894, has been widely used during more than half a century. It has been partly or completely revised at various short intervals, and for the present edition has been entirely reset.

The number of pages has been increased. This increase is due to some extent to the use of a larger and improved type-face and the *additions* to the text have been kept to a minimum consistent with dealing with all important recent advances. It would have been easy to overburden the book with new matter, but the authors feel that it is imperative to keep in mind the actual need of the student.

Very considerable revision of the text of the last edition has also been effected. Most of the structural formulae of cyclic compounds have been presented differently, so that they may be more readily understood. More attention has been paid to nomenclature and the use of different names for a given compound, in order to help students to pass from the name to the constitutional formula and *vice versa*.

The chapter on alkyl compounds of nitrogen, phosphorus, arsenic, silicon, and metals has been divided into two, and a short chapter on ethylenic and acetylenic compounds has been added, as well as many brief sections on, for example, petrol, synthetic anti-malarials, penicillin, etc. Some small portions of the text of Part III have been transferred to Part II and *vice versa*.

Perhaps the most noteworthy addition is the introduction, early in Part II, of an elementary account of the conception of resonance and of frequent references to this subject thereafter.

In spite of the changes which have been made, the general plan of the book, and any distinctive features which it may have, are unaltered and remain as in the original and later editions.

It is intended as a text-book, as an introduction to the study of Organic Chemistry, and the subject matter (of Parts I and II) corresponds approximately with that which is usually covered during a two-years' course of lectures.

With the aid of the explanatory notes and two sizes of type the text is so arranged that the course of the beginner is clearly indicated ;

he will not, therefore, be hampered by the premature study of matters beyond his needs. Having made sufficient progress, he begins the study of the summaries and other more advanced matter (in smaller type) which he has previously passed over. He will then have covered the ground usually necessary for (at least) a pass degree.

If that is his only object the greater part of Chapters 39-41 may perhaps be omitted, as these parts of the book are intended more particularly for pharmaceutical and medical students, or those reading for an honours degree. The last chapter, on dyes and their applications, is also probably beyond the needs of pass degree requirements.

One of the principal objects throughout has been to treat the subject from a practical point of view, for without a good grounding in laboratory work sound foundations cannot be laid. For this reason the preparation of many typical compounds is described in sufficient detail to enable even a beginner to carry out the operations with little supervision. A list of such preparations is given just before the Index.

Another important branch of practical work has been borne in mind, namely the identification of organic compounds. A few general directions are given, with various examples, and also sufficient data, chemical and physical, for the identification or reference to their types of most if not all of the compounds which are usually considered suitable for such exercises.

Very particular attention has been directed to the evidence on which a given structural formula is based, even in very simple cases, so that the student may be gradually trained to correlate the properties and the constitution of a compound. When he can do so, and the general reactions of the principal radicals have been mastered, structural formulae should be easily interpreted, all that they imply should be realised, and thus the study of organic chemistry should be very greatly simplified.

Many references have been made to the commercial preparation and uses of organic compounds, especially to those which are now manufactured from petroleum.

F. STANLEY KIPPING.
F. BARRY KIPPING.

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ORGANIC CHEMISTRY

Part II

CHAPTER 22

PRODUCTION, PURIFICATION, AND PROPERTIES OF BENZENE

Destructive Distillation of Coal. When coal is strongly heated, out of contact with the air, it undergoes very complex changes, and yields a great variety of gaseous, liquid, and solid volatile products, together with a non-volatile residue of coke. This process of dry, or destructive, distillation is carried out on the large scale in the manufacture of **coal-gas,** for which purpose the coal is heated in fire-clay or iron retorts, provided with air-tight doors; the gas and other volatile products escape from the retorts through pipes, and when distillation is at an end, the red-hot **coke,** a porous mass of impure carbon, containing the ash or mineral matter of the coal, is withdrawn. Nearly half a million tons of coal per week are thus carbonised in Great Britain.

The hot coal-gas passes first through a series of pipes or *condensers*, kept cool by immersion in water, or simply by exposure to the air, and, as its temperature falls, it deposits a considerable proportion of **tar** and **gas-liquor,** which are run together into a large tank; the gas is then passed through, and sprayed with, water, in *washers* and *scrubbers*, and, after having been further freed from tar, ammonia, carbon dioxide, and hydrogen sulphide, by suitable processes, it is led into the gas-holder and used for illuminating and heating purposes. The volume percentage composition of purified coal-gas is, very roughly: $H_2 = 47$, $CH_4 = 36$, $CO = 8$, $CO_2 = 2$, $N_2 = 3$, and hydrocarbons (acetylene, ethylene, benzene, etc.), other than methane, = 4, but varies *widely* with the nature of the coal and the temperature of the retorts.

The coal-tar and the gas-liquor in the tank separate into two

layers ; the upper one (gas-liquor or ammoniacal-liquor) is a yellow, unpleasant-smelling, aqueous solution of ammonium hydrogen carbonate, ammonium hydrosulphide, and numerous other compounds, from which some of the ammonia and ammonium salts of commerce are obtained. The lower layer in the tank is a thick, black, oily liquid of specific gravity 1·1-1·2, known as coal-tar. It is a mixture of a great number of organic compounds, and, although at one time it was considered to be an obnoxious by-product, it is now the source of very many substances of great industrial importance.

[1] More than 200 compounds have been proved to be present in coal-tar, but not all of these in any given sample ; most of them are aromatic compounds (p. 400). Very large quantities of coal are also destructively distilled in coke-ovens, in the manufacture of coke for metallurgical operations ; the products are similar to those obtained in a gas-works. The tar from the *low temperature carbonisation* of coal, for the production of a smokeless fuel (*Coalite*), contains a much larger proportion of aliphatic substances (p. 400) than does ordinary coal-tar.

Fractional Distillation of Coal-tar. In order to separate its components, the tar is submitted to fractional distillation ; it is heated in large wrought-iron stills or retorts, the vapours are condensed in long iron or lead worms immersed in water, and the liquid distillate is collected in fractions. The point at which the receiver should be changed is ascertained by means of a thermometer, which dips into the tar, as well as by the character of the distillate. Sometimes this distillation is carried out under reduced pressure ; there is then less decomposition of some of the valuable components of the tar.

In this way the tar is separated into the following fractions of which the given temperature limits are only approximations :

I. Light oil or crude naphtha	Collected up to 170°
II. Middle oil or carbolic oil	Collected from 170–230°
III. Heavy oil or creosote oil	Collected from 230–270°
IV. Anthracene oil	Collected above 270°
V. Pitch	Residue in the still

I. The first crude fraction separates into two layers—namely, gas-liquor, which the tar always retains to some extent, and an oil

[1] The consideration of those portions of the text printed in smaller type, except details of the preparation of typical compounds, may be postponed until the more important and elementary subject matter has been studied.

which is lighter than water, of specific gravity about 0·975 (hence the name *light oil*). This oil is first redistilled and the distillate is collected in three portions—namely, from 80–110°, 110–140°, and 140–170° respectively. All these fractions consist principally of **hydrocarbons,** but contain basic substances, such as **pyridine,** acidic substances, such as **phenol** or **carbolic acid,** and various other compounds; they are, therefore, separately agitated, first with caustic soda, which removes the phenols (p. 478), and then with sulphuric acid, which dissolves the basic substances, and are washed with water after each treatment; afterwards they are again distilled. The oil, obtained in this way from the fraction collected between 80 and 110°, consists principally of the hydrocarbons, **benzene** and **toluene,** and is sold as '90% benzol'; that obtained from the fraction 110–140° consists essentially of the same two hydrocarbons (but in different proportions), together with **xylene,** and is sold as '50% benzol.' These two products are not usually further treated by the tar-distiller, but are worked up elsewhere in the manner described later. The oil from the fraction collected between 140 and 170° consists of the hydrocarbons, xylene, pseudocumene, mesitylene, etc., and is employed principally as **'solvent naphtha,'** also as 'burning naphtha.'

Commercial '90% benzol' contains about 70%, and '50% benzol,' about 46% of pure benzene; each term refers to the proportion of the mixture which passes over below 100° when the commercial product is first distilled. Benzene, toluene, and xylene are known commercially as benzol, toluol, and xylol respectively.

II. The second crude fraction, or middle oil, collected between 170 and 230°, has a specific gravity of about 1·02, and consists principally of **naphthalene** and **carbolic acid.** When it is cooled, the naphthalene separates in crystals, which are drained and pressed to squeeze out liquid carbolic acid and other substances; the crude crystalline product is further purified by treatment with caustic soda and dilute sulphuric acid successively, and is finally sublimed or distilled. The oil from which the crystals have been separated is agitated with warm caustic soda, which dissolves the carbolic acid and other phenols; the solution is then drawn off from the insoluble portions and treated with sulphuric acid, whereon crude carbolic acid separates as an oil, which is washed with water and distilled; it is thus separated into crystalline carbolic acid and a

liquid mixture of phenols (cresylic acids), used in making plastics, disinfectants, etc.

III. The third crude fraction, collected between 230 and 270°, is a greenish-yellow, fluorescent oil, specifically heavier than water ; it contains **carbolic acid, cresol, naphthalene, anthracene,** and other substances, and is chiefly employed under the name of **' creosote oil '** for the preservation of timber.

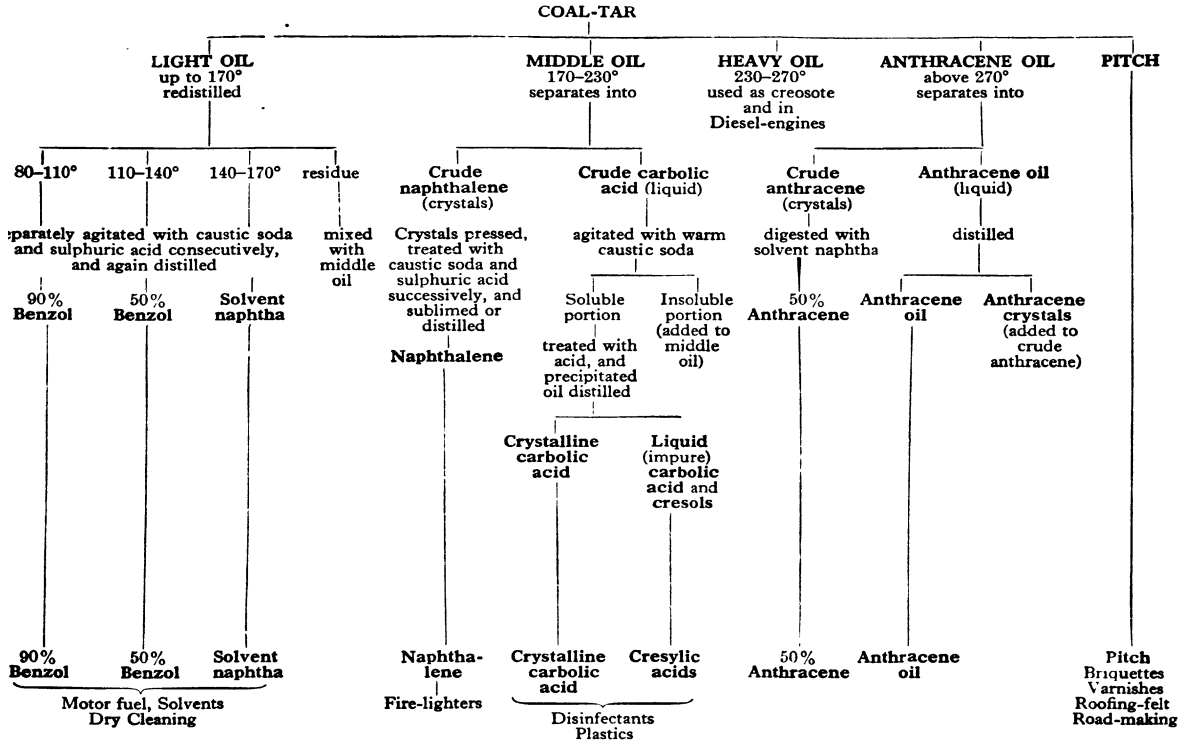
IV. The fourth crude fraction, collected at 270° and upwards, consists of **anthracene, phenanthrene,** and other hydrocarbons, which are solid at ordinary temperatures, and which are deposited in crystals as the fraction cools ; after having been freed from oil by pressure, and further purified by digestion with solvent naphtha (which dissolves the other hydrocarbons more readily than it does the anthracene), the product is sold as ' 50% anthracene,' and is employed in the manufacture of various dyes. The oil drained from the anthracene is redistilled, to obtain a further quantity of the crystalline product, the non-crystallisable portions being known as **' anthracene oil.'**

V. The **pitch** in the still is run out while it is hot, and is employed for the preparation of varnishes, for the protection of wood and metal work, and for the production of asphalt.

A very large quantity of tar which has been freed from the more volatile components only, is used in road-making.

The table, opposite, summarises the results of tar distillation and shows the more important commercial products and a few of their uses ; most of the components of the tar, however, are employed principally in the manufacture of dye-stuffs, explosives, plastics, drugs, and aromatic compounds in general.

The Isolation of Benzene. The crude ' 90% benzol ' of the tar-distiller consists essentially of a mixture of benzene and toluene, with small proportions of xylene and other substances ; on further fractional distillation it gives commercial benzene of high quality, which can be used for all ordinary purposes, but which still retains small proportions of toluene, paraffins, carbon disulphide, and other substances. For further purification, the benzene may be cooled in a freezing-mixture and the crystals quickly separated by filtration from the mother-liquor, which contains most of the impurities ; after this process has been repeated, the hydrocarbon should boil constantly at 80–81°.


COAL-TAR
LIGHT OIL
up to 170°
redistilled
MIDDLE OIL
170–230°
separates into
HEAVY OIL
230–270°
used as creosote
and in
Diesel-engines
ANTHRACENE OIL
above 270°
separates into
PITCH
80–110°
110–140°
140–170°
residue
Crude naphthalene (crystals)
Crude carbolic acid (liquid)
Crude anthracene (crystals)
Anthracene oil (liquid)
separately agitated with caustic soda and sulphuric acid consecutively, and again distilled
mixed with middle oil
Crystals pressed, treated with caustic soda and sulphuric acid successively, and sublimed or distilled
agitated with warm caustic soda
digested with solvent naphtha
distilled
90% Benzol
50% Benzol
Solvent naphtha
Naphthalene
Soluble portion
Insoluble portion (added to middle oil)
Anthracene oil
Anthracene crystals (added to crude anthracene)
treated with acid, and precipitated oil distilled
50% Anthracene
Crystalline carbolic acid
Liquid (impure) carbolic acid and cresols
90% Benzol
50% Benzol
Solvent naphtha
Naphthalene
Crystalline carbolic acid
Cresylic acids
50% Anthracene
Anthracene oil
Pitch
Briquettes
Varnishes
Roofing-felt
Road-making
Motor fuel, Solvents
Dry Cleaning
Fire-lighters
Disinfectants
Plastics

Even after having been submitted to crystallisation as well as distillation, the benzene is not pure, and when it is shaken with cold concentrated sulphuric acid, the latter is blackened owing to its having charred and dissolved the impurities ; pure benzene, on the other hand, does not char with sulphuric acid, so that when the impure liquid is repeatedly shaken with small quantities of the acid, until the latter ceases to be discoloured, most or all of the foreign substances are removed.

Coal-tar benzene, which has not been purified in this way, contains a sulphur compound, C_4H_4S, named *thiophene* (p. 587) which was discovered by V. Meyer ; the presence of thiophene is readily detected by shaking the sample with a little concentrated sulphuric acid and a trace of isatin (an oxidation product of indigo, p. 594), whereon the acid assumes a beautiful blue colour (*indophenin* reaction). Thiophene resembles benzene so closely in chemical and physical properties that it cannot be easily separated from the latter; it may, however, be extracted with sulphuric acid (above), which sulphonates and dissolves thiophene more readily than it does the hydrocarbon.

Although a very large proportion of the benzene of commerce ('benzol') is prepared from coal-tar,[1] the hydrocarbon is also present in small proportions in wood-tar, in certain varieties of petroleum, and in the tarry distillate of many other substances, such as shale, peat, etc.; it may, in fact, be produced, together with related compounds, by passing the vapour of alcohol, ether, petroleum, or of many other substances through a red-hot tube. Benzene is now manufactured by such methods from petroleum (p. 412).

Benzene, C_6H_6, was discovered by Faraday in 1825 in the gas produced by the destructive distillation of vegetable oils and, twenty years later, was found in coal-tar by Hofmann.

It may be produced *synthetically* by merely heating acetylene at a dull-red heat,

$$3C_2H_2 = C_6H_6 ;$$

many other hydrocarbons (toluene, diphenyl, indene, naphthalene, anthracene, phenanthrene, etc.) are formed at the same time.

Acetylene, *free from air*, is collected over mercury in a piece of hard glass-tubing, closed at one end and bent at an angle of about 120° ; the tube is about half-filled with the gas, a piece of copper

[1] Sometimes coal-gas is washed (stripped) with some heavy oil, such as creosote, in order to extract from it benzene and other volatile hydrocarbons.

gauze is wrapped round a portion of the horizontal limb (as shown, Fig. 23), and this portion is then carefully heated with a Bunsen burner. After a short time fumes appear, and minute drops of liquid condense on the colder parts of the tube. When it has been heated during about fifteen minutes, the tube is allowed to cool; the mercury then rises above its original level.

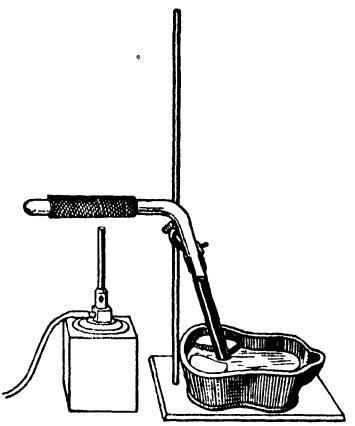


Fig. 23

This conversion of acetylene into benzene is a process of polymerisation, and was first accomplished by Berthelot. It is a particularly important synthesis of benzene from its elements, since acetylene may be produced by the direct combination of carbon and hydrogen or from calcium carbide.

Benzene may also be obtained by heating benzoic acid [1] (p. 512) or sodium benzoate with soda-lime, a reaction which recalls the formation of methane from sodium acetate,

$$C_6H_5 \cdot COONa + NaOH = C_6H_6 + Na_2CO_3.$$

All other benzene derivatives may be converted into the parent hydrocarbon by appropriate methods.

The analysis of benzene shows that it consists of 92·3% of carbon and 7·7% of hydrogen, a result which gives the empirical formula, CH; since the vapour density of benzene is 39, its molecular weight is 78, which corresponds with the *molecular formula*, C_6H_6.

At ordinary temperatures benzene is a colourless, highly refractive, mobile liquid of specific gravity 0·8788 at 20°, which boils at 80·2°; when it is cooled in a freezing-mixture it affords a crystalline mass, melting at 5·5°. It has a burning taste, a peculiar, not unpleasant smell, and is highly inflammable, burning with a luminous, very smoky flame, which is indicative of its richness in carbon; the luminosity of an ordinary coal-gas flame, in fact, is partly due to the presence of benzene. Although practically insoluble in water,

[1] The names benzene, benzol and benzine are derived indirectly from that of gum benzoin, the original source of benzoic acid.

benzene is miscible with liquids such as ether, alcohol, and petrol; it readily dissolves fats, resins, iodine, and other substances which are insoluble in water, and for this reason is extensively used as a solvent and for cleaning purposes; it is also employed as a motor-fuel, and for the manufacture of nitrobenzene (p. 435) and many other intermediates for the production of dyes, drugs, etc.

Benzene is very stable and, except when it is burned, is resolved into simpler substances only with great difficulty; when it is boiled with concentrated alkalis, for example, it undergoes no change, and even when it is heated with solutions of such vigorous oxidising agents as chromic acid or potassium permanganate, it is only very slowly attacked and decomposed, carbon dioxide, water, and traces of other substances being formed. Under certain conditions, however, benzene readily yields *substitution* products; concentrated nitric acid, even at ordinary temperatures, converts the hydrocarbon into *nitrobenzene* by the substitution of the univalent nitro-group, $-NO_2$, for an atom of hydrogen,

$$C_6H_6+HNO_3 = C_6H_5\cdot NO_2+H_2O;$$

and concentrated sulphuric acid, slowly at ordinary, more rapidly at higher, temperatures, transforms it into *benzenesulphonic acid*,

$$C_6H_6+H_2SO_4 = C_6H_5\cdot SO_3H+H_2O.$$

Chlorine and bromine, in the absence of direct sunlight and at ordinary temperatures, react with benzene only very slowly, yielding *substitution* products, such as *chlorobenzene*, C_6H_5Cl, *bromobenzene*, C_6H_5Br, *dichlorobenzene*, $C_6H_4Cl_2$, etc.; when, however, some halogen carrier (p. 422), such as iron or iodine, is present, action takes place readily at ordinary temperatures, even in the dark, substitution products again being formed.

In bright sunlight the hydrocarbon is rapidly converted into *additive* products, such as *benzene hexachloride*, $C_6H_6Cl_6$, and *benzene hexabromide*, $C_6H_6Br_6$, by direct combination with six (but not more than six) atoms of the halogen.

It also combines with (molecular) hydrogen in the presence of catalysts, giving *hexahydrobenzene*, C_6H_{12} (p. 406).

CHAPTER 23

CONSTITUTION OF BENZENE AND ISOMERISM OF BENZENE DERIVATIVES

It will be seen from the facts just stated that although benzene, like the paraffins, is extremely stable, it differs from the latter very considerably in chemical behaviour, more especially in being comparatively readily acted on by nitric acid and by sulphuric acid; further, when its properties are compared with those of the unsaturated hydrocarbons of the olefine or acetylene series, the contrast is even more striking, because the very high proportion of carbon to hydrogen in its molecule, C_6H_6, would seem to indicate a close relation to these and other unsaturated compounds.

In order, then, to obtain some clue to the constitution of benzene, it is clearly of importance to consider carefully the properties of some unsaturated hydrocarbons of known constitution, and to ascertain in what respects they differ from those of benzene; for this purpose the compound *dipropargyl* (p. 105), may well be chosen, as it is isomeric with benzene and is known to have the structure,

$$CH{:}C\cdot CH_2\cdot CH_2\cdot C{:}CH.$$

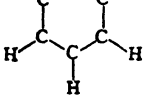
Now, in spite of their isomerism, dipropargyl and benzene are completely different in chemical behaviour; the former is very unstable, readily undergoes polymerisation, combines energetically with bromine, giving *additive* compounds, and is rapidly oxidised by various reagents; it shows, in fact, all the properties of an unsaturated hydrocarbon of the acetylene series. Benzene, on the other hand, is extremely stable, is comparatively slowly acted on by bromine, giving (usually) *substitution* products, and is oxidised only with difficulty even by the most vigorous reagents. Since, therefore, dipropargyl must be represented by the above formula in order to account for its method of formation and chemical properties, the constitution of benzene could not possibly be expressed by any similar formula, such as,

$$CH_3\cdot C{:}C\cdot C{:}C\cdot CH_3 \quad \text{or} \quad CH_2{:}C{:}CH\cdot CH{:}C{:}CH_2,$$

because compounds similar in constitution are always more or less similar in properties, and any such formula would not afford the slightest indication of the fundamental differences between benzene and ordinary unsaturated hydrocarbons of the olefine or acetylene series.

Again, a great many compounds, which are known to be derivatives of benzene, contain more than six atoms of carbon ; when, however, such compounds are treated in a suitable manner, they are easily converted into substances containing six, but not *less* than six, atoms of carbon. This fact shows that in these benzene derivatives there are six atoms of carbon which are in a different state of combination from the others and form a stable core or *nucleus* ; any additional carbon atoms which do not constitute a part of this nucleus are easily attacked and removed.

These and many other facts, which were established during the investigation of benzene and its derivatives, led Kekulé (1865) to conclude that *the six carbon atoms in benzene form a closed chain or nucleus* : that *the molecule of benzene is symmetrical* : and that *each carbon atom is directly united with one* (and only one) *atom of hydrogen*, as represented below,



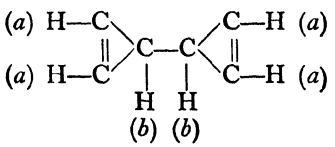
Isomerism of Benzene Derivatives

The most convincing evidence that the molecule of benzene is *symmetrical* is based on a study of the isomerism of benzene derivatives. It has been proved in the course of many years that it is possible, directly or indirectly, to substitute 1, 2, 3, 4, 5, or 6 univalent atoms or groups for a corresponding number of the hydrogen atoms in benzene, compounds such as *bromobenzene*, C_6H_5Br, *dinitrobenzene*, $C_6H_4(NO_2)_2$, *trimethylbenzene*, $C_6H_3(CH_3)_3$, *tetrachlorobenzene*, $C_6H_2Cl_4$, *pentamethylbenzene*, $C_6H(CH_3)_5$, and *hexacarboxybenzene*, $C_6(COOH)_6$, being produced ; the substituting atoms or groups, moreover, may be identical or different.

The examination of such substitution products has shown that when only *one* atom of hydrogen is displaced by any given atom or group, the same compound is always produced—that is to say, *the mono-substitution products of benzene exist in one form only*; when, for example, *phenol*, $C_6H_5 \cdot OH$, is prepared, no matter what may be its source or how the hydroxyl group has been substituted for an atom of hydrogen, the same substance is always produced.

This might be explained, of course, by the assumption that one particular hydrogen atom was always displaced by hydroxyl; when, for example, acetic acid is treated with sodium hydroxide, since only one of the four hydrogen atoms is displaceable, the same salt is invariably produced. In the case of benzene, however, it has been shown that although every one of the six hydrogen atoms may be displaced in turn by a given substituent, the same substance is always formed (p. 387).

The only possible conclusion to be drawn from this fact is that *all* the hydrogen atoms are in exactly similar positions relatively to the rest of the molecule; if this were not so, and the constitution of benzene were represented by any formula such as the following,



it would be possible to obtain isomeric *mono*-substitution products. Such a formula might well account for the existence of a stable nucleus, but would show some of the hydrogen atoms (*a*) as differently situated from the others (*b*).

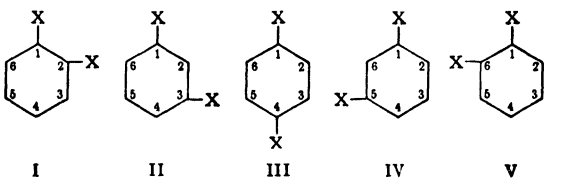
By the substitution of *two* univalent atoms or groups for two of the atoms of hydrogen in benzene, *three*, but not more than three, isomerides are obtained; there are, for example, three *dinitrobenzenes*, $C_6H_4(NO_2)_2$, three *dibromobenzenes*, $C_6H_4Br_2$, three *dihydroxybenzenes*, $C_6H_4(OH)_2$, three *nitrohydroxybenzenes*, $C_6H_4(NO_2) \cdot OH$, and so on.

Now the existence of the three isomerides can be easily accounted for with the aid of the closed chain structure given on p. 380, which, for this purpose, may conveniently be represented by a hexagon,

numbered as shown, the symbols C and H and the lines which are there drawn between them being omitted, for the sake of simplicity :



Suppose that any mono-substitution product, C_6H_5X, which, as already stated, exists in one form only, is converted into a di-substitution product, $C_6H_4X_2$; then if the position occupied by the atom or group X, which is first introduced, is numbered 1, the second atom or group may have substituted any one of the hydrogen atoms at 2, 3, 4, 5, or 6, giving a substance the constitution of which might be represented by one of the following five formulae : [1]



These five formulae, however, represent *three* isomeric substances, and three only. The formula (IV) represents a compound in which the several atoms occupy the same relative positions as in the substance represented by (II), and for the same reason the formula (V) is identical with (I). Although there is at first sight an apparent difference, a little consideration will show that this is simply due to the fact that the formulae are viewed from one point only ; if the formulae (IV) and (V) are written on thin paper and then viewed *through* the paper, it will be seen that they are identical with (II) and (I) respectively. Each of the formulae (I), (II), and (III), however, represents a different substance, because in no two cases are all the atoms in the same relative positions ; in other words, such *di-substitution products of benzene exist in three isomeric forms.*

In the foregoing examples the two substituent atoms or groups have been considered to be identical ; but even when they are different, experience has shown that only three di-substitution

[1] Strictly speaking, these are merely symbols, but are usually called formulae because they serve as substitutes for the latter.

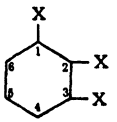
products can be obtained, and this fact, again, is explained by the accepted formula. When in the above five symbols a Y is written in the place of one X, to express a difference in the substituent groups, it will be seen that, as before, the formula (I) is identical with (V), and (II) with (IV), but that (I), (II), and (III) all represent different arrangements of the atoms—that is to say, three different substances.

These three isomerides of any di-substitution product of benzene are distinguished as follows: Those which have the constitution represented by the formula (I) are called **ortho**-compounds, and the substituent atoms or groups are said to be in the *ortho-* or 1:2-position to one another; those which may be represented by the formula (II) are termed **meta**-compounds, and the substituents are said to occupy the *meta-* or 1:3-position; the term, **para,** is applied to compounds represented by the formula (III), in which the atoms or groups are situated in the *para-* or 1:4-position.

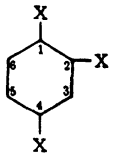
Ortho-compounds, then, are those in which it is concluded, for reasons given later (p. 395), that the two substituent atoms or groups are combined with carbon atoms, which are themselves *directly united*. Instead of the constitution of any *ortho*-compound being expressed by the formula (I), which represents the substituent atoms or groups as combined with the carbon atoms 1 and 2, the result would be just the same if the substituents were shown to be united with the carbon atoms 2 and 3, 3 and 4, 4 and 5, 5 and 6, or 6 and 1; all such arrangements would be identical because the benzene molecule is symmetrical, and the numbering of the carbon atoms simply a matter of convenience. In a similar manner the substituents in *meta*-compounds may be represented as combined with any two carbon atoms which are not themselves directly united, but linked together by one carbon atom; it is quite immaterial which two carbon atoms are chosen, since the 1:3-, 2:4-, 3:5-, 4:6-, and 5:1-positions are identical as regards their relation to all the other atoms of the molecule. For the same reason *para*-compounds may be represented by showing the substituents in the 1:4-, 2:5-, or 3:6-position.

When more than two atoms of hydrogen in benzene are displaced, it has been found that the number of isomerides varies according as the substituent atoms or groups are identical or not. By displacing *three* atoms of hydrogen by three *identical* atoms or groups, *three* isomerides can be obtained, three *trimethylbenzenes*, $C_6H_3(CH_3)_3$,

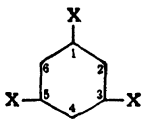
for example, being known. As before, the existence of these isomerides can be easily accounted for, since their constitutions may be represented as follows :



1:2:3 or Adjacent



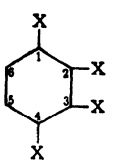
1:2:4 or Unsymmetrical



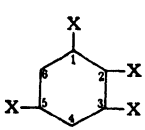
1:3:5 or Symmetrical

No matter in what other positions the substituents are placed, it will be found that the arrangement is the same as that represented by one of these three formulae ; the position 1:2:3, for example, is identical with 2:3:4, 3:4:5, etc. ; 1:3:4 with 2:4:5, 3:5:6, etc. ; and 1:3:5 with 2:4:6. For distinguishing such tri-substitution products without the use of numbers the terms given above are employed and the word *vicinal* is also often used instead of adjacent.

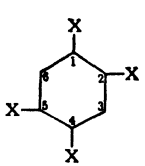
The tetra-substitution products of benzene, in which all the substituents are identical, also exist in three isomeric forms as shown below :



1:2:3:4



1:2:3:5



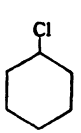
1:2:4:5

When, however, five or six atoms of hydrogen are displaced by identical atoms or groups, only one substance is produced.

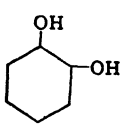
When more than two atoms of hydrogen are displaced by atoms or groups which are not all identical, the number of isomerides which can be obtained is very considerable. In the case of any tri-substitution product, $C_6H_3X_2Y$, for example, six isomerides might be formed, as may be easily seen by assigning a definite position, say 1, to Y ; the isomerides would then be represented by formulae in which the groups occupied the positions 1:2:3, 1:2:4, 1:2:5, 1:2:6, 1:3:4, or 1:3:5, all of which would be different (compare p. 399). In a similar manner the number of isomerides theoretically obtainable in the case of all benzene derivatives, however complex, may be deduced with the aid of the hexagon symbol.

All the cases of isomerism considered up to the present have been due to the different relative positions of the substituents combined with the benzene nucleus; as, however, many benzene derivatives contain groups of atoms, which themselves exhibit isomerism, such groups may give rise to isomerides comparable with those of the paraffins, alcohols, etc. There are, for example, two isomeric hydrocarbons, $C_6H_5 \cdot C_3H_7$, namely, *propylbenzene*, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH_3$, and iso*propylbenzene*, $C_6H_5 \cdot CH(CH_3)_2$, just as there are two isomerides of the composition, C_3H_7I. As, moreover, propyl- and *iso*propyl-benzene, $C_6H_5 \cdot C_3H_7$, are isomeric with the three (ortho-, meta-, and para-) *methylethylbenzenes*, $C_6H_4(C_2H_5) \cdot CH_3$, and also with the three (adjacent, symmetrical, and unsymmetrical) *trimethylbenzenes*, $C_6H_3(CH_3)_3$, there are in all eight hydrocarbons of the molecular formula, C_9H_{12}, derived from benzene.

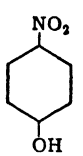
In studying the isomerism of benzene derivatives, the clearest impressions will be gained by making use of a simple, unnumbered hexagon to represent C_6H_6, and by expressing the constitutions of simple substitution products by formulae (or symbols), such as,



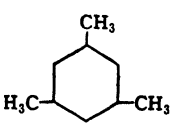
Chlorobenzene



Dihydroxybenzene



Nitrophenol



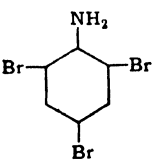
Trimethylbenzene

Omission of the symbols C and H is of little, if any, disadvantage, because, in order to convert the above into the ordinary molecular formulae, it is only necessary to write C_6 instead of the hexagon, and then to count the unoccupied corners of the hexagon to find the number of hydrogen atoms of the nucleus, the substituent atoms or groups being added afterwards. In the case of *chlorobenzene*, for example, there are five unoccupied corners, so that the molecular formula is C_6H_5Cl; in the case of *trimethylbenzene* there are three, and the formula, therefore, is $C_6H_3(CH_3)_3$.

For the distinction of isomeric di-derivatives instead of the terms *ortho-*, *meta-*, and *para-*, the letters *o*, *m*, and *p* respectively are used, as, for example, o-*dinitrobenzene*, m-*nitroaniline*, p-*nitrophenol*, and so on. The relative positions of the atoms or groups may also

be expressed by numbers; o-*chloronitrobenzene*, for example, is 1:2-*chloronitrobenzene*, or $C_6H_4<^{Cl\ (1)}_{NO_2(2)}$ or $C_6H_4\overset{1}{Cl}\cdot\overset{2}{NO_2}$, the corresponding *para*-compound is 1:4-*chloronitrobenzene*, $C_6H_4<^{Cl\ (1)}_{NO_2(4)}$ or $C_6H_4\overset{1}{Cl}\cdot\overset{4}{NO_2}$, and so on.

In the case of the tri-derivatives the terms symmetrical, unsymmetrical, and adjacent (or vicinal) are commonly employed when all the atoms or groups are the same, but when they are different the constitution of the compound is expressed with the aid of numbers; the *tribromoaniline* of the constitution,

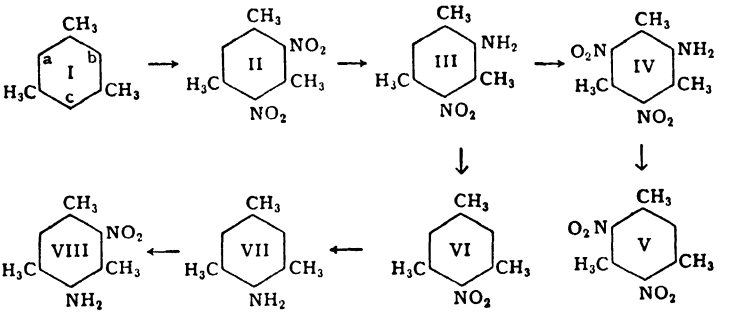


for example, is represented by $C_6H_2Br_3\cdot NH_2$ [$\overset{1}{NH_2}:\overset{2}{Br}:\overset{4}{Br}:\overset{6}{Br}$], or by $C_6H_2Br_3\cdot NH_2$ [NH_2:3Br = 1:2:4:6], but it is of course quite immaterial from which corner of the hexagon the numbering is commenced. This compound may also be called 2:4:6-tribromoaniline, which implies that the unnumbered amino-group occupies position 1.

As an illustration of the manner in which it has been proved that at least three of the hydrogen atoms in benzene are identically situated, the case of mesitylene (trimethylbenzene), investigated by Ladenburg, may be considered: Mesitylene, (I), was converted into dinitromesitylene, (II), which when partially reduced gave a nitromesidine, (III). This base (in the form of its acetyl derivative, p. 446), gave the nitro-compound, (IV), from which, by the displacement of the amino-group, there was obtained a dinitromesitylene, (V); this product was identical with (II), and therefore the hydrogen atoms *a* and *b* occupy identical positions in the molecule of mesitylene.

Starting from (III), the nitro-compound (VI) was obtained by substituting an atom of hydrogen for the amino-group, and then by reduction the base (VII) was prepared; this substance (as acetyl derivative) gave on nitration a nitroaminomesitylene, (VIII), which was identical with (III); the hydrogen atoms *b* and *c*, or *a* and *c*

(because the nitro-group may have displaced the atom *a* or *b*) are therefore identically situated. But since $a = b$, $a = b = c$. It is also proved by these results that mesitylene must be 1:3:5-trimethylbenzene, as already assumed.



These results may also be summarised as follows :—

	a	*b*	*c*		*a*	*b*	*c*
II	H	NO_2	NO_2	→ VI	H	H	NO_2
III	H	NH_2	NO_2	→ VII	H	H	NH_2
IV	NO_2	NH_2	NO_2		H	NO_2	NH_2
V	NO_2	H	NO_2	VIII {		or	
					NO_2	H	NH_2

II = V, $\therefore a = b$ VIII = III, $\therefore c = a$ or b

$\therefore a = b = c$.

Ladenburg also showed that four of the six hydrogen atoms in benzene are similarly situated. Phenol (hydroxybenzene), $C_6H_5 \cdot OH$, with the aid of phosphorus pentabromide, may be directly converted into bromobenzene, C_6H_5Br, and the latter may be transformed into benzoic acid (benzenecarboxylic acid), $C_6H_5 \cdot COOH$, with the aid of sodium and carbon dioxide ; as these three substances are produced from one another by simple reactions, there is every reason to suppose that the carboxyl group in benzoic acid is united with the same carbon atom as the bromine atom in bromobenzene and the hydroxyl group in phenol ; that is to say, that the same hydrogen atom (A) has been displaced in all three cases. Now three different hydroxybenzoic acids of the composition, $C_6H_4(OH) \cdot COOH$, are known, and these three compounds may be either converted into, or obtained from, benzoic

acid, $C_6H_5 \cdot COOH$, the difference between them being due to the fact that the hydroxyl group has displaced a different hydrogen atom (B, C, D) in each case. Each of these hydroxybenzoic acids forms a calcium salt which yields phenol when it is heated (the carboxyl group being displaced by hydrogen), and the three specimens of phenol thus produced are identical with the original phenol; it is evident, therefore, that at least four (A, B, C, D) hydrogen atoms in benzene occupy the same relative positions in the molecule. By analogous methods it can be shown that this is true of all six hydrogen atoms.

The main evidence that the molecule of benzene consists of a symmetrical closed chain of six CH groups as suggested by Kekulé may now be summarised as follows:

(1) Benzene behaves towards nitric and sulphuric acids and as a rule also towards halogens as a saturated compound, and not as if it had a structure similar to that of dipropargyl or other unsaturated hydrocarbon.

(2) Benzene is very stable and all its derivatives, containing more than six carbon atoms, can be converted by suitable means into substances containing only six carbon atoms. These six atoms, therefore, form a stable core or nucleus.

(3) It has been proved that all the six hydrogen atoms in benzene are identically situated.

(4) The results of the study of the isomerism of its substitution products accord completely with the view that the molecule of benzene consists of a closed chain of six carbon atoms, each of which is combined with an atom of hydrogen.

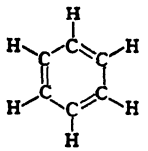
There is, however, one important point which has still to be discussed—namely, the best way of representing more fully the state of combination of the carbon atoms.

The structural formulae of organic compounds are based on the assumption that carbon is always quadrivalent,[1] but the hexagonal symbol (p. 380) shows only three valencies of each carbon atom, and the question remains how can the fourth one be so represented as to give the clearest indication of the structure of benzene?

Many chemists have attempted to answer this question, and several constitutional formulae for benzene have been put forward; that suggested by Kekulé, (1), was for a long time considered to be the

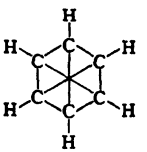
[1] In a relatively insignificant number of compounds carbon acts as a tervalent element, but such substances are unsaturated and usually unstable.

most satisfactory, but others, such as those of Claus, (II), and Ladenburg, (III), at one time received support:



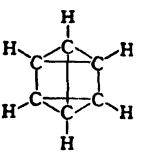
Kekulé

I



Claus
(Diagonal formula)

II



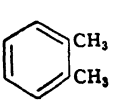
Ladenburg
(Prism formula)

III

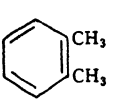
In Kekulé's formula, a double bond is drawn between alternate carbon atoms, which implies that their state of combination is the same as in ethylene and other olefines; in the formulae of Claus and Ladenburg, on the other hand, each carbon atom is represented as being directly united with three others, but with a different three in the two cases.

At the present time all debatable benzene formulae except Kekulé's have been discarded, after very careful consideration; but even that of Kekulé has been adversely criticised for two reasons:

(1) If the molecule contains alternate single and double links, every *o*-compound, such as *o*-xylene, might exist in two structurally isomeric forms, (IV) and (V); in (IV) the substituents are combined with carbon atoms which are themselves united by a single bond, but in (V) there is a double bond between the same two carbon atoms:



IV



V

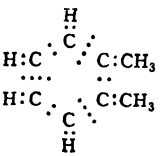
No such isomeric o-*derivatives have ever been obtained.*[1]

(2) Benzene behaves predominantly as a saturated hydrocarbon and shows, in a few cases only, the additive reactions which are indicated by the presence of double bonds in its molecule.

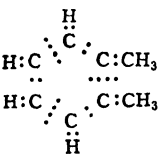
[1] *Meta*-derivatives, C_6H_4XY, and many other benzene substitution products might also show a similar isomerism which, however, has never been observed.

Both these objections to Kekulé's formula were countered by the suggestion that the positions of the double bonds in the molecule are not fixed but undergo a rapid and continuous oscillation or interconversion ; if so it would be impossible to distinguish between (IV) and (V), and the molecule would not contain ordinary ethylenic bonds.

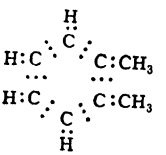
This view may be considered more fully and for this purpose the electronic formulae (VI) and (VII) are used as it may then be easier perhaps to picture the postulated interconversion :



VI



VII



VIII

Thus, it is obvious that, by a redistribution of electrons, (VI) could change into (VII), and by a corresponding transformation in the reverse direction (VII) would again become (VI).

But suppose that during these changes the process of electronic redistribution is suddenly stopped and fixed at a stage halfway to its completion (just as a pendulum might be arrested at the lowest point in its swing), and that something of this sort actually occurs to the electrons of *o*-xylene, (VI) and (VII) ; the result would be a new type of structure, which might be indicated by (VIII). In such a molecule there would be no single (two electrons) or double (four electrons) bonds and no isomeric *o*-xylenes, but all the carbon atoms would be united by some type of bond of an intermediate character ; such a molecule, moreover, might well—as does *o*-xylene —fail to show the ordinary reactions of an olefinic compound. That changes in the distribution of the electrons of a molecule may actually occur, with results such as those crudely indicated above, is now generally accepted in the theory of resonance (about 1931) of which a brief outline follows.

Theory of Resonance

The molecules of many organic compounds can be represented by two (or more) structural or electronic formulae both (or all) of

which accord with the ordinary valency rules. It can be shown mathematically, however, that such molecules would have a greater stability (less energy) if their electronic structures were actually a sort of mean or average of those of the theoretically possible forms. A compound (e.g. xylene) in the molecule of which such a redistribution of electrons is possible is said to show *resonance*; in its most stable condition, it is said to exist in the *mesomeric* state (Ingold). The two or more structures (e.g. IV and V or VI and VII) for which the mesomeric state is substituted may be termed resonating structures, *resonators* or *contributors* to the mesomeric state. In all such resonating molecules the positions of the atoms must be very nearly the same in both (or all) contributors, so that there would be little change in energy in passing from one to the other.

In the case of a compound to which can be assigned two electronic formulae only, of identical stability (compare benzene, p. 392), the electronic distribution in the mesomeric state is *exactly* intermediate between those of its contributors. In other cases (e.g. o-xylene) it approximates more closely to that of the more stable form; the various structures are then said to contribute unequally to the mesomeric state according to their stabilities.

The properties of a compound in the mesomeric state are, broadly, a mean or average of those of its contributors, but the characteristics of the more, or most, stable of these may predominate and the increased stability due to resonance may suppress some of the reactions which might otherwise have seemed probable from the structures of the contributors.

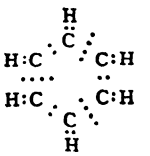
The most important result of resonance, and indeed the reason of its occurrence, is that the molecule has less energy in the mesomeric state than in any other possible condition. The estimated loss of energy is known as the *resonance* energy.[1]

Now the Kekulé molecule of benzene, and that of xylene, fulfil the above conditions of resonance, and both may exist in the mesomeric state.

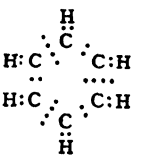
There is, however, a difference between the resonance of benzene and that of xylene. A redistribution of the benzene electrons in (IX), similar to that assumed in the case of *o*-xylene, would give (X); and

[1] The heat of combustion of benzene (per gram molecule) is 39,000 cal. less than that calculated for the Kekulé formula; this, therefore, is the resonance energy of benzene.

although at first sight these two formulae may seem to be different, they are in fact identical, since either may be superposed on the other. Nevertheless, if models were used, with which such a redistribution could be demonstrated, it would be seen that a *change* in structure occurs during the passage of (IX) into (X), or *vice versa*. The two identical structures, (IX) and (X), may consequently be regarded as two *exactly* equal contributors to the mesomeric state.[1]



IX



X

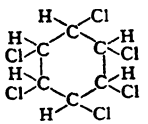
Such is a very rough outline of the present view of the structure of benzene. It is assumed that the mesomeric molecule contains neither single nor double bonds of the usual kind ; all the carbon to carbon bonds are identical and of a new type and the molecule cannot be represented by a conventional formula, electronic or otherwise. This is not surprising ; what is remarkable is the fact that the formulae hitherto used, based on such simple conventions, fulfil their purpose so well. The representation of planetary electrons by fixed dots is obviously an unsatisfactory makeshift ; moreover, in the mesomeric state the electrons may not be definitely shared by the atoms at the extremities of a bond but may be free to roam over many atoms of the molecule.

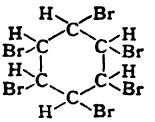
Until, therefore, the resonance structure of benzene has been more firmly established and can be satisfactorily expressed, Kekulé's formula will be used, but it must always be borne in mind that the hydrocarbon and its derivatives do not show many of the additive reactions associated with the representation of double bonds.

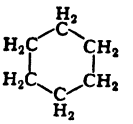
The resonance theory is not, of course, restricted to the hydrocarbons mentioned above, but is generally applicable, not only to benzenoid (p. 400), but also to various types of aliphatic compounds ; other examples of its use are given later (pp. 438, 517).

[1] The mesomeric form is often referred to as a *hybrid*. Apart from its association with the somewhat derogatory 'mongrel,' the word hybrid seems to be unsuitable, especially in those cases in which the parents (contributors) are identical molecules.

Additive Products of Benzene. As already stated (p. 378) benzene combines directly with chlorine or bromine in bright sunlight, giving benzene hexachloride, $C_6H_6Cl_6$, or hexabromide, $C_6H_6Br_6$; it also unites with molecular hydrogen in the presence of nickel and gives hexahydrobenzene.







If, during such reactions, the mesomeric benzene molecule first passes into the Kekulé structure, it might seem possible to limit the additive process and to obtain a *di-* and then a *tetra*-additive product; so far this does not seem to have been done, possibly because such intermediate compounds would be olefinic and rapidly change into fully saturated substances. In numerous cases, however, di- and tetra-additive products of benzene *derivatives* have been prepared and found to undergo the ordinary olefinic reactions (Part III).

CHAPTER 24

THE ORIENTATION OF BENZENE DERIVATIVES AND GENERAL PROPERTIES OF AROMATIC COMPOUNDS

Orientation of Benzene Derivatives

SINCE the di- and other substitution products of benzene exist in isomeric forms, it is now necessary to consider how the constitution of any such derivative is established ; that is to say, how the relative positions of the nuclear substituents are ascertained ; this process is known as *orientation.*

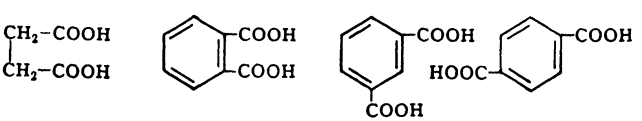
Now the methods which are adopted in the orientation of *di*-substitution products at the present time are comparatively simple, but they are based on the results of work which has extended over many years. One of the more important results of such work has been to prove that a given di-substitution product of benzene may be converted by more or less direct methods into many of the other di-substitution products of the *same type.* Ortho-*dinitrobenzene*, $C_6H_4(NO_2)_2$, for example, may be transformed into o-*diamino-benzene*, $C_6H_4(NH_2)_2$, o-*dihydroxybenzene*, $C_6H_4(OH)_2$, o-*dibromo-benzene*, $C_6H_4Br_2$, o-*dimethylbenzene*, $C_6H_4(CH_3)_2$, and so on ; corresponding changes also take place with *meta-* and *para*-compounds. If, therefore, it can be found to which type a given di-substitution product belongs, the orientation of other di-substitution products, which may be derived from, or converted into, this compound, are thereby determined. There are, for example, three *dinitrobenzenes*, melting at 90°, 118°, and 173° respectively ; now if it could be proved that the compound melting at 90° is a *meta*-derivative, then it might be concluded that the diamino-, dihydroxy-, dibromo-, and other di-derivatives of benzene, obtained from this particular dinitro-compound by substituting other atoms or groups for the two nitro-groups, must also be *meta*-compounds ; it would also be known that the di-derivatives of benzene obtained from the other two dinitrobenzenes, melting at 118° and 173° respectively, in a similar manner, are either *ortho-* or *para*-compounds as the case may be.

In a few reactions, particularly in those which take place at a high temperature, the initial product may undergo a subsequent

change ; an *ortho-* or *para*-compound, for example, may be transformed into a *meta*-derivative (compare p. 480), but such behaviour is exceptional.

Obviously, then, it is necessary, in the first place, to orientate or determine the constitutions of those di-derivatives, which are afterwards to be used as standards.

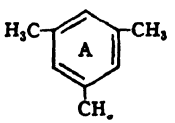
As an illustration of the methods and arguments originally employed in the solution of problems of this nature, the cases of the dicarboxy- and dimethyl-derivatives of benzene may be considered. Of the three benzenedicarboxylic acids, $C_6H_4(COOH)_2$, one—namely, *phthalic acid* (p. 520)—is very readily converted into its anhydride, but all attempts to prepare the anhydrides of the other two acids (iso*phthalic acid* and *terephthalic acid*, p. 522) have been unsuccessful. It is assumed, therefore, that the acid which gives the anhydride is the *o*-compound, because, from a study of the behaviour of many other dicarboxylic acids of *known* structure, it has been found that anhydride formation takes place most readily when the two carboxyl groups are severally combined with two carbon atoms, which are themselves directly united, as, for example, in the case of succinic acid. Thus, if the graphic formulae of succinic acid and of the three isomeric benzenedicarboxylic acids are compared, it will be evident that the relative positions of the two carboxyl groups in the *o*-compound seem to be the same as in succinic acid, but this is quite otherwise in the case of the *m*- and *p*-compounds :



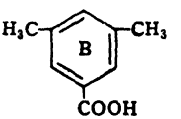
For this reason, phthalic acid may be provisionally regarded as *ortho*-benzenedicarboxylic acid.

Again, the hydrocarbon, *mesitylene*, one of the three *trimethylbenzenes*, may be produced synthetically from acetone (p. 401), and its formation in this way can be explained in a simple manner, only on the assumption that mesitylene is the *symmetrical* trimethylbenzene of the constitution, (A, p. 396). When this hydrocarbon is carefully oxidised, it yields an acid, (B), of the composition, $C_6H_3(CH_3)_2 \cdot COOH$ (by the conversion of one of the methyl groups into carboxyl), from which a *dimethylbenzene*, $C_6H_4(CH_3)_2$, (C), is easily obtained by heating the acid with soda-lime. This

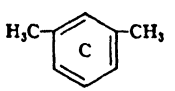
dimethylbenzene, therefore, is a *meta*-compound, because no matter which of the original three methyl groups in mesitylene has been finally displaced by hydrogen, the remaining two must occupy the *m*-position. Now when this *m*-dimethyl-benzene is oxidised with chromic acid, it is converted into a dicarboxylic acid, (D)—namely, iso*phthalic acid*, $C_6H_4(COOH)_2$—which, there-



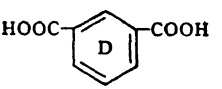
Mesitylene



Mesitylenic acid



Dimethylbenzene
(*m*-Xylene)



*Iso*phthalic acid

fore, must also be regarded as a *meta*-compound. The constitutions of two of the three isomeric dicarboxy-derivatives of benzene having been thus determined, that of the third—namely, *terephthalic acid*, the *para*-compound—is also settled.

The three dicarboxylic acids having been orientated, it is a comparatively simple matter to determine the structures of the three dimethylbenzenes ; as one of them is already known to be the *meta*-compound, all that is necessary is to submit each of the other two to oxidation, and that which gives phthalic acid is the *ortho*-compound, whilst that which yields terephthalic acid is the *para*-derivative. Moreover, the orientation of any other di-substitution product of benzene may now be accomplished, provided that it is possible to convert the compound into one of these standards by simple substitutions. If, for example, directly, or indirectly, the following substitutions could be carried out,

$$C_6H_4(NO_2)_2 \longrightarrow C_6H_4(NH_2)_2 \longrightarrow C_6H_4(OH)_2 \longrightarrow C_6H_4Br_2 \longrightarrow C_6H_4(CH_3)_2,$$

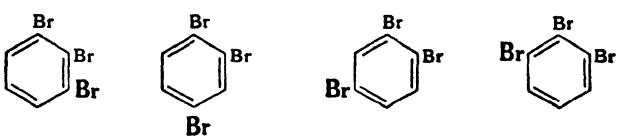
and the final product is proved to be *para*-dimethylbenzene, *all* the compounds concerned must also be classed as *para*-derivatives of benzene, unless there is convincing evidence to the contrary.

As the methods of orientation which have just been indicated are based principally on arguments drawn from analogy, or deductions as to the probable course of a given reaction, the conclusions to

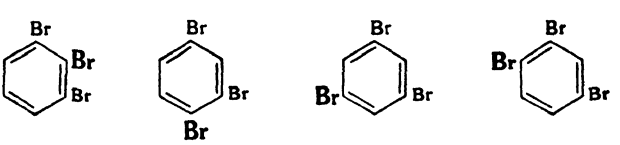
which they lead cannot be accepted without reserve ; there are, however, other ways in which it is possible to distinguish between *ortho*-, *meta*-, and *para*-compounds, without making any assumptions, and, of these, that employed by Körner in 1874 is the most important.

Körner's method for the orientation of di-substitution products of benzene is based on the fact that when any benzene derivative, $C_6H_4X_2$, is converted into a tri-derivative by the further displacement of hydrogen of the nucleus, the number of isomerides which may be obtained from an *ortho*-, *meta*-, or *para*-compound is different in all three cases ; if, therefore, the number of these products can be ascertained, the constitution or orientation of the original di-derivative is established.

Thus, during the investigation of the *dibromobenzenes*, $C_6H_4Br_2$, three isomerides, melting at +7°, −7°, and 87° respectively, were discovered and for their orientation each of these isomerides is separately converted into a *tribromobenzene*, $C_6H_3Br_2 \cdot Br$; then, from the *ortho*-dibromo-compound, it is possible to obtain *two*, but only two, tribromobenzenes, because, although there are four hydrogen atoms, any one of which may be displaced, the third formula shown below is identical with the second, and the fourth with the first, the relative positions of all the atoms being the same in the two cases respectively : [1]

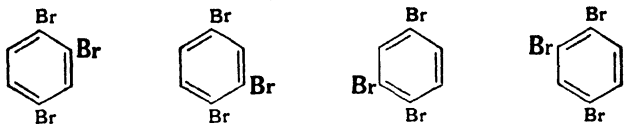


If, however, the dibromobenzene is the *meta*-compound, it might yield *three*, but only three, isomeric tri-derivatives, which would be represented by the first three of the following formulae, the fourth being identical with the second :



[1] It is of course immaterial from which corner of the hexagon the numbering starts.

Finally, if the substance is *para*-dibromobenzene, it could give *one* tri-derivative only, as the following four formulae are identical, and represent the 1:2:4-derivative :



Experiments showed that the dibromobenzene melting at +7° gave *two* tribromobenzenes (m.p. 44° and 88° respectively); it is, therefore, the *ortho*-compound. The isomeride melting at −7° gave *three* such derivatives (m.p. 44°, 88°, and 120° respectively), and is thus proved to be the *meta*-compound ; the isomeride melting at 87° gave only *one* (m.p. 44°), and, therefore, is the *para*-compound. Obviously this method may be applied in the case of *any* di-substitution product, $C_6H_4X_2$, provided that the derivatives, $C_6H_3X_2Y$ (Y may or may not be identical with X), can be separated and analysed.

At the present time, the orientation of any new di-derivative of benzene is usually an easy task, because the new substance may be converted into one or other of the many compounds of known constitution by simple substitutions.

From the account of Körner's method given above it will be seen that *one* of the three isomeric tribromobenzenes (m.p. 44°) is obtained from the *ortho*-, the *meta*- and the *para*-di-derivative ; this particular compound must be the 1:2:4-tribromo-derivative, which therefore has itself been orientated. The second compound (m.p. 88°) formed from *o*-dibromobenzene is therefore the 1:2:3-tri-derivative, which is identical with one of the compounds obtained from *m*-dibromobenzene ; the remaining tribromobenzene (m.p. 120°), obtained together with the 1:2:3- and the 1:2:4-compounds from *m*-dibromobenzene must be the 1:3:5-tri-substitution product. These three compounds might then serve for the orientation of other tri-derivatives of benzene, $C_6H_3X_3$, which might be obtained from them by the direct displacement of their bromine atoms.

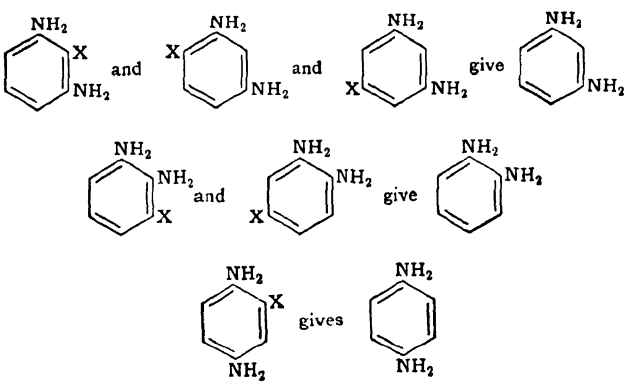
Körner did not actually prepare the tri- from the di-bromo-derivatives directly ; he first converted the latter separately into their nitro-substitution products, $C_6H_3Br_2 \cdot NO_2$,[1] isolated the

[1] These compounds crystallise readily and are more easily separated from one another than the tribromo-derivatives.

various isomerides formed from each, and then displaced the nitro-group by bromine by the usual methods. In this way, therefore, the orientation of the *six* isomeric *nitrodibromobenzenes*, and the *six* isomeric *aminodibromobenzenes*, obtained from them by reduction, was also accomplished.

Although simple in theory, the experimental difficulties of Körner's method are very considerable partly owing to the directing influence of the substituents already present. Thus, although theoretically any *meta*-compound, for example, should yield three tri-derivatives, one or two of these may be formed in such small quantities, if at all, that their isolation and identification may be a very difficult task.

The converse of Körner's method was used by Griess, who heated each of the six known diaminobenzoic acids with lime: the phenylenediamine obtained from three of these acids is clearly the *meta*-compound, that formed from two of the acids only is the *ortho*-base, and that obtained from one acid only is the *para*-derivative (X = COOH):



General Properties of Aromatic Compounds

The examples given in the foregoing pages will have afforded some indication of the large number of compounds, which it is possible to prepare from benzene, by the substitution of various elements or groups for atoms of hydrogen. As the substances formed in this way, and many other benzene derivatives, which occur in nature, are obtained from coal-tar, or may be prepared synthetically, retain to a greater or less extent the characteristic chemical behaviour of benzene, and differ in many respects from

the paraffins, alcohols, acids, and all other compounds previously described (Part I), it is convenient to consider benzene and its derivatives separately.

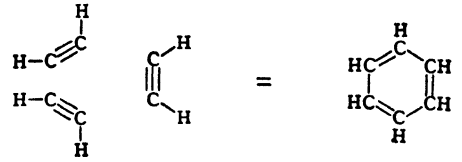
Classification of Organic Compounds.—Organic compounds, therefore, are classed in two principal divisions, the **fatty** or **aliphatic** (Gr. *aleiphar*, fat) and the **aromatic.** The word 'fatty,' originally applied to some of the higher fat-like acids of the $C_nH_{2n}O_n$ series, is now used to denote all compounds which may be considered as derivatives of methane; all those described in Part I belong to the fatty or *aliphatic* division or series. Benzene, its derivatives, and related compounds, are classed as *aromatic*, a term first applied to certain naturally occurring compounds (which were afterwards proved to be benzene derivatives) on account of their notable aromatic odour.

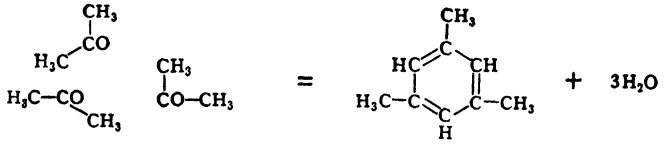
The fundamental distinction between aliphatic and aromatic compounds is one of *structure.* All derivatives of benzene, and all other compounds which contain a *closed chain* or nucleus *similar to* that of benzene, are classed as aromatic or *benzenoid.* Aliphatic compounds, on the other hand, such as $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_3$, $CH_2(OH) \cdot CH(OH) \cdot CH_2(OH)$, and $COOH \cdot CH_2 \cdot CH_2 \cdot COOH$, do not contain a closed chain, but an *open chain*[1] of carbon atoms; all such compounds, moreover, may be regarded as derived from methane by a series of simple steps.

It must not be supposed, however, that all aromatic compounds are sharply distinguished from all aliphatic or fatty substances, or that either class can be defined in very exact terms. The mere fact that the constitution of a substance must be represented by a closed chain formula does not make it an aromatic compound; succinimide, for example, although it is a closed chain compound, is clearly a member of the aliphatic series, because of its relationship to succinic acid, into which it is very easily converted. Although, again, the members of the aromatic group may all be regarded as derivatives of benzene, this hydrocarbon and many other aromatic compounds may be directly obtained from members of the fatty series by simple reactions; conversely, many aromatic compounds may be converted into those of the aliphatic series.

[1] The term *open chain* corresponds with the chain-like appearance of the structural formulae as usually written, and is not intended to convey any idea of the arrangement of the atoms in space (compare p. 45); when the carbon atoms at the ends of an open chain are united a *closed chain* or ring compound results.

Some examples of the production of aromatic, from aliphatic, compounds have already been given—namely, the formation of benzene by the polymerisation of acetylene, and that of mesitylene by the condensation of acetone; these two changes may be expressed graphically in the following manner,





and may be regarded as typical reactions, because many other substances, similar in constitution to acetylene and acetone respectively, may be caused to undergo analogous transformations.

Bromoacetylene, CBr:CH, for example, is converted into symmetrical tribromobenzene when it is exposed to direct sunlight,

$$3C_2HBr = C_6H_3Br_3;$$

and methylethyl ketone is transformed into symmetrical triethylbenzene when it is distilled with sulphuric acid,

$$3CH_3 \cdot CO \cdot C_2H_5 = C_6H_3(C_2H_5)_3 + 3H_2O.$$

The acetylene synthesis has been used for making '*heavy*' benzene (*hexadeuterobenzene*), C_6D_6, from C_2D_2.

As examples of the conversion of aromatic into aliphatic compounds the following may be given: Benzene, treated with a mixture of sulphuric acid and potassium chlorate, gives *trichloroacetylacrylic acid*, $CCl_3 \cdot CO \cdot CH{:}CH \cdot COOH$, and in the presence of vanadium pentoxide, it can be directly oxidised by free oxygen to maleic acid, from which malic acid can be prepared. Benzene combines directly with ozone (3 mol.) and the product is decomposed by water giving glyoxal. Phenol, with hydrogen, in the presence of nickel (p. 404) gives cyclo*hexanol*, $C_6H_{11} \cdot OH$, which on oxidation is converted, first into cyclo*hexanone*, $C_6H_{10}O$, and then into adipic acid, $COOH \cdot [CH_2]_4 \cdot COOH$.

It is also possible to convert a few aromatic into aliphatic compounds by direct reduction ; salicylic acid (p. 533), for example, is thus transformed into pimelic acid.

General Character of Aromatic Compounds. Although it is impossible to class all organic compounds as either aliphatic or aromatic, because many substances are known which form connecting links between the two groups (p. 585), those which are benzenoid differ materially from those of the aliphatic division in constitution, and consequently also in properties.

In general, aromatic compounds contain a larger percentage of carbon than do those of the aliphatic series and are usually crystalline at ordinary temperatures.

Unlike aliphatic compounds, which are very rarely coloured, many aromatic substances, especially those which contain nitrogen, have a more or less intense colour and some may be used as dyestuffs.[1] They are, as a rule, less readily resolved into simpler substances than are the members of the aliphatic series (except the very stable paraffins), although in most cases they are more easily converted into substitution products.

Aromatic compounds give substitution products with (1) *halogens*, (2) *nitric acid*, (3) *sulphuric acid* :

$$C_6H_6+Cl_2 = C_6H_5Cl+HCl,$$
$$C_6H_6+HNO_3 = C_6H_5\cdot NO_2+H_2O,$$
$$C_6H_6+H_2SO_4 = C_6H_5\cdot SO_3H+H_2O.$$

Their behaviour with nitric acid and with sulphuric acid is particularly characteristic, and distinguishes them from nearly all fatty compounds ; with concentrated nitric acid, as a rule, they readily give *nitro*-derivatives, and with concentrated sulphuric acid they give *sulphonic acids*.

Aliphatic compounds rarely give nitro- or sulphonic-derivatives under such conditions, but are oxidised and resolved into two or more substances.

The readiness with which the hydrogen atoms of the nucleus are displaced by halogen, nitro- or sulphonic groups varies very greatly; benzene itself is not very reactive, but when one hydrogen atom of the nucleus has been displaced by particular groups, further substitution often occurs with very great facility. Although halogens,

[1] Failing a statement to the contrary, however, it may be inferred that a compound is colourless.

nitric acid and sulphuric acid, are the main reagents by which aromatic compounds are directly changed, it is possible by indirect methods to displace the hydrogen atoms of the nucleus by many other groups such as HO—, NH_2—, OCH—, etc., as will be shown later.

When aromatic nitro-compounds are suitably reduced, they are converted into *amino*-compounds,

$$C_6H_5 \cdot NO_2 + 6H = C_6H_5 \cdot NH_2 + 2H_2O,$$
$$C_6H_4(NO_2)_2 + 12H = C_6H_4(NH_2)_2 + 4H_2O.$$

These amino-derivatives differ from the aliphatic amines in at least one very important respect, inasmuch as they are converted into *diazonium* compounds (p. 454) on treatment with a nitrite and a dilute acid in the cold ; this behaviour is highly characteristic, and the diazonium compounds form one of the more interesting and important classes of aromatic substances.

When the hydrogen atoms in benzene are displaced by groups or radicals which are composed of several atoms, these groups are often spoken of as **side chains:** the aliphatic groups in *ethylbenzene*, $C_6H_5 \cdot CH_2 \cdot CH_3$, *benzyl alcohol*, $C_6H_5 \cdot CH_2 \cdot OH$, and *methylaniline*, $C_6H_5 \cdot NH \cdot CH_3$, for example, would be called side chains, whereas the term, as a rule, would not be used in the case of *phenol*, $C_6H_5 \cdot OH$, *nitrobenzene*, $C_6H_5 \cdot NO_2$, etc., where the substituent groups are comparatively simple, and do not contain carbon atoms.

Now the behaviour of any particular atom or group in an aliphatic side chain, although influenced to some extent by the fact that the side chain is united with the benzene nucleus, is on the whole very similar to that which this atom or group shows in aliphatic compounds. The consequence is that aromatic compounds, containing side chains of this kind, have not only the properties characteristic of benzenoid compounds, but show also, to a certain extent, the behaviour of aliphatic substances. *Benzyl chloride*, $C_6H_5 \cdot CH_2Cl$, for example, may be directly converted into the nitro-derivative, $C_6H_4(NO_2) \cdot CH_2Cl$, and the sulphonic acid, $C_6H_4(SO_3H) \cdot CH_2Cl$, reactions characteristic of aromatic compounds. In addition, the —CH_2Cl group may be transformed into —$CH_2 \cdot OH$, —CHO, —COOH, and so on, just as may the —CH_2Cl group in ethyl chloride, and in all cases the products retain certain characteristics of aliphatic substances so long as the side chain remains. The

carbon atoms of the side chains, moreover, can be attacked and separated from the rest of the molecule, leaving the closed chain or nucleus intact; when *ethylbenzene*, $C_6H_5 \cdot CH_2 \cdot CH_3$, or *propylbenzene*, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH_3$, for example, is boiled with chromic acid, the side chain undergoes oxidation, and benzoic acid, $C_6H_5 \cdot COOH$, is produced in each case; from this acid benzene may be easily obtained, the carbon atoms of the nucleus remaining unchanged during these transformations.

In addition to the numerous compounds derived from benzene by direct substitution, the aromatic group also includes a great many other substances, which are more distantly related to benzene, and which can only be regarded as derived from it indirectly. The hydrocarbon *diphenyl*, $C_6H_5—C_6H_5$, for example, which is formed by the union of two *phenyl* or $C_6H_5—$ groups, just as dimethyl or ethane, $CH_3—CH_3$, is produced by the combination of two methyl groups, is an important member of the aromatic division, and, like benzene, is capable of yielding a very large number of derivatives. Other hydrocarbons are known which contain two or more closed carbon chains, similar to that of benzene, combined in different ways; as, for example, naphthalene (p. 538) and anthracene (p. 557). There are also substances, such as pyridine (p. 568) and quinoline (p. 577), in which a nitrogen atom occupies the position of one of the CH groups of the aromatic nucleus.

All these, and many other related types of compounds, are classed as aromatic, or benzenoid, because they show the general behaviour already described and resemble benzene more or less closely in constitution.

The Reduction of Aromatic Compounds

It has already been pointed out that benzene does not show the ordinary behaviour of unsaturated aliphatic compounds, but that, under certain conditions, it forms additive compounds by direct combination with atoms of chlorine or bromine. This fact proves that benzene is not really a saturated compound, like methane or ethane, for example, both of which are quite incapable of yielding derivatives except by substitution. Nevertheless, as a rule, the conversion of benzene and its derivatives into additive products is much less readily accomplished than is that of unsaturated aliphatic compounds; the halogen acids, for example, which unite directly

with many unsaturated aliphatic compounds, have no such action on benzene and its derivatives, and even in the case of the halogens, direct combination occurs only under particular conditions.

For these reasons, although benzene was discovered in 1825, very few additive compounds prepared directly from the hydrocarbon or its derivatives were known until a very much later date. In addition to the halogen additive products already mentioned (p. 393) *hexahydrobenzene*, C_6H_{12} (now called cyclo*hexane*), had been obtained in small quantities in an impure condition by heating benzene with hydriodic acid at a high temperature (Berthelot), but no satisfactory method for the reduction of the hydrocarbon or of its homologues had been discovered.

The investigations of Sabatier and Senderens (1897–1905) completely altered this situation. These chemists showed that in the presence of certain metals, more especially nickel, *in a particular state* (p. 407), many types of aliphatic compounds combine with hydrogen under suitable conditions; the only noteworthy exceptions are the paraffins, their ethers, their amino- and hydroxy-derivatives, and their carboxylic acids. In some cases, as, for example, in that of acetylene, it is only necessary to pass the mixture of the two gases over suitably prepared nickel at ordinary temperatures: a reaction then takes place with the development of heat, and in the presence of a sufficiently large excess of hydrogen, ethane is practically the only product. As a rule, however, a mixture of the vapour of the organic compound and hydrogen is passed over a layer of the catalyst, which is heated at a suitable temperature, usually in the neighbourhood of 130–200°. For each particular reaction there is an optimum temperature which is found experimentally, and unless the conditions are suitably chosen, the reaction may take a course quite different from that which is expected or desired.

Under suitable conditions, ethylene can be reduced quantitatively to ethane, and other olefines to the corresponding paraffins. Unsaturated alcohols, such as allyl alcohol, unsaturated esters, such as ethyl acrylate, and unsaturated acids, such as crotonic acid, can be similarly transformed into the corresponding saturated compounds. Other types of aliphatic compounds are likewise reduced; nitriles, for example, give primary, and carbylamines give secondary amines. Aldehydes and ketones are converted into the corresponding primary or secondary alcohols, and in the latter case the products

are as a rule free from pinacols. Olefinic aldehydes and ketones are generally first reduced to the corresponding paraffin derivatives, which may then be further converted into the saturated primary or secondary alcohols.

In the course of time Sabatier's discovery of the catalytic action of nickel was applied to the hardening of oils, a process in which the unsaturated acids, contained as glycerides in natural fats and oils, are converted into saturated compounds.

In other investigations it was shown that benzene combines readily with hydrogen in the presence of the nickel catalyst, and is easily transformed into cyclo*hexane*; also that the homologues of benzene and many other types of aromatic compounds can be converted into their hexahydro-derivatives in a similar manner. This discovery made it possible to prepare, not only in the laboratory, but on a large scale, many compounds which, previously, were rarely encountered in the study of organic chemistry, and which formed a connecting link between the aromatic and the open chain aliphatic compounds; such reduction products which still contain a closed chain of six carbon atoms are derivatives of cyclo*hexane*, and belong to the class of *cyclo*paraffins.

Homologues of benzene, hydrocarbons such as naphthalene (p. 538) and anthracene, and other *benzenoid* compounds, can be reduced in a similar manner, and in these cases it is often possible to isolate more than one reduction product; thus from naphthalene either the *tetrahydro*-derivative, $C_{10}H_{12}$, or the *decahydro*-derivative, $C_{10}H_{18}$ (p. 546), can be prepared, according to the temperature employed.

The monohydroxy- and monoamino-substitution products of benzene and its homologues, which are described later, are reduced to the corresponding *cyclo*hexane-derivatives; but the bases may be partly transformed into the cyclic hydrocarbons with the formation of ammonia, and other secondary reactions may also take place to a considerable extent. Aromatic carboxylic acids cannot be easily reduced by this method, but the esters of the monocarboxylic acids combine readily with hydrogen, and the products, on hydrolysis, give the corresponding *cyclo*hexanecarboxylic acids.

An aromatic compound, in the molecule of which there is an unsaturated side chain, may undergo reduction in various stages. Styrene, for example (p. 419), may be reduced first to ethylbenzene (at 300°), and then to ethyl*cyclo*hexane (at 180°). Similarly benz-

aldehyde (p. 499) and acetophenone (p. 505) may be reduced first to the corresponding aromatic hydrocarbons (toluene and ethylbenzene respectively), and then, by lowering the temperature, to the corresponding *cyclo*paraffins.

When nickel is used and the temperature is raised above about 250°, the reduction of benzene becomes less complete, and ceases at about 300° ; above this temperature, in the presence of the nickel catalyst, *cyclo*hexane decomposes into benzene and hydrogen,[1] and a portion of the hydrocarbon is reduced to methane.

The nickel used in the above described reactions is obtained by dissolving the metal in nitric acid (free from halogen compounds), igniting the nitrate at a dull red heat until decomposition is complete, and then reducing the oxide in a stream of pure hydrogen at a temperature of about 300°. Another method is to agitate pumice (crushed to pieces of a suitable size) with a paste of thoroughly washed, precipitated nickel hydroxide, and then to heat the dried material in a stream of pure hydrogen until the oxide is partially or completely reduced.

The metal thus obtained varies in colour from light brown to black ; it is frequently pyrophoric, and in any case is readily oxidised on exposure to the air ; for this reason the reduction of the oxide is carried out in the tube, which is to be used later in the reduction of the organic compound.

It is of the greatest importance that the hydrogen used in the preparation of the catalyst, and for the reduction of the organic compound, should be pure, or at any rate free from even traces of halogen, sulphur, arsenic, and phosphorus compounds, many of which poison the catalyst and render it useless. Even with pure hydrogen, the presence of traces of such impurities may entirely prevent reduction ; thus, benzene containing traces of thiophene (p. 587) cannot be reduced, although the presence of a considerable proportion of carbon disulphide does not prevent the conversion of the hydrocarbon into *cyclo*hexane.

Hydrogen from a cylinder or generated from zinc and diluted, pure hydrochloric acid may be purified by passing it through alkaline permanganate, then through a tube containing copper at a dull red heat, and finally through tubes containing moistened alkali ; it is not essential to free the gas from water vapour.

The catalyst may be prepared and used in an ordinary combustion tube, partly immersed in a layer of sand contained in an

[1] A reaction of this nature, in which hydrogen is eliminated, is an example of *dehydrogenation*.

iron gutter; one or two thermometers, with their bulbs in the sand, are also usually employed. If the substance to be reduced is sufficiently volatile, it may be placed in a distillation flask heated at a suitable temperature, and there vaporised in the stream of hydrogen; if not, it may be dropped from a separating-funnel into the vertical limb of a T-piece, the hydrogen being passed through the horizontal portion. In the latter case, if the liquid is not completely vaporised before it enters the combustion tube, the exit end of the T-piece is lengthened sufficiently to allow any liquid to drop into a porcelain boat, placed in the combustion tube and heated at a suitable temperature; if the catalyst gets soaked by the liquid its efficiency may be seriously diminished. Readily volatile solids of low melting-point can be treated as liquids, but those of high melting-point or of low volatility are heated in a porcelain boat placed near the inlet of the hydrogen.

In 1927 a new very active form of nickel catalyst was introduced by Raney; it is prepared by fusing a mixture of about equal parts of aluminium and nickel at 1200–1500° and treating the resulting alloy with alkali to remove the aluminium. The nickel must then be preserved under an organic liquid as it is pyrophoric. *Raney nickel* is very much more active than other forms of the metal and reduction can be carried out at a lower temperature in the liquid state or in solution in a suitable solvent; acetone and oximes, for example, are reduced at room temperature. Sugars may be reduced to polyhydric alcohols. Aromatic compounds are usually reduced at 120–175° under 100 atmospheres pressure.

CHAPTER 25

HOMOLOGUES OF BENZENE AND RELATED HYDROCARBONS

BENZENE, the simplest aromatic hydrocarbon, is also the first member of a homologous series of the general formula, C_nH_{2n-6}; the hydrocarbons of this series are derived from benzene by the substitution of alkyl groups for hydrogen atoms, just as the homologous series of paraffins is derived from methane. *Toluene* or *methylbenzene*, $C_6H_5 \cdot CH_3$, is the only homologue of the molecular formula, C_7H_8, but the next higher member, C_8H_{10}, occurs in four isomeric forms —namely, as *ethylbenzene*, $C_6H_5 \cdot C_2H_5$, and as ortho-, meta-, and para-*dimethylbenzene*, $C_6H_4(CH_3)_2$; higher up the series, the number of theoretically possible isomerides rapidly increases. By the substitution of a methyl group for one atom of hydrogen in the hydrocarbons, C_8H_{10}, for example, eight isomerides, C_9H_{12}, may theoretically be obtained, and are, in fact, known (p. 385).

Owing to this rapid increase in the number of isomerides, as the series is ascended, and to the differences in the properties of these isomerides, but more especially because, as a rule, only the lower members are of much importance, the classification of aromatic compounds into various homologous series does not very much simplify their study; nevertheless *general* methods of preparation may be given and also the general properties of particular groups common to the homologues.

Many of the hydrocarbons of the C_nH_{2n-6} series, and others described later, occur in coal-tar, from which they are isolated; it is, however, very difficult to obtain any of them in a pure state directly from this source, by fractional distillation alone, as the boiling-points of some of the isomerides lie very close together and also differ very little from those of certain other types of compounds which are present.

The homologues of benzene may be obtained by the following general methods:

(1) Benzene (or one of its homologues) is treated with an alkyl halide in the presence of anhydrous aluminium chloride (*Friedel and Crafts' reaction*); under these conditions hydrogen atoms of

the nucleus are displaced by alkyl groups. Benzene and methyl chloride, for example, give *toluene*, $C_6H_5 \cdot CH_3$, *xylene*, $C_6H_4(CH_3)_2$, *trimethylbenzene*, $C_6H_3(CH_3)_3$, etc., whereas *ethylbenzene*, with the same alkyl compound, yields *methylethylbenzene*, $C_6H_4(CH_3) \cdot C_2H_5$, *dimethylethylbenzene*, $C_6H_3(CH_3)_2 \cdot C_2H_5$, and so on,

$$C_6H_6 + CH_3Cl = C_6H_5 \cdot CH_3 + HCl,$$
$$C_6H_6 + 2CH_3Cl = C_6H_4(CH_3)_2 + 2HCl,$$
$$C_6H_5 \cdot C_2H_5 + CH_3Cl = C_6H_4(CH_3) \cdot C_2H_5 + HCl.$$

Anhydrous benzene, or one of its homologues (1 part),[1] is placed in a flask connected with a reflux condenser, and *anhydrous* aluminium chloride (about $\frac{1}{3}$ part) is added; the apparatus and materials must be dry, and it is essential that the aluminium chloride should be of good quality (samples which have absorbed atmospheric moisture, and which look white and powdery, are practically useless). The theoretical quantity of the alkyl halide is then (passed or) dropped into the hydrocarbon, and the mixture is afterwards heated on a water-bath until the evolution of halogen acid is at an end. In some cases, ether, carbon disulphide, or petrol is mixed with the original hydrocarbon merely to dilute it. When the product is quite cold, water is gradually added to it, or *vice versa*, in order to dissolve the aluminium compounds, and after having been separated, and dried with calcium chloride, the mixture of hydrocarbons is submitted to fractional distillation; in some cases a preliminary distillation in steam is advisable.

It is probable that an aluminium compound, such as C_6H_6, $AlCl_3$, is first formed, and then reacts with the alkyl halide, aluminium chloride being regenerated,

$$C_6H_6, AlCl_3 + CH_3Cl = C_6H_5 \cdot CH_3 + AlCl_3 + HCl.$$

Anhydrous ferric or zinc chloride may be employed in the place of aluminium chloride, but, as a rule, not so successfully. Friedel and Crafts' reaction is also applicable to phenolic ethers (p. 484), but not, as a rule, to other derivatives of aromatic hydrocarbons.

When the higher normal alkyl halides are used, the Friedel-Crafts reaction is often accompanied by an isomerisation of the alkyl group and a derivative of a secondary or tertiary paraffin is produced; *n*-propyl bromide, for example, with benzene and aluminium chloride, gives *iso*propylbenzene.

The orientation of the product of such reactions cannot be safely predicted by the rule given on p. 433, and may vary with the experi-

[1] In this and subsequent preparations, the 'parts' are by weight and the chosen quantities will depend, of course, on the amount of product required.

mental conditions and with the catalyst (below); as a rule the use of a high temperature and an excess of the catalyst tends to give *m*-products.

The Friedel-Crafts reaction is reversible and polyalkylbenzenes may lose alkyl groups when heated with aluminium chloride; hexamethylbenzene thus gives mixtures of penta-, tetra-, etc., alkyl compounds and methyl chloride.

Other catalysts, such as boron trifluoride or hydrogen fluoride, may be used in the place of one of the chlorides already mentioned and in such cases instead of the alkyl halide an olefine or an alcohol may be employed; with these catalysts also the aromatic hydrocarbon or the phenolic ether can be replaced by a phenol. With boron trifluoride, for example, propylene, *n*-propyl and *iso*propyl alcohols all give *iso*propylbenzene or (mainly) *p*-di-*iso*propylbenzene, with benzene; propyl chloride and aluminium chloride give mainly the *m*-di-*iso*propyl derivative. Similarly, in the presence of hydrogen fluoride, propylene and benzene give *iso*propylbenzene, whereas propylene and phenol give 2:4:6-tri-*iso*propylphenol.

(2) An ethereal solution of a halogen derivative of benzene or of one of its homologues and an alkyl halide, is heated with sodium or potassium (*Fittig's* reaction); this method of formation is similar to that by which the higher paraffins may be synthetically produced from alkyl halides (Wurtz), and has the great advantage over Friedel and Crafts' method that the constitution of the product is known. *Bromobenzene* and methyl iodide, for example, give *toluene*, whereas o-, m-, and p-*bromotoluene* and ethyl iodide yield o-, m-, and p-*methylethylbenzene* respectively.

$$C_6H_5Br+CH_3I+2Na = C_6H_5\cdot CH_3+NaI+NaBr,$$

$$C_6H_4Br\cdot CH_3+C_2H_5I+2K = C_6H_4<\begin{matrix}CH_3\\C_2H_5\end{matrix}+KBr+KI.$$

The bromo- or iodo-derivatives of the aromatic hydrocarbons are usually employed because the chloro-derivatives do not react so readily; the alkyl iodides are also used in preference to the chlorides or bromides because they undergo change most easily.

The first stage seems to be the formation of a sodium alkyl or aryl compound, $RI+2Na = RNa+NaI,$

which then, with the other halide forms the hydrocarbon.

Three hydrocarbons, R·R, R′R′, R·R′, may thus result, but could usually be easily separated as they would have very different boiling-points.

(3) The carboxy-derivatives of benzene, or of its homologues, are heated with soda-lime, a method analogous to that employed for the conversion of the fatty acids into paraffins,

$$C_6H_4(CH_3)\cdot COONa+NaOH = C_6H_5\cdot CH_3+Na_2CO_3,$$
$$C_6H_4(COONa)_2+2NaOH = C_6H_6+2NaCO_3.$$

(4) The vapour of a hydroxy-derivative of benzene, or of one of its homologues, is passed over strongly heated zinc-dust,

$$C_6H_5\cdot OH+Zn = C_6H_6+ZnO,$$
$$C_6H_4(CH_3)\cdot OH+Zn = C_6H_5\cdot CH_3+ZnO.$$

(5) A ketone or aldehyde is reduced by the Clemmensen method,

$$C_6H_5\cdot CO\cdot CH_3+4H = C_6H_5\cdot CH_2\cdot CH_3+H_2O.$$

This method is particularly useful in the case of the higher *n*-alkyl derivatives which cannot be obtained by the Friedel-Crafts reaction. The necessary ketones are readily made by a modified Friedel-Crafts reaction (p. 504).

(6) Coal, wood, peat, etc., are destructively distilled, or the vapour of some aliphatic compound is passed through a strongly heated tube (p. 376) which may contain a suitable catalyst: with chromium oxide at 400°, for example, *n*-hexane gives benzene, *n*-heptane, toluene, and *n*-octane mainly *o*-xylene. Such methods are now used for the manufacture of aromatic hydrocarbons from petroleum.

(7) An aromatic Grignard reagent is treated with dimethyl sulphate,

$$CH_3\cdot C_6H_4\cdot MgBr+2(CH_3)_2SO_4 = CH_3\cdot C_6H_4\cdot CH_3+CH_3Br+(CH_3SO_4)_2Mg.$$

(8) A sulphonic acid is hydrolysed (p. 473).

General Properties. Most of the homologues of benzene are mobile liquids; one or two, however, are crystalline at ordinary temperatures. They all distil without decomposition, are volatile in steam, and burn with a smoky flame; they are insoluble in water, but miscible with (anhydrous) alcohol, ether, petrol, etc.; they dissolve fats and many other substances which are insoluble in water.

Just as in other homologous series, the homologues of benzene show a gradual variation in *physical properties* with increasing

molecular weight, but owing to the large number of isomerides, this is obvious only when *corresponding* compounds are compared, as, for example, the following *mono*-substitution products :

	Sp. gr. at 0°	B.p.
Benzene, C_6H_6	0·899	80·2°
Toluene, C_7H_8	0·882	110·6°
Ethylbenzene, C_8H_{10}	0·883	136°
Propylbenzene, C_9H_{12}	0·881	159°

There are, however, three hydrocarbons isomeric with ethylbenzene (p. 409) and seven isomeric with propylbenzene (p. 385), so that, after toluene, the homologous series branches and the gradual variation in properties is obscured.

Isomeric *di*-substitution products usually differ little in physical properties, but the extent of this difference is rather variable ; the three xylenes, $C_6H_4(CH_3)_2$, for example, have the following constants :—

	o-Xylene	*m*-Xylene	*p*-Xylene
Sp. gr. at 0°	0·893	0·881	0·880
B.p.	143°	139°	138° (m.p. 14°)

As a general rule, to which, however, there are many exceptions, *para*- melt at a higher temperature than the corresponding *meta*-compounds, and the latter usually melt at a higher temperature than the corresponding *ortho*-compounds. This applies to all benzene derivatives, not to hydrocarbons only.

The homologues of benzene show the characteristic chemical behaviour of the parent hydrocarbon, inasmuch as they readily yield halogen, nitro-, and sulphonic derivatives ; toluene, for example, gives *chlorotoluene*, $C_6H_4(CH_3)Cl$, *nitrotoluene*, $C_6H_4(CH_3)\cdot NO_2$, and *toluenesulphonic acid*, $C_6H_4(CH_3)\cdot SO_3H$; xylene yields *chloroxylene*, $C_6H_3(CH_3)_2Cl$, *nitroxylene*, $C_6H_3(CH_3)_2\cdot NO_2$, and *xylenesulphonic acid*, $C_6H_3(CH_3)_2\cdot SO_3H$.

In these, and in all similar reactions, the product generally consists of a mixture of isomerides, and the course of the reaction depends both on the nature of the aromatic compound and on the conditions of the experiment (p. 432) ; as a rule, the greater the number of alkyl groups in the hydrocarbon, the more readily does it yield halogen, nitro-, and sulphonic-derivatives.

All the homologues of benzene are very stable, and are with

difficulty resolved into compounds containing a smaller number of carbon atoms; certain oxidising agents, however, such as chromic acid, potassium permanganate, and *dilute* nitric acid, act on them slowly, the alkyl groups or side chains being attacked, and, as a rule, converted into carboxyl groups; toluene and ethylbenzene, for example, give benzoic acid, whereas the xylenes yield dicarboxylic acids (p. 519),

$$C_6H_5\cdot CH_3+3O = C_6H_5\cdot COOH+H_2O,$$
$$C_6H_5\cdot CH_2\cdot CH_3+6O = C_6H_5\cdot COOH+CO_2+2H_2O,$$
$$C_6H_4(CH_3)_2+6O = C_6H_4(COOH)_2+2H_2O.$$

Although in most cases oxidation leads to the formation of a carboxy-derivative of benzene, the stable benzene nucleus remaining unchanged, some of the homologues are completely oxidised to carbon dioxide and water (p. 417), and benzene itself undergoes a similar change on prolonged and vigorous treatment.

Groups of atoms derived from aromatic hydrocarbons are classed as *aryl* radicals. The mono- and di-substitution products of benzene, for example, may be regarded as compounds of the univalent radical, *phenyl*, C_6H_5—, or **Ph**, and of the bivalent radical, *phenylene*, $C_6H_4<$, respectively, as in *phenylamine* (aniline), $C_6H_5\cdot NH_2$, and in o-, m-, and p-*phenylenediamine*, $C_6H_4(NH_2)_2$. From toluene there are derived the radicals, *tolyl*, $CH_3\cdot C_6H_4$—, and *benzyl*, $C_6H_5\cdot CH_2$—, according as hydrogen of the nucleus, or of the side chain, has been removed. Similarly *xylyl*, $C_6H_4(CH_3)\cdot CH_2$—, and *xylylene*, $C_6H_4(CH_2—)_2$ are terms used in naming xylene derivatives.

Such nomenclature, however, is not employed very systematically, as, although the compound, $C_6H_5\cdot CH_2\cdot OH$, for example, is called *benzyl alcohol*, the isomeric hydroxy-toluenes, $C_6H_4(CH_3)\cdot OH$, are usually known as the (*o.m.p.*) cresols (p. 487) and not as tolyl alcohols; other nuclear substitution products such as the chloro-toluenes, $C_6H_4(CH_3)Cl$, are usually named as derivatives of the hydrocarbon.

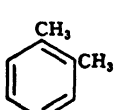
Toluene, $C_6H_5.CH_3$ (methylbenzene, phenylmethane), is prepared commercially from the light oil separated from coal-tar (p. 372), from certain varieties of petroleum, and from *n*-heptane. It may be obtained by heating toluic acid with soda-lime (p. 519), or by any of the other general reactions given above; also by the destructive distillation of balsam of Tolu (hence the name toluene) and other resins.

Commercial coal-tar toluene (toluol) is impure, and when shaken with concentrated sulphuric acid it colours the acid brown or black. Even after repeated fractional distillation, it contains *methylthiophene*, C_5H_6S, a homologue of thiophene (p. 587), and shows the indophenin reaction (with isatin and concentrated sulphuric acid).

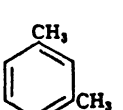
Toluene is a mobile liquid of sp. gr. 0·882 at 0°, boiling at 111°; it does not solidify even at −28°, and cannot, therefore, like benzene, be easily purified by crystallisation. It resembles benzene very closely, but is more reactive, and differs from it principally in those properties which are due to the presence of the methyl group. Its behaviour with nitric acid and with sulphuric acid, for example, is similar to that of benzene, inasmuch as it yields nitro- and sulphonic derivatives; these compounds, moreover, exist in three isomeric (*o.m.p.*) forms, since they are di-substitution products of benzene. Owing to the presence of the methyl group, toluene shows in some respects the properties of a paraffin. The hydrogen of this methyl group may be displaced by chlorine, for example, and the latter by a hydroxyl or amino-group, by methods exactly similar to those employed in bringing about corresponding changes in aliphatic compounds; substances such as $C_6H_5 \cdot CH_2Cl$, $C_6H_5 \cdot CH_2 \cdot OH$, and $C_6H_5 \cdot CH_2 \cdot NH_2$, are thus obtained. This behaviour, perhaps, was to be expected, since toluene or phenylmethane is a mono-substitution product of methane just as much as a derivative of benzene.

Toluene is extensively employed in the manufacture of various dye-intermediates described later, explosives, and saccharin (p. 518); it is also used as a fuel for internal combustion engines—usually in admixture with benzene and petrol.

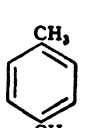
Xylenes. There are four hydrocarbons of the molecular formula, C_8H_{10}, homologues of toluene,



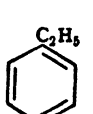
o-Xylene
b.p. 143°



m-Xylene
b.p. 139°



p-Xylene
b.p. 138°



Ethylbenzene
b.p. 136°

The three *xylenes* occur in coal-tar, and may be partially separated from the other components of 50% benzol (p. 373) by fractional

distillation. The portion which, after repeated distillation, boils at 138-142°, contains a large proportion (usually about 60%) of *m*-xylene and smaller ones of the *o*- and *p*-compounds ; the three isomerides cannot be easily separated from one another (or from all impurities) by further distillation, or by any simple means, although it is possible to do so by taking advantage of differences in their chemical behaviour.

m-Xylene is readily separated from the other isomerides with the aid of boiling dilute nitric acid, which oxidises *o*- and *p*-xylene to the corresponding toluic acids, $C_6H_4(CH_3)\cdot COOH$, but does not readily attack *m*-xylene ; the product is rendered alkaline, and the unchanged hydrocarbon is purified by distillation in steam and fractionation. The isolation of *o*- and *p*-xylene depends on the following facts : (1) When crude xylene is agitated with concentrated sulphuric acid, *o*- and *m*-xylene are converted into sulphonic acids, $C_6H_3(CH_3)_2\cdot SO_3H$; *p*-xylene remains undissolved, as it is only slowly acted on even by anhydrosulphuric acid. (2) The sodium salt of *o*-xylenesulphonic acid is less soluble in water than that of *m*-xylenesulphonic acid ; it is purified by recrystallisation and heated with hydrochloric acid under pressure, whereby it is converted into *o*-xylene.

The three xylenes may all be prepared by one or other of the general methods ; when, for example, methyl chloride is passed into benzene in the presence of aluminium chloride, *m*-xylene and a small quantity of the *p*-compound are obtained,

$$C_6H_6+2CH_3Cl = C_6H_4(CH_3)_2+2HCl ;$$

toluene, under the same conditions, yields, of course, the same two substitution products. The non-formation of *o*-xylene in these two reactions shows that the methyl group first introduced into the benzene molecule exerts a directing or *orientating influence* on the position taken up by the second one (p. 433).

o-*Xylene* is obtained free from its isomerides by treating *o*-bromotoluene with methyl iodide and sodium,

$$C_6H_4{<}\begin{matrix}CH_3\\Br\end{matrix}+CH_3I+2Na = C_6H_4{<}\begin{matrix}CH_3\\CH_3\end{matrix}+NaBr+NaI ;$$

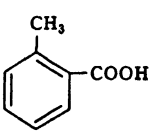
p-*xylene* is also produced in a similar manner from *p*-bromotoluene ; m-*xylene* might be obtained by treating *m*-bromotoluene with methyl

iodide and sodium, but is more easily prepared by heating mesitylenic acid (p. 418) with soda-lime,

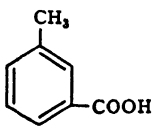
$$C_6H_3(CH_3)_2{\cdot}COOH = C_6H_4(CH_3)_2 + CO_2.$$

These isomerides may also be obtained from the Grignard compounds of the corresponding bromotoluenes (p. 412).

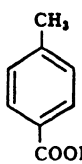
The three xylenes are very similar in physical properties (p. 413), and are mobile, rather pleasant-smelling, inflammable liquids (*p*-xylene melts at 14°), which distil without decomposition, and are readily volatile in steam. They also resemble one another in chemical properties, although in some respects they show very important differences.[1] On oxidation, under suitable conditions, they are all converted in the first place into monocarboxylic acids,



o-Toluic acid



m-Toluic acid



p-Toluic acid

On further oxidation the second methyl group undergoes a like change, and the three corresponding dicarboxylic acids, $C_6H_4(COOH)_2$, are formed (p. 519).

The three hydrocarbons show, however, a marked dissimilarity towards oxidising agents. With chromic acid, *o*-xylene is completely oxidised to carbon dioxide and water, whereas *m*- and *p*-xylene yield the dicarboxylic acids, results very different from those obtained with dilute nitric acid (p. 416). The behaviour of the three hydrocarbons towards sulphuric acid is also different (p. 416).

Ethylbenzene, $C_6H_5{\cdot}C_2H_5$ (phenylethane), an isomeride of the xylenes, occurs in coal-tar, and may be obtained by the general methods. It is prepared on the large scale from a mixture of benzene and ethylene in the presence of aluminium chloride and is used for making styrene (p. 419). It boils at 136°, and, on

[1] The xylenes, like other isomerides, afford further examples of the fact that the properties of a compound are not entirely determined by those of its constituent groups but by the structure of the molecule as a whole.

oxidation with dilute nitric acid or chromic acid, it is converted into benzoic acid,

$$C_6H_5 \cdot CH_2 \cdot CH_3 + 6O = C_6H_5 \cdot COOH + CO_2 + 2H_2O.$$

The next member of the series, C_9H_{12}, exists, as already pointed out (p. 385), in eight isomeric forms, of which the three trimethylbenzenes and *iso*propylbenzene are the more important.

Mesitylene, symmetrical or 1:3:5-trimethylbenzene, occurs in small quantities in coal-tar, but is best prepared by distilling a mixture of acetone (2 vol.), concentrated sulphuric acid (2 vol.), and water (1 vol.), and then fractionating the distillate,

$$3(CH_3)_2CO = C_6H_3(CH_3)_3 + 3H_2O.$$

The formation of mesitylene in this way is of interest, not only because it affords a means of synthesising the hydrocarbon from its elements, but also because it throws light on the constitution of the compound.

Although the change is most simply expressed by the graphic equation already given (p. 401), it might be assumed that the acetone is first converted into $CH_3 \cdot C(OH):CH_2$ (by isomeric change), or into $CH_3 \cdot C \vdots CH$, and that mesitylene is then produced by a secondary reaction. Whatever view is adopted, as to the various stages of the reaction (unless, indeed, highly improbable assumptions are made), it would seem, however, that the constitution of the product must be expressed by a *symmetrical* formula; this inference has been fully confirmed by other evidence (p. 386).

Mesitylene is a mobile, pleasant-smelling liquid, boiling at 165°, and volatile in steam; when treated with concentrated nitric acid, it yields *mononitro-* and *dinitro-mesitylene*, whereas with a mixture of nitric and sulphuric acids it is converted into *trinitro-mesitylene*, $C_6(NO_2)_3(CH_3)_3$. On oxidation with dilute nitric acid, it yields *mesitylenic acid*, $C_6H_3(CH_3)_2 \cdot COOH$, *uvitic acid*, $C_6H_3(CH_3)(COOH)_2$, and *trimesic acid*, $C_6H_3(COOH)_3$, by the successive transformation of methyl into carboxyl groups.

Pseudocumene, or 1:2:4-trimethylbenzene, and *hemimellitene*, or 1:2:3-trimethylbenzene, also occur in small quantities in coal-tar, and are very similar to mesitylene in properties; on oxidation, they yield various acids by the conversion of one or more methyl into carboxyl groups.

Cumene, $C_6H_5 \cdot CH(CH_3)_2$ (*iso*propylbenzene), is usually obtained from coal-tar; it may be prepared by treating a mixture of *iso*propyl (or propyl) bromide and benzene with aluminium chloride,

$$C_6H_6 + C_3H_7Br = C_6H_5 \cdot C_3H_7 + HBr.$$

It boils at 153° and, on oxidation with dilute nitric acid, it is converted into benzoic acid.

Cymene, $C_6H_4(CH_3) \cdot C_3H_7$ (*p*-methyl*iso*propylbenzene), is a hydrocarbon of considerable importance, and occurs in the ethereal oils or essences of many plants; it may be obtained in many ways, as, for example, by heating camphor with phosphorus pentoxide,

$$C_{10}H_{16}O = C_{10}H_{14} + H_2O,$$

and by heating oil of turpentine with concentrated sulphuric acid,

$$C_{10}H_{16} + O = C_{10}H_{14} + H_2O;$$

these reactions are not so simple as they would seem to be and very complex changes take place in both.

Cymene is also produced by heating thymol or carvacrol (p. 488), with phosphorus pentasulphide (which acts as a reducing agent),

$$C_6H_3(OH) < \begin{matrix} CH_3 \\ C_3H_7 \end{matrix} + 2H = C_6H_4 < \begin{matrix} CH_3 \\ C_3H_7 \end{matrix} + H_2O.$$

It has been synthesised from *p*-bromo*iso*propylbenzene, methyl iodide, and sodium—a reaction which proves its constitution.

Cymene is a pleasant-smelling liquid of sp. gr. 0·87 at 0°, and boils at 177°; on oxidation with dilute nitric acid, it yields p-*toluic acid*, $C_6H_4(CH_3) \cdot COOH$, and *terephthalic acid*, $C_6H_4(COOH)_2$.

Styrene, $C_6H_5 \cdot CH{:}CH_2$ (phenylethylene), may be taken as a typical example of an aromatic hydrocarbon containing an *unsaturated* side chain. It is prepared on the large scale, for the manufacture of synthetic rubber and plastics, by dehydrogenating ethylbenzene; it can also be produced from cinnamic acid (p. 526). It boils at 145°, and in chemical properties shows a very close resemblance to ethylene, of which it is the phenyl substitution product. With bromine, for example, it yields a dibromo-additive compound, $C_6H_5 \cdot CHBr \cdot CH_2Br$ (*dibromoethylbenzene*), and when treated with hydrogen and a catalyst, it undergoes reduction to *ethylbenzene*, $C_6H_5 \cdot CH_2 \cdot CH_3$.

Diphenyl, Diphenylmethane, and Triphenylmethane

All the hydrocarbons hitherto described contain only *one* benzene nucleus, and may be regarded as derived from benzene by the substitution of alkyl groups for atoms of hydrogen; there are, however, several other types of aromatic hydrocarbons, which include compounds of considerable importance.

Diphenyl, $C_6H_5 \cdot C_6H_5$, is not a homologue of benzene, and its molecule contains *two* benzene nuclei. It occurs in coal-tar and may be obtained by treating an ethereal solution of bromobenzene with sodium,

$$2C_6H_5Br + 2Na = C_6H_5 \cdot C_6H_5 + 2NaBr,$$

a reaction which is analogous to the formation of ethane (dimethyl) from methyl iodide; but many other changes occur and the yield is very poor. It is also produced in the preparation of phenyl magnesium bromide (p. 431).

Diphenyl is prepared on the large scale by passing benzene vapour through molten lead,

$$2C_6H_6 = C_6H_5 \cdot C_6H_5 + H_2.$$

The product is fractionated, and the diphenyl is purified by distillation and recrystallisation.

Diphenyl melts at 71°, boils at 254°, and is sometimes used to maintain a constant high temperature; when oxidised with chromic acid it yields benzoic acid, $C_6H_5 \cdot COOH$, one of the benzene nuclei giving rise to —COOH. Its behaviour with halogens, nitric acid, and sulphuric acid is similar to that of benzene, substitution products being formed.

Diphenyl and its substitution derivatives are often readily prepared by heating aromatic halogen compounds with finely divided copper or bronze (Ullmann),

$$2C_6H_4(NO_2)Cl + 2Cu = C_6H_4(NO_2) \cdot C_6H_4 \cdot NO_2 + Cu_2Cl_2.$$

Diphenylmethane, $C_6H_5 \cdot CH_2 \cdot C_6H_5$, also contains *two* benzene nuclei; it may be regarded as derived from methane by the substitution of two phenyl groups for two atoms of hydrogen, just as toluene or phenylmethane may be considered as a monosubstitution product of methane.

Diphenylmethane may be prepared by treating benzene with benzyl chloride (p. 430) in the presence of aluminium chloride,

$$C_6H_6+C_6H_5\cdot CH_2Cl = C_6H_5\cdot CH_2\cdot C_6H_5+HCl.$$

It melts at 26·5°; when treated with nitric acid, it yields nitro-derivatives in the usual way, and on oxidation with chromic acid, it is converted into diphenyl ketone or *benzophenone*, $C_6H_5\cdot CO\cdot C_6H_5$ (p. 506), and then into benzoic acid.

Triphenylmethane, $(C_6H_5)_3CH$, is the parent substance of an important group of compounds, all of which contain *three* benzene nuclei. It is formed when benzal chloride (p. 430) is treated with benzene in the presence of aluminium chloride,

$$C_6H_5\cdot CHCl_2+2C_6H_6 = (C_6H_5)_3CH+2HCl,$$

and also when a mixture of chloroform and benzene is warmed with aluminium chloride,

$$CHCl_3+3C_6H_6 = (C_6H_5)_3CH+3HCl.$$

It is best prepared by treating a mixture of benzene and carbon tetrachloride with aluminium chloride and reducing the resulting triphenylmethyl chloride by the addition of ether in the presence of the aluminium chloride,

$$3C_6H_6+CCl_4 = (C_6H_5)_3CCl+3HCl,$$
$$(C_6H_5)_3CCl+(C_2H_5)_2O = (C_6H_5)_3CH+CH_3\cdot CHO+C_2H_5Cl.$$

Triphenylmethane melts at 94°, and boils at 358°; it is readily soluble in ether and benzene, but only sparingly so in cold alcohol. When treated with fuming nitric acid, it is converted into a yellow, crystalline *trinitro*-derivative, $CH(C_6H_4\cdot NO_2)_3$, which, like other nitro-compounds, is readily reduced to the corresponding *triamino-compound*, $CH(C_6H_4\cdot NH_2)_3$; many derivatives of this base are employed as dyes.

On oxidation with chromic acid, triphenylmethane is converted into *triphenyl carbinol*, $(C_6H_5)_3C\cdot OH$ (m.p. 164°), a compound which can also be obtained by treating benzophenone (p. 506) or ethyl benzoate (p. 513) with phenyl magnesium bromide.

CHAPTER 26

HALOGEN DERIVATIVES OF BENZENE AND OF ITS HOMOLOGUES

THE action of chlorine and bromine on benzene varies with the conditions (p. 378). At ordinary temperatures, in the absence of direct sunlight, *substitution* products are slowly formed ; this action is greatly hastened by the presence of a halogen carrier, such as iodine, iron, aluminium, etc.[1] In the presence of direct sunlight, however, or in the dark in the complete absence of water, the hydrocarbon yields *additive* compounds by direct combination with six atoms of the halogen (p. 378).

The homologues of benzene also show a notable behaviour ; when treated with chlorine or bromine at ordinary temperatures in the absence of direct sunlight, they are converted into *substitution* products by the displacement of hydrogen of the *nucleus*, and, as in the case of benzene itself, the reaction is greatly promoted by the presence of a halogen carrier ; under these conditions toluene, for example, gives a mixture of o- and p-*chloro-* or *bromo-toluenes*,

$$C_6H_5 \cdot CH_3 + Cl_2 = C_6H_4Cl \cdot CH_3 + HCl.$$

When, on the other hand, no halogen carrier is present, and the hydrocarbons are treated with chlorine or bromine at their boiling-points, or in direct sunlight, they yield derivatives by the displacement of hydrogen of the *side chain* ; when, for example, chlorine is passed into *boiling* toluene, the three hydrogen atoms of the methyl group are successively displaced, *benzyl chloride*, $C_6H_5 \cdot CH_2Cl$, *benzal chloride*, $C_6H_5 \cdot CHCl_2$, and *benzotrichloride*, $C_6H_5 \cdot CCl_3$, being formed ; xylene, likewise, when heated at its boiling-point and treated with bromine, gives the compounds,

$$C_6H_4 < \begin{matrix} CH_2Br \\ CH_3 \end{matrix} \quad \text{and} \quad C_6H_4 < \begin{matrix} CH_2Br \\ CH_2Br \end{matrix}$$

[1] The action of iodine has already been mentioned (p. 179). Iron, aluminium, antimony, and certain other metals act as halogen carriers, possibly because their chlorides ($FeCl_3$, $AlCl_3$, $SbCl_5$) combine with hydrocarbons, etc., and give products, which are then decomposed by the halogen, with the formation of the metallic chloride and a halogen substitution product of the organic compound.

Although these statements are true in the main, it must not be supposed that, under any conditions, substitution takes place *only* in the nucleus *or* in the side chain, as the case may be; in the presence of a halogen carrier, relatively small quantities of halogen derivatives are formed by the displacement of hydrogen of the side chain, and at the boiling-point of the hydrocarbon, or in direct sunlight, hydrogen of the nucleus is displaced to some extent.

Iodine, as a rule, does not act on aromatic hydrocarbons, but at high temperatures a reversible reaction may occur,

$$C_6H_6+I_2 \rightleftarrows C_6H_5I+HI.$$

When, however, iodic acid, or some other substance which decomposes hydrogen iodide, is present, iodo-derivatives may sometimes be prepared by direct treatment with the halogen at high temperatures.

Preparation. (1) Chloro- and bromo-derivatives of benzene and of its homologues may be prepared by the direct action of chlorine and bromine on the hydrocarbons; such a process in which hydrogen is displaced by the use of the *free halogen* is termed *chlorination* or *bromination* as the case may be. The conditions to be maintained depend, as explained above, on whether hydrogen of the nucleus or of the side chain is to be displaced. If, for example, toluene is to be converted into p-*chlorobenzyl chloride*, $C_6H_4Cl\cdot CH_2Cl$, the hydrocarbon might be first treated with chlorine at ordinary temperatures in the presence of iodine; the p-*chlorotoluene*, $C_6H_4Cl\cdot CH_3$, thus formed (separated from the accompanying *ortho*-compound [1]), would then be boiled in a flask connected with a reflux condenser, and a stream of dry chlorine led into it.

In all operations of this kind the theoretical quantity, or a slight excess of halogen, is employed. The required amount of bromine is weighed, but for chlorination the gas is passed through the hydrocarbon until the theoretical gain in weight has taken place; the halogen should be dried, as, in the presence of water, oxidation products of the hydrocarbon may be formed.

(2) A *very important* general method for the preparation of aromatic halides, in which the halogen is combined with carbon of the *nucleus*, consists in the decomposition of the diazonium salts as

[1] In this particular case the separation of the *o*- and *p*-compounds is a task of very great difficulty as they boil at very nearly the same temperature.

described later (p. 456). Nearly *all* iodo-compounds are perforce obtained by this reaction, which affords a means of indirectly substituting any of the halogens, not only for hydrogen, but also for nitro- or amino-groups.

The conversion of benzene or toluene, for example, into a mono-halogen derivative by this method involves the following steps :

$$\underset{\text{Benzene}}{C_6H_6} \longrightarrow \underset{\text{Nitrobenzene}}{C_6H_5\cdot NO_2} \longrightarrow \underset{\text{Aminobenzene}}{C_6H_5\cdot NH_2} \longrightarrow \underset{\text{Phenyldiazonium chloride}}{C_6H_5\cdot N_2Cl} \longrightarrow \underset{\text{Chlorobenzene}}{C_6H_5Cl}$$

$$\underset{\text{Toluene}}{C_6H_5\cdot CH_3} \rightarrow \underset{\text{Nitrotoluene}}{C_6H_4<^{CH_3}_{NO_2}} \rightarrow \underset{\text{Aminotoluene}}{C_6H_4<^{CH_3}_{NH_2}} \rightarrow \underset{\text{Tolyldiazonium bromide}}{C_6H_4<^{CH_3}_{N_2Br}} \rightarrow \underset{\text{Bromotoluene}}{C_6H_4<^{CH_3}_{Br}}$$

The preparation of a *di*-halogen derivative may sometimes be carried out in a similar manner, the hydrocarbon being first converted into the *di*-nitro-derivative ; in most cases, however, it is necessary to prepare the *mono*-halogen compound by one of the methods already given, convert it into its nitro-derivative, and then displace the nitro-group by a second halogen atom in the prescribed manner :

$$\underset{\text{Bromobenzene}}{C_6H_5Br} \longrightarrow \underset{\text{Nitrobromobenzene}}{C_6H_4<^{Br}_{NO_2}} \longrightarrow \underset{\text{Aminobromobenzene}}{C_6H_4<^{Br}_{NH_2}} \longrightarrow \underset{\text{Bromophenyldiazonium chloride}}{C_6H_4<^{Br}_{N_2Cl}} \longrightarrow \underset{\text{Bromochlorobenzene}}{C_6H_4<^{Br}_{Cl}}$$

(3) Aromatic halides are sometimes obtained by treating phenols (p. 478) with the tri- or penta-halogen derivatives of phosphorus, but the main reactions are similar to those which occur in the case of aliphatic hydroxy-compounds (footnote, p. 108) ; phenols which contain a nitro-group in the *o*- or *p*-position, however, often give a good yield of the corresponding nitrohalogen derivative,

$$C_6H_4<^{NO_2}_{OH} + PCl_5 = C_6H_4<^{NO_2}_{Cl} + POCl_3 + HCl.$$

An aromatic alcohol (p. 495) may also give the corresponding halogen derivative with a phosphorus halide, but usually much better results are obtained with a halogen acid,

$$C_6H_5\cdot CH_2\cdot OH + HCl = C_6H_5\cdot CH_2Cl + H_2O.$$

(4) Halogen derivatives may also be obtained by heating sulphonyl chlorides (p. 473) with phosphorus pentachloride,

$$C_6H_5\cdot SO_2Cl + PCl_5 = C_6H_5Cl + POCl_3 + SOCl_2,$$

and (5) by heating halogen acids with soda-lime,

$$C_6H_4Br \cdot COONa + NaOH = C_6H_5Br + Na_2CO_3.$$

This last reaction shows the great stability of the halogen-carbon bond in such compounds.

(6) Compounds containing the group $—CH_2Cl$ directly united with the nucleus may often be prepared by treating suitable aromatic substances with paraformaldehyde and hydrogen chloride in the presence of zinc (or aluminium) chloride (*chloromethylation*),

$$3C_6H_6 + (CH_2O)_3 + 3HCl = 3C_6H_5 \cdot CH_2Cl + 3H_2O.$$

Properties. At ordinary temperatures, most of the *mono*-halogen derivatives of benzene and its simpler homologues are liquids ; the *di-* and *tri*-halogen derivatives, however, are generally crystalline. They are all insoluble, or nearly so, in water, but soluble in alcohol, ether, etc. ; many are readily volatile in steam, and also distil without decomposition. The boiling-point is higher, and the specific gravity greater, than that of the parent hydrocarbon, and rises as bromine is substituted for chlorine, or iodine for bromine.

	B.p.	Sp. gr. at 0°
Benzene	80·2°	0·899
Chlorobenzene	132°	1·128
Bromobenzene	156°	1·517
Iodobenzene	188°	1·857

They are not nearly so inflammable as the hydrocarbons, and the vapours of many of them (p. 431) have a very irritating action on the eyes and respiratory organs.

When the halogen is united with carbon of the benzene nucleus, it is, as a rule, very firmly combined, and *cannot be displaced* by a hydroxy- or amino-group, with the aid of aqueous alkalis, moist silver oxide, or alcoholic ammonia, nor will it react with potassium cyanide, diethyl sodiomalonate, etc. Such halides, moreover, cannot be converted into less saturated compounds with *alcoholic potash*, in the same way as ethyl bromide, for example, may be converted into ethylene ; in fact, no benzene derivative containing less than six univalent atoms, or their valency equivalent, is known. If, however, hydrogen of the nucleus has been displaced by one or more nitro-groups, as well as by a halogen, the latter often becomes much more reactive ; o- and p-*chloronitrobenzene*, $C_6H_4Cl \cdot NO_2$, for example, are moderately easily changed by

alcoholic potash, and by alcoholic ammonia at high temperatures, yielding the corresponding nitrophenols, $C_6H_4(OH)\cdot NO_2$, and nitroanilines, $C_6H_4(NH_2)\cdot NO_2$, respectively; m-*chloronitrobenzene*, however, is not changed under these conditions, a fact which shows that such isomerides sometimes differ very considerably in chemical properties (footnote, p. 417).

Halogen atoms of the side chains are very much less firmly combined than are those of the nucleus, and may be displaced by hydroxy- or amino-groups just as can those of alkyl halides; *benzyl chloride*, $C_6H_5\cdot CH_2Cl$, for example, is converted into *benzyl alcohol*, $C_6H_5\cdot CH_2\cdot OH$, by boiling sodium carbonate solution, and when heated with alcoholic ammonia, it yields *benzylamine*, $C_6H_5\cdot CH_2\cdot NH_2$ (p.452):

Halogen atoms of the nucleus, as well as those of the side chain, are displaced by hydrogen with the aid of hydriodic acid and red phosphorus at high temperatures, or of sodium amalgam and aqueous alcohol; the former, however, are much less readily displaced than the latter. Halogen derivatives of both types give Grignard compounds and undergo the Fittig reaction.

Chlorobenzene, C_6H_5Cl (phenyl chloride), may be described as a typical example of those derivatives in which the halogen is combined with carbon of the nucleus. It may be prepared by *Sandmeyer's* reaction—that is to say, by treating an aqueous solution of phenyldiazonium chloride with cuprous chloride (p. 456); this method, therefore, affords a means of preparing chlorobenzene, not only from the diazonium salt, but also indirectly from aniline, nitrobenzene, and benzene, in the manner already indicated (p. 424).

Aniline (20 g.) is *diazotised* in the manner described later (p. 457), and the solution of the diazonium chloride is added slowly to a boiling solution of cuprous chloride (10 g.) in concentrated hydrochloric acid (about 100 c.c.); the chlorobenzene is then distilled in steam, washed with a solution of sodium hydroxide, separated, dried, and distilled.

On the large scale chlorobenzene is obtained (together with o- and p-*dichlorobenzenes*, $C_6H_4Cl_2$, *trichlorobenzenes*, $C_6H_3Cl_3$, etc., by *chlorinating* benzene in the presence of a carrier (iron), and fractionating the product; also by the interaction of benzene, hydrogen chloride and air at 250° in the presence of a catalyst (*Raschig* process).

It should be noted that chlorobenzene and other *nuclear* halogen

derivatives, unlike the alkyl halides, *cannot* be prepared by treating the corresponding hydroxy-compounds (phenols) with a halogen acid.

Chlorobenzene is a mobile, pleasant-smelling liquid; it boils at 132°, and is readily volatile in steam. Like benzene, it is capable of yielding nitro-, amino-, and other derivatives; it *differs* from the alkyl halides in being unchanged by water, boiling alkalis, moist silver oxide, metallic salts, and alcoholic ammonia, but with sodium hydroxide solution in an autoclave *at 300°* it gives phenol.

Chlorobenzene reacts with chloral in the presence of sulphuric acid, to give pp'-*dichlorodiphenyltrichloroethane*,[1]

$$CCl_3 \cdot CHO + 2C_6H_5Cl = CCl_3 \cdot CH(C_6H_4Cl)_2 + H_2O.$$

This compound, known as D.D.T., is an important insecticide, especially for body lice; it was used with great success to control a typhus epidemic in Naples in 1944. Benzene hexachloride (p. 378) is also employed as an insecticide (*Gammexane*).

Bromobenzene, C_6H_5Br (phenyl bromide), may be prepared from phenyldiazonium sulphate by Sandmeyer's reaction, using cuprous bromide (p. 456); also by *brominating* benzene in the presence of iron.

Benzene (1 part, say 10 g.),[2] together with bright iron wire (about 0·2 g.) is placed in a flask provided with a reflux condenser, and the bromine (2 parts)[3] is added gradually from a stoppered funnel, the bent stem of which passes through the cork of the flask; the hydrogen bromide which is evolved may be absorbed in a tower containing moist coke. The product is washed well with water and dilute caustic soda successively, dried, and fractionated. The p-*dibromobenzene* (m.p. 87°; b.p. 219°), which may be formed in the above reaction, remains as a residue if the distillation is continued only until the thermometer rises to about 170°; it solidifies when cold, and may be recrystallised from aqueous alcohol.

Bromobenzene boils at 156°.

Iodobenzene, C_6H_5I (phenyl iodide), cannot be obtained by the action of iodine alone on benzene (p. 423); it is most conveniently

[1] The letters *pp'* show that the chlorine atoms in *both* benzene nuclei are in the *para*-position.

[2] Compare footnote (p. 410).

[3] Very great care must be taken with this most dangerous liquid, and the operation should be carried out in a fume chamber.

prepared by decomposing phenyldiazonium sulphate with potassium iodide in aqueous solution,

$$C_6H_5 \cdot N_2 \cdot SO_4H + KI = C_6H_5I + KHSO_4 + N_2.$$

Aniline (1 part) is *diazotised* with sodium nitrite and sulphuric acid (p. 457), the cold solution of the diazonium sulphate is treated with a concentrated solution of potassium iodide (2½ parts), and the mixture is gradually heated until nitrogen is no longer evolved ; the iodobenzene is then separated by steam distillation, washed with dilute caustic soda, dried, and distilled.

Iodobenzene boils at 188°.

The variation in the physical properties of chloro-, bromo-, and iodo-benzene (p. 425) should be noted ; as the halogen atoms in these compounds are so firmly combined, these and other nuclear halogen derivatives of benzene, unlike the alkyl halides, are little used as reagents, except for the preparation of *aryl* Grignard compounds (p. 431).

Iodobenzene dichloride, $C_6H_5 \cdot ICl_2$, separates in yellow crystals when iodobenzene is dissolved in chloroform and dry chlorine is passed into the *well-cooled* solution. It is slowly decomposed by dilute caustic soda (4–5%), and in the course of 6–8 hours at ordinary temperatures, it is converted into *iodosobenzene*,

$$C_6H_5ICl_2 + 2NaOH = C_6H_5IO + 2NaCl + H_2O,$$

which can be separated by filtration, washed with water, and dried on porous earthenware.

Iodosobenzene, C_6H_5IO, is a yellow solid, and is moderately easily soluble in warm water and alcohol ; it explodes at about 210°. It has *basic* properties, and reacts with acids, forming a salt and water,

$$C_6H_5IO + 2C_2H_4O_2 = C_6H_5I(C_2H_3O_2)_2 + H_2O ;$$

it is also an oxidising agent, and liberates iodine from potassium iodide in acid solution,

$$C_6H_5IO + 2HI = C_6H_5I + I_2 + H_2O.$$

When iodosobenzene is submitted to distillation in steam, it undergoes a most interesting reaction, giving iodobenzene, which distils with the water, and *iodoxybenzene*, which is non-volatile,

$$2C_6H_5IO = C_6H_5I + C_6H_5IO_2.$$

Iodoxybenzene, $C_6H_5IO_2$, separates in colourless needles when the aqueous solution is evaporated to a small volume and then allowed to cool ; it explodes at about 230°. Unlike iodosobenzene,

it does not show basic properties, but it is an oxidising agent and (1 mol.) liberates iodine (4 atoms) from hydrogen iodide.

When a mixture of iodosobenzene and iodoxybenzene is shaken with water and freshly precipitated silver oxide, interaction takes place and *diphenyliodonium hydroxide* is formed,

$$C_6H_5IO+C_6H_5IO_2+AgOH = (C_6H_5)_2I\cdot OH+AgIO_3.$$

This product is a strongly basic hydroxide which has only been prepared in solution and in the form of its salts, such as the iodide, $[(C_6H_5)_2I]I$; it is a very interesting fact that such derivatives of tervalent iodine should show basic properties.

These remarkable compounds were discovered and investigated by Willgerodt and by V. Meyer; analogous compounds may be prepared from other iodo-derivatives in which the iodine atom is directly united with the benzene (or a benzenoid) nucleus, but the dichlorides of aliphatic iodides, such as $C_2H_5\cdot ICl_2$, only exist at very low temperatures.

Chlorotoluene, $C_6H_4Cl\cdot CH_3$ (tolyl chloride), being a di-substitution product of benzene, exists in three isomeric forms, only two of which—namely, the *o*- and *p*-compounds—are produced when *cold* toluene is treated with chlorine in the presence of iodine or iron; all three isomerides may be separately obtained from the corresponding toluidines by Sandmeyer's method (p. 426), and are often prepared in this way:

$$C_6H_4{<}\begin{matrix}NH_2\\CH_3\end{matrix} \longrightarrow C_6H_4{<}\begin{matrix}N_2Cl\\CH_3\end{matrix} \longrightarrow C_6H_4{<}\begin{matrix}Cl\\CH_3\end{matrix}$$

Toluidine — Tolyldiazonium chloride — Chlorotoluene

The chlorotoluenes resemble chlorobenzene in most respects, but, since they contain a methyl group, they may be oxidised to the corresponding *chlorobenzoic acids*, $C_6H_4Cl\cdot COOH$, just as toluene may be transformed into benzoic acid.

The isomeric *bromotoluenes* are prepared by methods similar to those used in the case of the chloro-compounds and the *iodotoluenes* are obtained by diazotising the toluidines and treating the diazonium salts with potassium iodide (p. 457).

The boiling- (and melting-) points of these compounds are given below:

	o- (b.p.)	*m*- (b.p.)	*p*- (b.p.)	*p*- (m.p.)
Chlorotoluene	159°	162°	162°	7·5°
Bromotoluene	181°	184°	184°	28°
Iodotoluene	211°	213°	211°	36°

Benzyl chloride, $C_6H_5 \cdot CH_2Cl$, although isomeric with the three chlorotoluenes, differs from them very widely in many respects, and is an example of that class of halogen compounds in which the halogen is present in the *side chain*. It may be obtained by treating benzyl alcohol (p. 495) with hydrogen chloride, but is usually prepared by passing chlorine into *boiling* toluene,

$$C_6H_5 \cdot CH_3 + Cl_2 = C_6H_5 \cdot CH_2Cl + HCl.$$

The toluene is contained in a flask which is heated on a sand-bath and connected with a reflux condenser; a stream of dry chlorine is then passed into the boiling liquid, until the theoretical gain in weight has taken place, and the product is purified by fractional distillation; the action takes place most rapidly in strong sunlight.

Benzyl chloride is an unpleasant-smelling liquid, boiling at 179°; it is practically insoluble in water, but is miscible with most organic liquids. It behaves like other aromatic compounds towards nitric acid, by which it is converted into a mixture of isomeric nitro-derivatives, $C_6H_4(NO_2) \cdot CH_2Cl$. At the same time, however, it has many properties in common with the alkyl halides; thus it is slowly decomposed by boiling water, yielding the corresponding hydroxy-compound, *benzyl alcohol*,

$$C_6H_5 \cdot CH_2Cl + H_2O = C_6H_5 \cdot CH_2 \cdot OH + HCl,$$

and it reacts with alcoholic ammonia, potassium cyanide, silver acetate, and many other compounds, giving benzyl derivatives corresponding with those obtained from the alkyl halides.

Benzal chloride or **benzylidene dichloride,**[1] $C_6H_5 \cdot CHCl_2$, may be obtained by treating benzaldehyde with phosphorus pentachloride,

$$C_6H_5 \cdot CHO + PCl_5 = C_6H_5 \cdot CHCl_2 + POCl_3,$$

but it is prepared on the large scale by chlorinating toluene, just as described in the case of benzyl chloride, except that the process is continued until twice as much chlorine has reacted. It boils at 207°, and is slowly hydrolysed by water, more quickly by aqueous alkalis and milk of lime, giving benzaldehyde (p. 499), for the preparation of which it is used.

[1] The name *benzal* or *benzylidene* is given to the group of atoms, $C_6H_5 \cdot CH<$, which is analogous to ethylidene, $CH_3 \cdot CH<$.

Benzotrichloride, $C_6H_5 \cdot CCl_3$ (phenylchloroform), is also prepared by chlorinating boiling toluene ; it boils at 214°, and when heated with water, it is slowly converted into benzoic acid,

$$C_6H_5 \cdot CCl_3 + 2H_2O = C_6H_5 \cdot COOH + 3HCl.$$

Those toluene derivatives in which the halogen is in the side chain are lachrymatory (benzyl bromide was used in the war of 1914-18), but the chlorotoluenes, in which the halogen is combined with carbon of the nucleus, have hardly any action on the eyes. The three side chain halogen derivatives of toluene are all important because of their use in the large-scale preparation of benzyl alcohol, benzaldehyde and benzoic acid respectively.

Aromatic Grignard Reagents

Many aromatic halogen derivatives, like the alkyl halides, react readily with magnesium in the presence of pure ether, and the *Grignard reagents* which are thus formed show the reactions of those of the aliphatic series.

Phenyl magnesium bromide, $C_6H_5 \cdot MgBr$, and **benzyl magnesium chloride,** $C_6H_5 \cdot CH_2 \cdot MgCl$, are common reagents of this type. They are decomposed by water, giving benzene and toluene respectively so that the aromatic monohalides may be easily transformed into the parent hydrocarbons.

The aromatic or *aryl* Grignard reagents are very easily prepared, and are very much used in the synthesis of secondary and tertiary aryl alcohols (p. 497), and of aryl derivatives of both metals and non-metals.

CHAPTER 27

NITRO-COMPOUNDS

IT has already been stated that one of the more characteristic properties of aromatic compounds is the readiness with which they may be converted into nitro-derivatives, by the direct substitution of nitro-groups for hydrogen of the *nucleus* ; the compounds formed in this way are of very great importance, more especially because it is from them that the amino- and diazonium compounds are commonly prepared.

Preparation. Many aromatic compounds are *nitrated*—that is to say, converted into their nitro-derivatives—when they are treated with concentrated nitric acid (sp. gr. 1·3–1·5), in the cold or at ordinary temperatures, and under such conditions a mononitro-compound is usually produced ; benzene, for example, yields *nitrobenzene*, and toluene, a mixture of o- and p-*nitrotoluenes*,

$$C_6H_6+HNO_3 = C_6H_5\cdot NO_2+H_2O,$$
$$C_6H_5\cdot CH_3+HNO_3 = C_6H_4(CH_3)\cdot NO_2+H_2O.$$

Some aromatic compounds, however, are only very slowly attacked by nitric acid alone ; in such cases a mixture of concentrated nitric and sulphuric acids is used. This mixture is also employed in many cases, even when nitric acid alone might be used, because nitration then takes place more readily. When a large excess of such a mixture is used, and especially when heat is applied, the aromatic compound may be converted into (a mixture of isomeric) dinitro- or trinitro-derivatives ; benzene, for instance, yields a mixture of three *dinitrobenzenes*, the principal product, however, being the *meta*-compound,

$$C_6H_6+2HNO_3 = C_6H_4(NO_2)_2+2H_2O.$$

In the process of *nitration* the aromatic compound is added to the acid or *vice versa* in *small* quantities at a time, otherwise the reaction may be too violent ; in all such experiments particular precautions must be taken to avoid accidents.

Generally speaking, the number of hydrogen atoms displaced by nitro-groups is the larger the higher the temperature and the more concentrated the acid, or mixture of acids, employed, but depends

to an even greater extent on the nature of the substance undergoing nitration ; as a rule, the introduction of nitro-groups is facilitated when certain other atoms or groups, especially hydroxyl or alkyl groups, have already been substituted for hydrogen of the nucleus (p. 434). The *nature* of these atoms or groups, moreover, determines the position taken up by the entering nitro-group ; if the original substituent is NO_2, COOH, or SO_3H, the *m*-nitro-derivative is formed, whereas, when it is a halogen, or an alkyl, amino-, or hydroxy-group, a mixture of the *o*- and *p*-nitro-derivatives is produced.

This *directing* or *orientating* influence of an atom or group, already combined with the nucleus, on the position which is taken up by a second substituent, is not restricted to the case of a nitro-group, but is observed in the formation of *all* benzene substitution products, except, of course, in that of the mono-derivatives ; so regularly, in fact, is this influence exercised that it is possible to summarise the course of those reactions, which give di-substitution products, in the following statements :

The relative position taken up by one of the following atoms or groups, Cl, Br, NO_2, SO_3H, which are capable of *directly* displacing hydrogen of the nucleus, depends on the nature of the atom or group, A, already united with the nucleus.

When A is NR_2, NHR, NH_2, $NH \cdot CO \cdot CH_3$, OH, CH_3 (or other alkyl group), Cl, Br, I, or $CH{:}CH \cdot COOH$, the product consists almost entirely of a mixture of the *para*- and the *ortho*-compounds.[1]

When, on the other hand, A is CN, SO_3H, CHO, $CO \cdot R$, COOH, or NMe_3^+, a *meta*-derivative is the principal product, and relatively very small quantities of the *ortho*- and *para*-compounds are formed.

This general behaviour may also be summarised in the following empirical rule : When the atom directly united to the nucleus is combined to any *different* element by a double (or treble) bond, or a co-ordinate covalency, or has a positive charge, *meta*-substitution occurs ; otherwise, *ortho*- and *para*-derivatives are formed.[2]

These statements also hold good when two identical atoms or groups are introduced in one operation, since the change really takes place in *two stages* ; when benzene, for example, is treated

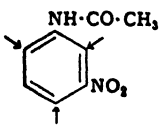
[1] In a Friedel and Crafts reaction the orientation of the product is often anomalous.

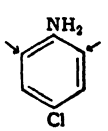
[2] Although this rule applies in all the above cases it is not universal ; the CCl_3 group, for example, is *m*-orientating.

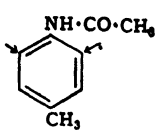
with nitric acid, *meta*-dinitrobenzene is the principal product, whereas bromine gives mainly *para*-dibromobenzene. It is very important to remember this *orientating* effect of particular atoms and groups and, for example, that *meta*-nitrochlorobenzene may be obtained by chlorinating nitrobenzene, but *not* by nitrating chlorobenzene.

Not only is the orientation of the product controlled in this way, but also the rapidity of the reaction ; thus amino-, hydroxyl, and to a less extent alkyl groups, greatly facilitate substitution, whilst the *m*-directing groups have the opposite effect. The halogens are peculiar in being *op*-directing and yet having a retarding effect.

It is often possible, therefore, to predict roughly the orientation of the product or products when a di- is converted into a trisubstituted benzene derivative ; if, for example, *m*-nitroacetanilide were nitrated it would be safe to assume that substitution would not occur in the *m*-position to the nitro-group and that with *p*-chloroaniline it would take place mainly in the *o*-position to the amino-group. Similarly, in the bromination or nitration of *p*-acetotoluide, substitution would be anticipated almost exclusively in the *o*-position to the acetylamino-group. The actual results are indicated by the arrows in the following formulae :







Properties. As a rule nitro-derivatives of aromatic hydrocarbons are colourless, or very nearly so ; as they are usually crystalline they often serve for the identification of aromatic hydrocarbons and liquid aromatic compounds in general. Many of them are volatile in steam, but, with the exception of certain mononitro-derivatives, they cannot be distilled under atmospheric pressure, because when heated strongly they decompose, sometimes with explosive violence ; an explosion may also occur when they are heated with sodium, in testing for nitrogen. They are generally very sparingly soluble in water, but more so in benzene, ether, alcohol, etc. As in the case of the nitroparaffins (p. 192), the nitro-group is very firmly combined, and, as a rule, is not displaced by the hydroxyl group even when the compound is heated with aqueous or alcoholic potash.

The most important reaction of the nitro-compounds—their behaviour on reduction—is described later (p. 439).

Nitrobenzene, $C_6H_5.NO_2$, is usually prepared in the laboratory by slowly adding to benzene (10 parts) a mixture of nitric acid of sp. gr. 1·45 (12 parts), and concentrated sulphuric acid (16 parts), the temperature being kept below about 40°.

The benzene is placed in a flask and the acid mixture is *slowly* added from a dropping funnel (which is *not* fitted into a cork). The contents of the flask are kept cool in water and are given a rotatory motion during the operation. As soon as all the acid has been added, the product is heated at about 80° during half an hour or so, then cooled, and poured into 5–10 vol. of water; the nitrobenzene is separated with the aid of a tap-funnel, washed with a little dilute alkali until free from acid, and well shaken with a few small lumps of anhydrous calcium chloride; as these dissolve, more are added from time to time, until the nitrobenzene becomes clear. The oil is then filtered into a distillation flask and fractionated (if incompletely dried, the contents of the flask crackle and splutter when heat is applied); the liquid collected from about 200–215° is sufficiently free from impurity for ordinary purposes, and any dinitrobenzene which may have been formed will be obtained as a residue.

On the large scale, nitrobenzene is prepared in a similar manner, but the operation is carried out in iron vessels provided with stirrers; the product is separated from the acid mixture and exposed to a current of steam until free from benzene.

Nitrobenzene is a very pale-yellow oil of sp. gr. 1·2 at 20°, and has a strong smell, which is very like that of benzaldehyde (p. 499); it boils at 211°, is volatile in steam, and is miscible with organic liquids, but is practically insoluble in water. In spite of the fact that it is poisonous, it was formerly employed, instead of oil of bitter almonds, for flavouring and perfuming purposes, under the name of 'essence of mirbane'; its principal use, however, is for the manufacture of aniline (p. 443). It may often prove to be a useful solvent instead of more volatile liquids.

***m*-Dinitrobenzene,** $C_6H_4(NO_2)_2$, is easily obtained, together with small proportions of the *o*- and *p*-dinitro-compounds, by the nitration of nitrobenzene (or of benzene).

Nitrobenzene (1 part) is gradually run into a mixture of nitric acid (sp. gr. 1·5; 1½ parts) and concentrated sulphuric acid (1½ parts) to which a few small pieces of unglazed earthenware have

been added to prevent bumping; the flask is then cautiously heated on a sand-bath, until a drop of the oil solidifies completely when it is stirred with cold water. When cold, the mixture is poured into a large volume of water, and the solid is separated by filtration, washed with water, and recrystallised from hot alcohol until its melting-point is constant; the *o*- and *p*-compounds, which together form only about 8% of the original product, remain in the mother-liquors.

m-Dinitrobenzene crystallises in very pale-yellow needles, melts at 90°, and is volatile in steam; it is only very sparingly soluble in boiling water and is very poisonous. On reduction with alcoholic ammonium sulphide, it is first converted into m-*nitroaniline* (p. 447), and then into m-*phenylenediamine* (m-*diaminobenzene*), $C_6H_4(NH_2)_2$ (p. 448).

o-*Dinitrobenzene* and p-*dinitrobenzene* are colourless and melt at 118° and 173° respectively; the former may be obtained from the mother-liquor from the crystallisation of the crude *m*-compound (above) and the latter by oxidising quinone dioxime (p. 507) with nitric acid. They resemble the corresponding *m*-compound in their behaviour on reduction, and in most other respects. *o*-Dinitrobenzene, however, differs notably from the other two isomerides, inasmuch as with boiling caustic soda, it yields o-*nitrophenol* (p. 484), and with alcoholic ammonia, at moderately high temperatures, it gives o-*nitroaniline* (p. 447). A similar behaviour is observed in the case of other *o*-dinitro-compounds, the presence of the one nitro-group rendering the other more easily displaceable.

Symmetrical or 1:3:5-*trinitrobenzene*, $C_6H_3(NO_2)_3$, is formed when the *m*-dinitro-compound is heated with a mixture of nitric and anhydrosulphuric acids; it is colourless, and melts at 121–122°.

It is best prepared by oxidising T.N.T. (p. 437) with dichromate and sulphuric acid and then heating the resulting *trinitrobenzoic acid* with water,

$$C_6H_2(NO_2)_3 \cdot CH_3 \longrightarrow C_6H_2(NO_2)_3 \cdot COOH \longrightarrow C_6H_3(NO_2)_3.$$

The halogen derivatives of benzene are readily nitrated, yielding, however, the *o*- and *p*-mononitro-derivatives only, according to the orientation rule (p. 433); the *m*-nitro-halogen compounds, therefore, are prepared by chlorinating or brominating nitrobenzene. All these nitro-halogen derivatives are crystalline, and, as will be seen from the following table, their melting-points exhibit the

regularity already mentioned (p. 413) except in the case of m-*iodonitrobenzene* :

		Ortho	*Meta*	*Para*
Chloronitrobenzene,	$C_6H_4Cl \cdot NO_2$	33°	46°	83°
Bromonitrobenzene,	$C_6H_4Br \cdot NO_2$	42°	56°	127°
Iodonitrobenzene,	$C_6H_4I \cdot NO_2$	54°	38°	174°

They are, on the whole, very similar in chemical properties, except that, as already pointed out, the *o*- and *p*-compounds differ notably from the *m*-compounds in their behaviour with alcoholic potash and ammonia, a difference which recalls that shown by the three dinitrobenzenes.

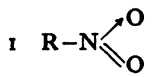
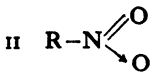
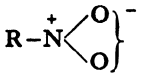
The nitrotoluenes, $C_6H_4(CH_3) \cdot NO_2$, are important, because they serve for the preparation of the toluidines (p. 448). The *o*- and *p*-compounds are prepared by nitrating toluene, and may be separated by fractional distillation under reduced pressure, combined with crystallisation at low temperatures ; o-*nitrotoluene* melts at −4°, and boils at 222°, whereas p-*nitrotoluene* melts at 52°, and boils at 238°. m-*Nitrotoluene* is also formed in very small proportions by nitrating toluene ; it melts at 16°, and boils at 230°.

Trinitrotoluene, $C_6H_2(CH_3)(NO_2)_3$[$3NO_2$ = 2:4:6], manufactured by the further nitration of the mixture of *o*- and *p*-nitrotoluenes, is a very important explosive (T.N.T.) ; it melts at 81° without decomposition, but it can be detonated with mercury fulminate (p. 363) ; mixed with ammonium nitrate, it forms the explosive, *amatol*. *Ammonal* is a mixture of T.N.T., ammonium nitrate and aluminium.

The *trinitrobenzene* from T.N.T. (p. 436), on reduction, yields 1:3:5-triaminobenzene, which is converted into phloroglucinol (p. 492) by boiling hydrochloric acid.

Phenylnitromethane, $C_6H_5 \cdot CH_2 \cdot NO_2$, is an example of a compound which contains a nitro-group in the side chain. It is obtained by the interaction of *benzyl iodide*, $C_6H_5 \cdot CH_2I$, and silver nitrite, and is a liquid, boiling at 141° (35 mm.). Like the primary and secondary nitroparaffins, it is a *pseudo-acid* (p. 194), and gives, with sodium hydroxide, a salt, $[C_6H_5 \cdot CH{:}NOO]Na$, which is derived from the acid, $C_6H_5 \cdot CH{:}NO \cdot OH$; this acid is obtained as a crystalline precipitate (m.p. 84°) when the sodium salt is treated with a mineral acid in aqueous solution, but it soon undergoes change into phenylnitromethane, even at ordinary temperatures.

Structure of the nitro-group. According to the electronic theory of valency and the theory of resonance, if the nitro-group is represented by (I),[1] the conditions for resonance are satisfied and the (identical) contributory forms are (I) and (II). The actual state of the group, therefore, may be the mesomeric form, which might be roughly indicated by (III). The group, however, is usually represented by $-NO_2$.

I  II  III 

[1] In these and similar formulae a line indicates a pair of shared electrons of which one is supplied by each atom joined by the bond (covalency); an arrow implies that both electrons of the shared pair are contributed by the atom at the tail of the arrow (co-ordinate covalency). As the latter distribution produces charges on the atoms it may be alternatively represented by $\overset{+}{N}—\overset{-}{O}$.

CHAPTER 28

AMINO-COMPOUNDS AND AMINES

THE hydrogen atoms in aromatic compounds may be indirectly displaced by amino-groups, and in this way bases, such as *aniline*, $C_6H_5 \cdot NH_2$, *benzylamine*, $C_6H_5 \cdot CH_2 \cdot NH_2$, and *diaminobenzene*, $C_6H_4(NH_2)_2$, are produced. These compounds are analogous to, and have many properties in common with, the aliphatic amines, but as those which contain one or more nuclear amino-radicals differ in several respects from those in which this radical is present in the side chain, they may be considered as forming a separate group and distinguished as *amino-compounds*.

Amino-Compounds

The amino-compounds, therefore, are derived from benzene and other aromatic substances, by the substitution of one or more amino-groups for hydrogen atoms of the *nucleus*; they may be classed as mono-, di-, tri-, etc., amino-compounds, according to the number of such groups which they contain,

$C_6H_5 \cdot NH_2$	$C_6H_4(NH_2)_2$	$C_6H_3(NH_2)_3$
Aminobenzene (aniline)	Diaminobenzene	Triaminobenzene

With the exception of aniline, the homologous amino-compounds show the usual isomerism; there are, for example, three isomeric (o.m.p.) *diaminobenzenes*, and three isomeric (o.m.p.) *aminotoluenes*, or *toluidines*, $C_6H_4(CH_3) \cdot NH_2$; a fourth isomeride of the toluidines, namely, *benzylamine*, $C_6H_5 \cdot CH_2 \cdot NH_2$ (p. 452) is also known.

Preparation. The amino-compounds are nearly always prepared by the reduction of the nitro-compounds; various reducing agents, such as tin, zinc, or iron, with hydrochloric (or acetic) acid, are employed, and also a solution of stannous chloride in hydrochloric acid,

$$C_6H_5 \cdot NO_2 + 6H = C_6H_5 \cdot NH_2 + 2H_2O,$$
$$C_6H_4(CH_3) \cdot NO_2 + 6H = C_6H_4(CH_3) \cdot NH_2 + 2H_2O,$$
$$C_6H_5 \cdot NO_2 + 3SnCl_2 + 6HCl = C_6H_5 \cdot NH_2 + 3SnCl_4 + 2H_2O.$$

Reduction is usually effected merely by treating the nitro-compound with the reducing agent, when a vigorous reaction often

ensues, and the application of heat is seldom necessary except towards the end of the operation. The solution then contains the amino-compound, combined as a simple salt; when, however, tin, or stannous chloride, and hydrochloric acid have been used, a complex salt, B_2,H_2SnCl_6 (which often separates in crystals), may be produced from the hydrochloride of the base and the stannic chloride which has been formed. In either case the amino-compound is liberated by adding an excess of caustic soda (or lime), and is distilled in steam or extracted with ether or some other solvent; when tin, or stannous chloride, has been used, the acid solution may be treated with hydrogen sulphide, filtered, and evaporated, in order to obtain the hydrochloride of the amino-compound.

Nitro-compounds may also be reduced to amino-compounds in *alkaline* solution with hydrogen sulphide, or, more conveniently, with an alcoholic solution of ammonium sulphide (p. 447),

$$C_6H_5 \cdot NO_2 + 3H_2S = C_6H_5 \cdot NH_2 + 2H_2O + 3S;$$

a mixture of ferrous sulphate and an alkali hydroxide in aqueous solution is also frequently employed. Hydrogen, in the presence of platinum or Raney nickel (p. 408), may also be used.

When a compound contains two or more nitro-groups it may be partially reduced by treating its alcoholic solution either with the calculated quantity of stannous (or titanous) chloride and hydrochloric acid, or with ammonia and hydrogen sulphide; in the latter, as in the former case, one nitro-group is reduced before a second is attacked, so that if the current of gas is stopped at the right time (which must be ascertained by experiment), partial reduction only takes place. Dinitrobenzene, for example, can be converted into nitroaniline by either of these methods, the latter being the more convenient,

$$C_6H_4{<}^{NO_2}_{NO_2} + 3H_2S = C_6H_4{<}^{NO_2}_{NH_2} + 2H_2O + 3S.$$

Amino-compounds may also be obtained by reducing certain nitroso-derivatives (p. 451) and also azo- and hydrazo-compounds (p. 465).

The monoamino-derivatives of benzene, toluene, xylene, etc., are prepared commercially in large quantities by reducing the nitro-compounds with iron and hydrochloric acid.

The diamino-compounds, such as the o-, m-, and p-*diamino-benzenes* or *phenylenediamines*, $C_6H_4(NH_2)_2$, may be prepared by reducing either the corresponding *dinitrobenzenes*, $C_6H_4(NO_2)_2$, or the *nitroanilines*, $C_6H_4(NO_2)\cdot NH_2$.

Properties. The *monoamino*-compounds are mostly liquids, which distil without decomposition, and are specifically heavier than water; they have a faint but characteristic odour, and dissolve freely in organic solvents, but are only sparingly soluble in water; on exposure to air and light many darken, and ultimately become brown or black, so that colourless samples are seldom seen.

They are comparatively weak bases, and are *neutral* to litmus, in which respect they differ from the strongly basic aliphatic amines and from the aromatic amines, such as benzylamine (p. 452), which contain the amino-group in the *side chain*; for this and other reasons (p. 482), the phenyl group may be regarded as a negative or acidic radical. Nevertheless, the amino-compounds combine with acids to form salts, such as *aniline hydrochloride*, $C_6H_5\cdot NH_2,HCl$, and *phenylenediamine dihydrochloride*, $C_6H_4(NH_2)_2$, $2HCl$.[1] The simple salts of the amino-compounds are usually soluble in water, by which they are hydrolysed to a greater or less extent; they are completely decomposed by an excess of caustic alkali or alkali carbonate.

When two hydrogen atoms in ammonia are displaced by phenyl groups, as in *diphenylamine*, $(C_6H_5)_2NH$ (p. 452), the product is so feebly basic that its salts are almost completely hydrolysed by water. *Triphenylamine*, $(C_6H_5)_3N$ (p. 452), moreover, does not form salts.

In a similar manner, the hydroxy-, nitro-, and halogen derivatives of the amino-compounds, such as *aminophenol*, $C_6H_4(OH)\cdot NH_2$, *nitroaniline*, $C_6H_4(NO_2)\cdot NH_2$, *chloroaniline*, $C_6H_4Cl\cdot NH_2$, etc., are also weaker bases than the unsubstituted amino-compounds, because the presence of the negative group or atom, HO—, NO_2—, Cl—, etc., enhances the acidic character of the phenyl radical.

The amino-compounds *differ* from the aliphatic primary amines, and from those aromatic primary amines which contain the amino-group in the side chain, in their characteristic behaviour towards nitrous acid. Although, when their salts are *warmed* with nitrous acid (a nitrite and an acid) in aqueous solution, they yield phenols

[1] These formulae may also be written $[C_6H_5\cdot NH_3]Cl$ and $[C_6H_4(NH_3)_2]Cl_2$ respectively (p. 228).

by the substitution of the hydroxy- for the amino-group, just as the aliphatic amines give alcohols,

$$C_6H_5 \cdot NH_2 + NO_2H = C_6H_5 \cdot OH + N_2 + H_2O,$$
$$C_2H_5 \cdot NH_2 + NO_2H = C_2H_5 \cdot OH + N_2 + H_2O,$$

in the *cold* (usually at about 0°), under otherwise the same conditions, they are converted into *diazonium salts* (p. 454), substances which are not produced from the primary aliphatic amines.

It will be evident from the above statements that there are several important differences between the amino-compounds and the aliphatic primary amines, the character of an amino-group of the nucleus being influenced by its state of combination; nevertheless, except as regards those points already mentioned, amino-compounds have, on the whole, properties very similar to those of the aliphatic primary amines. Like the latter, they react readily with alkyl halides, yielding mono- and di-alkyl derivatives, such as *methylaniline*, $C_6H_5 \cdot NH \cdot CH_3$, *dimethylaniline*, $C_6H_5 \cdot N(CH_3)_2$, etc., and also quaternary ammonium salts such as *phenyltrimethylammonium iodide*, $C_6H_5 \cdot N(CH_3)_3I$, or $[C_6H_5 \cdot N(CH_3)_3]I$.

They are also readily changed by acid chlorides and anhydrides, yielding substances such as *acetanilide* and *acetotoluide*, which are closely allied to, and may be regarded as derived from, the aliphatic amides,

$$C_6H_5 \cdot NH_2 + CH_3 \cdot COCl = C_6H_5 \cdot NH \cdot CO \cdot CH_3 + HCl,$$
$$C_6H_4(CH_3) \cdot NH_2 + Ac_2O = C_6H_4(CH_3) \cdot NHAc + CH_3 \cdot COOH.$$

These *substituted amides* are crystalline, and serve for the identification of the (liquid) amino-compounds; like simple amides, they are hydrolysed by boiling acids or alkalis,

$$C_6H_4{<}\begin{matrix}CH_3\\NH \cdot CO \cdot CH_3\end{matrix} + H_2O = C_6H_4{<}\begin{matrix}CH_3\\NH_2\end{matrix} + CH_3 \cdot COOH.$$

Sulphuric acid, previously diluted with about an equal volume of water, is generally the most suitable reagent, but in some cases many hours may be necessary to complete the hydrolysis even at 100°.

The amino-compounds, like the aliphatic primary amines, give the carbylamine reaction; when *one drop* of aniline, for example, is heated with alcoholic potash and chloroform, an intensely nauseous smell is observed, due to the formation of phenylcarbylamine,

$$C_6H_5 \cdot NH_2 + CHCl_3 + 3KOH = C_6H_5 \cdot NC + 3KCl + 3H_2O.$$

Diamino- and *triamino-compounds*, such as the three (o.m.p.) *phenylenediamines* or *diaminobenzenes*, $C_6H_4(NH_2)_2$, and the *triaminobenzenes*, $C_6H_3(NH_2)_3$, are very similar to the monoamino-compounds in chemical properties, but differ from them usually in being solid, more readily soluble in water, and less volatile; triamino-compounds generally form salts, such as $C_6H_3(NH_2)_3,2HCl$, with only *two* equivalents of an acid.

Aniline and its Derivatives

Aniline, $C_6H_5 \cdot NH_2$ (aminobenzene, phenylamine), was first obtained by Unverdorben in 1826 by strongly heating indigo.[1] Runge in 1834 showed that aniline is contained in small quantities in coal-tar; its preparation from nitrobenzene was first accomplished by Zinin in 1841.

Aniline may be prepared by the reduction of nitrobenzene with iron and hydrochloric acid, a method which is used on a very large scale,

$$C_6H_5 \cdot NO_2 + 6H = C_6H_5 \cdot NH_2 + 2H_2O.$$

In the laboratory, nitrobenzene (25 g.) and iron borings (43 g.) are heated together on a water-bath in a litre flask, fitted with a short, wide air-condenser; concentrated hydrochloric acid (15 c.c.) is then added through the condenser in *small* quantities at a time in the course of about 20 minutes, after which heating is continued during about 15 minutes longer. The contents of the flask are *vigorously* shaken from time to time during the operation.

A concentrated solution of sodium hydroxide (about 5 g.) is then slowly added to the cooled product, and the liberated aniline is distilled in steam. The distillate is saturated with salt, and the base is separated, dried over solid alkali, decanted into a dry flask, and purified by distillation.

The quantity of hydrochloric acid used on the large scale is about $\frac{1}{10}$th of that calculated from the equation,

$$C_6H_5 \cdot NO_2 + 3Fe + 6HCl = C_6H_5 \cdot NH_2 + 3FeCl_2 + 2H_2O,$$

because in the presence of ferrous chloride, aniline is formed by other reactions, such as the following,

$$C_6H_5 \cdot NO_2 + 2Fe + 4H_2O = C_6H_5 \cdot NH_2 + 2Fe(OH)_2.$$

[1] The name aniline is derived from the Spanish *anil* or the Arabic *nīlī*, indigo.

For the preparation of aniline in the laboratory, tin and hydrochloric acid may also be employed,

$$2C_6H_5 \cdot NO_2 + 3Sn + 12HCl = 2C_6H_5 \cdot NH_2 + 3SnCl_4 + 4H_2O.$$

The operation is carried out with the apparatus just described, using nitrobenzene (25 g.), granulated tin (45 g.), and concentrated hydrochloric acid (90 c.c.), which is added in *small* portions at a time. The mixture is not heated, and must be cooled if the reaction becomes too violent. When all the acid has been added, the flask is left on a water-bath until drops of oil are no longer visible, and is then cooled until the product, *aniline stannichloride* (p. 440) begins to crystallise ; a cold solution of sodium hydroxide (45 g.) in water (about 100 c.c.) is added *very cautiously* in small quantities at a time, the flask being well shaken, and the liberated aniline is isolated, as described above.

Aniline is a *poisonous* oil, boiling at 184°, and having a faint odour, which is common to many amino-compounds ; it is sparingly soluble in water, and ordinary samples turn yellow when exposed to light and air, becoming ultimately almost black. Although neutral to litmus, it has basic properties, and, with acids, it forms soluble salts, such as aniline *hydrochloride*, $C_6H_5 \cdot NH_2$, HCl, and the rather sparingly soluble normal *sulphate*, $(C_6H_5 \cdot NH_2)_2$, H_2SO_4. The former, like the hydrochlorides of the aliphatic amines, forms complex salts with platinic and auric chlorides ; a moderately concentrated solution of the hydrochloride gives with platinic chloride, for example, the *platinichloride*, $(C_6H_5 \cdot NH_2)_2$, H_2PtCl_6, which is precipitated in yellow plates, and is only moderately soluble in cold water.

When one drop of aniline is heated with chloroform and alcoholic potash, it yields phenylcarbylamine, a substance readily recognised by its extremely disagreeable odour ; aniline may also be detected by treating its aqueous solution with bleaching-powder or sodium hypochlorite, when an intense purple colouration is produced.

These qualitative reactions, combined with a determination of the boiling-point, are sufficient for the identification of aniline ; if in the form of a salt, and the boiling-point of the base is not taken, aniline may be identified with the aid of its *acetyl* (*acetanilide*) or *benzoyl* derivative (*benzanilide*), or its *tribromo*-derivative (p. 446).

When acid solutions of the salts of aniline are treated with nitrous acid in the cold, diazonium salts (p. 454) are formed, but at

higher temperatures, the latter are decomposed, with the formation of phenol (p. 478).

Aniline is very largely employed in the manufacture of dyes, and in the preparation of a great many aromatic compounds such as quinone, quinoline, etc.

Acetanilide, $C_6H_5 \cdot NH \cdot CO \cdot CH_3$, is formed when aniline is treated with acetyl chloride or acetic anhydride.

The product of the (vigorous) reaction is treated with cold water, in order to extract the aniline hydrochloride or acetate, which is also formed, and the undissolved acetanilide is then recrystallised from boiling water.

It is conveniently prepared by boiling aniline (10 g.) with acetic acid (15 g.) in a reflux apparatus during 2–4 hours, when the aniline acetate which is first formed is slowly converted into acetanilide, with the elimination of water,

$$C_6H_5 \cdot NH_2, CH_3 \cdot COOH = C_6H_5 \cdot NH \cdot CO \cdot CH_3 + H_2O.$$

The conversion is not complete, because the reaction is reversible, but the acetanilide is easily separated from unchanged aniline acetate and purified, in the manner just described.

Acetanilide crystallises in plates, melts at 114°, and is very sparingly soluble in cold, but readily so in hot, water; when heated with acids or alkalis, it is hydrolysed, giving aniline and acetic acid (one or the other as a salt). It is used in medicine, under the name of *antifebrin* or *acetanilidum*, for reducing the body-temperature in cases of fever.

Formanilide, $C_6H_5 \cdot NH \cdot CHO$ (m.p. 50°), as well as *oxanilide*, $C_6H_5 \cdot NH \cdot CO \cdot CO \cdot NH \cdot C_6H_5$ (m.p. 254°), may be prepared by merely heating the corresponding aniline salts; *benzanilide*, $C_6H_5 \cdot NH \cdot CO \cdot C_6H_5$ (m.p. 163°), is very easily obtained by the Schotten-Baumann method (p. 514).

Thiocarbanilide, $S{:}C(NH \cdot C_6H_5)_2$, or *diphenylthiourea*, is prepared by passing the vapour of carbon disulphide into aniline, which is heated at about 100°, or by boiling a mixture of the two substances,

$$2C_6H_5 \cdot NH_2 + CS_2 = S{:}C(NH \cdot C_6H_5)_2 + H_2S;$$

it crystallises in plates, melting at 154°, and is used to hasten the vulcanisation of rubber. When it is boiled with concentrated

hydrochloric acid, it first yields *phenyl* iso*thiocyanate* (*phenyl mustard oil*) and aniline,

$$S:C(NH\cdot C_6H_5)_2+HCl = C_6H_5\cdot N:CS+C_6H_5\cdot NH_2, HCl,$$

and then *triphenylguanidine*, $C_6H_5\cdot N:C(NH\cdot C_6H_5)_2$ (m.p. 144°), and other products.

Phenyl *iso*thiocyanate, $C_6H_5\cdot N:CS$, is obtained as described above; it is a liquid (b.p. 221°), with a characteristic disagreeable smell. It reacts with alcohols giving phenylthiourethanes,

$$C_6H_5\cdot N:CS+C_2H_5\cdot OH = C_6H_5\cdot NH\cdot CS\cdot OC_2H_5,$$

and when heated with litharge it yields *phenyl carbimide*,

$$C_6H_5\cdot N:CS+PbO = C_6H_5\cdot N:CO+PbS.$$

Phenyl carbimide, *phenyl* iso*cyanate*, $C_6H_5\cdot N:CO$, usually prepared by heating aniline hydrochloride at about 200°, in a stream of carbonyl chloride, is an unpleasant smelling liquid, boiling at 164°. It is slowly decomposed by water, giving *diphenylurea*,

$$2C_6H_5\cdot N:CO+H_2O = (C_6H_5\cdot NH)_2CO+CO_2,$$

and is used for the characterisation of alcohols and amines (primary and secondary), with which it yields (crystalline) phenylurethanes and phenylurea derivatives respectively,

$$C_6H_5\cdot N:CO+C_2H_5\cdot OH = C_6H_5\cdot NH\cdot CO\cdot OC_2H_5,$$
$$C_6H_5\cdot N:CO+R_2NH = C_6H_5\cdot NH\cdot CO\cdot NR_2.$$

Halogen Substitution Products of Aniline. Aniline and, in fact, most amino-compounds are much more readily attacked by halogens than are the hydrocarbons. When aniline, for example, is treated with an excess of chlorine- or bromine-water, it is converted into *trichloroaniline*, $C_6H_2Cl_3\cdot NH_2$ (m.p. 77°), or *tribromoaniline*, $C_6H_2Br_3\cdot NH_2$ (m.p. 119°); both of these compounds contain the halogen atoms in the 2:4:6-positions and their salts are completely hydrolysed by water.

The o- and p-*chloroanilines*, $C_6H_4Cl\cdot NH_2$, may be prepared by passing chlorine into acetanilide, the *p*-derivative being obtained in the larger quantity. The two anilides are separated by crystallisation, and are then decomposed by boiling alkalis or acids,

$$C_6H_4Cl\cdot NH\cdot CO\cdot CH_3+H_2O = C_6H_4Cl\cdot NH_2+CH_3\cdot COOH.$$

The effect of introducing an acetyl radical into the amino-group (which is then said to be *protected* or *blocked*) is to make the aniline less reactive, but it is still far more so than benzene.

m-*Chloroaniline* is most conveniently prepared by the reduction of *m*-chloronitrobenzene, $C_6H_4Cl \cdot NO_2$ (a substance which is formed by chlorinating nitrobenzene in the presence of antimony). o-*Chloroaniline* and m-*chloroaniline* boil at 209° and 230° respectively; p-*chloroaniline* melts at 70° and boils at 232°.

The **nitroanilines,** $C_6H_4(NO_2) \cdot NH_2$, cannot be prepared by nitrating aniline, because the base undergoes oxidation and other complex changes occur; when, however, the amino-group is protected by the introduction of an acetyl radical, nitration takes place in a normal manner; the acetyl derivatives of o- and p-*nitroaniline* which are formed, are separated, and then converted into the corresponding nitroanilines by hydrolysis with diluted hydrochloric acid.

m-*Nitroaniline* is conveniently prepared by the partial reduction of *m*-dinitrobenzene with ammonium sulphide (p. 440).

m-Dinitrobenzene (2 parts), alcohol (6 parts), and strong ammonium hydroxide solution (1 part) are placed in a flask, and hydrogen sulphide is passed into the liquid, which, later on, is warmed from time to time. The dinitrobenzene gradually disappears and sulphur is deposited. The contents of the flask are tested at intervals, in order to ascertain when the stream of hydrogen sulphide should be stopped. For this purpose a small quantity of the solution and a portion of the deposit are evaporated together in a basin on the water-bath, and the residue is treated with cold dilute hydrochloric acid, which dissolves *m*-nitroaniline (in the form of its hydrochloride), but not dinitrobenzene or sulphur; the residue insoluble in dilute acid is then extracted with a little boiling alcohol, and the filtered solution is treated with water (or evaporated), in order to prove the presence or absence of *m*-dinitrobenzene (sulphur is only very sparingly soluble in alcohol). When the test portion gives a satisfactory result, the *m*-nitroaniline is extracted from the whole of the product in the manner just described, the acid solution is treated with an excess of caustic soda, and the precipitated base is purified by recrystallisation from boiling water or very dilute aqueous alcohol.

o-*Nitroaniline* melts at 71°, *m*- at 114°, and *p*- at 148°; they are all sparingly soluble in cold water, readily in alcohol, and on reduction they yield the corresponding o-, m-, and p-*phenylenediamines* (p. 448),

$$C_6H_4{<}\begin{matrix}NO_2\\NH_2\end{matrix} + 6H = C_6H_4{<}\begin{matrix}NH_2\\NH_2\end{matrix} + 2H_2O.$$

Homologues of Aniline. The **toluidines** or amino-toluenes, $C_6H_4(CH_3)\cdot NH_2$, may be prepared by reducing the corresponding *o*-, *m*-, and *p*-nitrotoluenes (p. 437), with iron or tin and hydrochloric acid, as described in the case of the preparation of aniline from nitrobenzene ; the *o*- and *p*-compounds may also be obtained from methylaniline (p. 450). Both o- and m-*toluidine* are oils, boiling at 201° and 203° respectively, but p-*toluidine* is crystalline, and melts at 45°, boiling at 200°.

The o-, m-, and p-*acetotoluides*, $CH_3\cdot C_6H_4\cdot NH\cdot CO\cdot CH_3$, melt at 110°, 65° and 145° respectively, the corresponding *benzotoluides*, $CH_3\cdot C_6H_4\cdot NH\cdot CO\cdot C_6H_5$, at 145°, 125°, and 158° respectively. These compounds may serve for the identification of the bases (p. 514).

When treated with nitrous acid, the toluidines yield diazonium salts, from which the corresponding cresols, $C_6H_4(CH_3)\cdot OH$, may be obtained (p. 487), and in all other reactions they show very great similarity to aniline ; *o*- and *p*-toluidine are much employed in the manufacture of dyes.

The **diaminobenzenes** or *phenylenediamines*, $C_6H_4(NH_2)_2$, are obtained by the reduction of the corresponding dinitrobenzenes, or the nitroanilines, and a general description of their properties has been given (p. 443) ; commercial preparations are often brown, as a result of atmospheric oxidation. o-*Phenylenediamine* melts at 102°, the *m*- and *p*-compounds at 63° and 147° respectively. m-*Phenylenediamine* gives an intense yellow colouration with a trace of nitrous acid, and is employed in water-analysis for the detection and estimation of nitrites ; both the *m*- and *p*-compounds are used in the manufacture of dyes.

Alkylanilines

Those derivatives of the amino-compounds, obtained by displacing one or both of the hydrogen atoms of the amino-group by alkyl radicals, are of considerable importance, and are usually known as **alkylanilines.** They are obtained by treating the amino-compounds with the alkyl halides, the reactions being analogous to those which occur in the formation of secondary, and tertiary, from primary, aliphatic amines,

$$C_6H_5\cdot NH_2 + RCl = C_6H_5\cdot NHR, HCl,$$
$$C_6H_5\cdot NHR + RCl = C_6H_5\cdot NR_2, HCl.$$

Instead of an alkyl halide, a mixture of an alcohol and an acid may be used, provided that a high temperature is employed; *methyl-* and *dimethyl-aniline*, for example, are prepared, on the large scale, by heating aniline with methyl alcohol and a little sulphuric acid at about 230° under pressure, whereas *ethyl-* and *diethyl-aniline* are manufactured in a similar manner, using hydrochloric acid and ethyl alcohol (1 or 2 mol.),

$$C_6H_5\cdot NH_2,\ HCl+C_2H_5\cdot OH = C_6H_5\cdot NH(C_2H_5),\ HCl+H_2O,$$
$$C_6H_5\cdot NH_2,\ HCl+2C_2H_5\cdot OH = C_6H_5\cdot N(C_2H_5)_2,\ HCl+2H_2O.$$

In these reactions the alcohol is first converted into an alkyl hydrogen sulphate, or an alkyl halide, which then reacts with the base.

Since methyl- and dimethyl-aniline cannot be separated by fractional distillation, the latter is prepared as described above, using an excess of methyl alcohol, whereas the former is more conveniently obtained by running aniline and formalin separately into a vessel containing warm caustic soda and zinc dust; condensation occurs giving complex compounds, $[—CH_2\cdot N(C_6H_5)—]_n$, which are then reduced mainly to methylaniline.

These mono- and di-alkyl derivatives are somewhat stronger bases than the amino-compounds from which they are formed, and are, in fact, similar in many very important ways to the secondary and tertiary aliphatic amines respectively; they may be regarded as derived from the primary and secondary aliphatic amines respectively, by the substitution of a phenyl group for a hydrogen atom, just as the secondary and tertiary aliphatic amines are obtained by the displacement of hydrogen atoms by alkyl groups. Methylaniline, for example, is also *phenylmethylamine*, and its properties are those of an aryl substitution product of methylamine.

The mono-alkylanilines, like secondary aliphatic amines, are converted into pale-yellow *nitrosoamines* on treatment with nitrous acid,

$$C_6H_5\cdot NH\cdot CH_3+HO\cdot NO = C_6H_5\cdot N(NO)\cdot CH_3+H_2O.$$

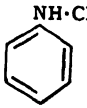
These nitrosoamines give Liebermann's nitroso-reaction (pp. 217, 482), and on reduction they yield a hydrazine derivative,

$$C_6H_5\cdot N(NO)\cdot CH_3+4H = C_6H_5\cdot N(NH_2)\cdot CH_3+H_2O,$$

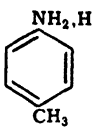
or are decomposed into ammonia and the alkylanilines from which they were derived,

$$C_6H_5\cdot N(NO)\cdot CH_3+6H = C_6H_5\cdot NH\cdot CH_3+NH_3+H_2O.$$

When the hydrochloride of an alkylaniline, such as *methylaniline* or *dimethylaniline*, is heated at 280–300°, the alkyl group leaves the nitrogen atom and displaces hydrogen of the nucleus (Hofmann),



Methylaniline hydrochloride



p-Toluidine hydrochloride

In the case of dimethylaniline the change takes place in two stages :

$$C_6H_5\cdot N(CH_3)_2 \longrightarrow C_6H_4\!<\!\begin{matrix}CH_3\\NH\cdot CH_3\end{matrix} \longrightarrow C_6H_3\!<\!\begin{matrix}CH_3\ (4)\\CH_3\ (2)\\NH_2\ (1)\end{matrix}$$

Dimethylaniline — Methyl-*p*-toluidine — Xylidine

In the first *isomeric change*, the alkyl group displaces hydrogen from the *para*-, and also from the *ortho*-position, but principally the former.

Methylaniline, $C_6H_5\cdot NH\cdot CH_3$, prepared as described above, boils at 194°, and has more strongly marked basic properties than aniline. On the addition of sodium nitrite to its solution in an excess of dilute hydrochloric acid, *methylphenylnitrosoamine*, $C_6H_5\cdot N(NO)\cdot CH_3$, is formed, and as this compound is *non-basic*, it separates as a light-yellow oil ; with concentrated acid, however, it is gradually converted into p-*nitrosomethylaniline*.

Methylacetanilide, $C_6H_5\cdot N(CH_3)\cdot CO\cdot CH_3$ (acetylmethylaniline), melts at 102°, and *methylbenzanilide* or *benzoylmethylaniline*, $C_6H_5\cdot N(CH_3)\cdot CO\cdot C_6H_5$, at 63°.

Ethylaniline, $C_6H_5\cdot NH\cdot C_2H_5$, boils at 205°.

Dimethylaniline, $C_6H_5\cdot N(CH_3)_2$, prepared as already described, is a strongly basic oil and boils at 193° ; it is largely used in the manufacture of dyes.

Diethylaniline, $C_6H_5\cdot N(C_2H_5)_2$, boils at 216°.

The *di*-alkylanilines, such as dimethylaniline, $C_6H_5\cdot N(CH_3)_2$, react very readily with nitrous acid (a behaviour which is *not* shown by tertiary aliphatic amines), intensely green nitroso-compounds (*not* nitroso*amines*) being formed, the —NO group displacing hydrogen of the *nucleus* from the *p*-position. These substances do

not give Liebermann's nitroso-reaction, and when reduced they yield derivatives of *p*-phenylenediamine,

$$C_6H_4<^{NO}_{N(CH_3)_2}+4H = C_6H_4<^{NH_2}_{N(CH_3)_2}+H_2O.$$

***p*-Nitrosodimethylaniline,** $(CH_3)_2N\cdot C_6H_4\cdot NO$, is prepared by treating dimethylaniline hydrochloride with nitrous acid.

Dimethylaniline (1 part) is dissolved in water (5 parts) and concentrated hydrochloric acid (2·5 parts), and to the *well-cooled* solution the theoretical quantity of sodium nitrite, dissolved in a little water, is slowly added. The yellow crystalline precipitate of p-*nitrosodimethylaniline hydrochloride* is separated by filtration, dissolved in water, and decomposed with sodium carbonate; the free base is extracted with, and crystallised from, ether.

It separates from ether in dark-green plates, melts at 93°, and is used for the manufacture of various dyes. When reduced with zinc and hydrochloric acid it is converted into p-*aminodimethylaniline* (above), and when boiled with caustic soda it is decomposed into dimethylamine and p-*nitrosophenol* (*quinone monoxime*, p. 507),

$$C_6H_4<^{NO}_{NMe_2}+H_2O = NHMe_2+C_6H_4<^{NO}_{OH} \text{ (or } O{:}C_6H_4{:}N\cdot OH).$$

The latter reaction, which is shown by the nitroso-compounds of all tertiary alkylanilines, is useful for the preparation of secondary aliphatic amines.

Tetryl, $C_6H_2(NO_2)_3\cdot N(CH_3)\cdot NO_2$, is a tetranitro-derivative of monomethylaniline, produced by the energetic nitration of dimethylaniline, during which one methyl group is lost as carbon dioxide. It is insoluble in water, melts at 131°, and is used as a detonating agent; with boiling alkalis it gives methylamine and picric acid (p. 485). *Tetranitroaniline*, $C_6H(NO_2)_4\cdot NH_2$ [$4NO_2 = 2{:}3{:}4{:}6$], prepared from *m*-nitroaniline in a similar manner, is also used in detonators.

Diphenylamine and Triphenylamine

The hydrogen atoms of the amino-group in aniline may also be displaced by phenyl radicals, the compounds *diphenylamine*, $(C_6H_5)_2NH$, and *triphenylamine*, $(C_6H_5)_3N$, being produced.

These substances can be obtained by heating aniline with bromo- or iodo-benzene in the presence of a catalyst, copper or bronze.

Diphenylamine, $(C_6H_5)_2NH$, is prepared commercially by heating aniline hydrochloride with aniline at about 200°, in closed vessels,

$$C_6H_5 \cdot NH_2, HCl + C_6H_5 \cdot NH_2 = (C_6H_5)_2NH + NH_4Cl.$$

It melts at 54°, boils at 302°, and is practically insoluble in water. It is only a feeble base, and its salts are decomposed by water; hence diphenylamine, unlike the great majority of bases, is not readily soluble in dilute mineral acids. Its solution in concentrated sulphuric acid gives, with a trace of nitric acid, an intense blue colouration, and therefore serves as a very delicate test for nitric acid or nitrates. Diphenylamine is used in the manufacture of dyes; also for experiments in which a constant high temperature is required.

When treated with potassium, diphenylamine yields a solid potassium derivative, $(C_6H_5)_2NK$, the presence of the two phenyl groups imparting an acidic character to the imino-group.

Triphenylamine, $(C_6H_5)_3N$, may be prepared by heating potassium diphenylamine with bromobenzene at 300°,

$$(C_6H_5)_2NK + C_6H_5Br = (C_6H_5)_3N + KBr,$$

or by heating diphenylamine with iodobenzene in the presence of copper. It melts at 127°, and does not combine with acids, or with alkyl halides.

Aromatic Amines

The aromatic amines, in which the amino-group is united with carbon of the *side chain*, are of far less importance than those in which the amino-group is nuclear, and, as will be seen from the following example, they closely resemble the aliphatic amines in their methods of preparation and chemical properties.

Benzylamine, $C_6H_5 \cdot CH_2 \cdot NH_2$, may be obtained by reducing phenyl cyanide (benzonitrile, p. 515) or benzaldoxime (p. 498),

$$C_6H_5 \cdot CN + 4H = C_6H_5 \cdot CH_2 \cdot NH_2,$$
$$C_6H_5 \cdot CH{:}NOH + 4H = C_6H_5 \cdot CH_2 \cdot NH_2 + H_2O,$$

by treating the amide of phenylacetic acid (p. 525) with bromine and potash,

$$C_6H_5 \cdot CH_2 \cdot CO \cdot NH_2 + Br_2 + 4KOH = C_6H_5 \cdot CH_2 \cdot NH_2 + 2KBr + K_2CO_3 + 2H_2O,$$

and by heating benzyl chloride with alcoholic ammonia,

$$C_6H_5 \cdot CH_2Cl + NH_3 = C_6H_5 \cdot CH_2 \cdot NH_2, HCl.$$

All these reactions are similar to those employed in the preparation of primary aliphatic amines.

Benzylamine is a pungent-smelling liquid, boiling at 185°; it closely resembles the aliphatic amines in nearly all respects, but differs from the amino-compounds (aniline, toluidine, etc.) in being strongly basic, alkaline to litmus, and readily soluble in water. Like other primary amines and amino-compounds, it gives the carbylamine reaction, but when solutions of its salts are treated with nitrous acid, it is converted into the corresponding alcohol (benzyl alcohol, p. 495), and *not* into a diazonium salt.

Secondary and tertiary aromatic amines are formed when a primary amine is heated with a *side chain* aromatic halide; when, for example, benzylamine is heated with benzyl chloride, both *dibenzylamine* and *tribenzylamine* are produced, just as diethylamine and triethylamine are obtained from ethylamine and ethyl bromide,

$$C_6H_5 \cdot CH_2 \cdot NH_2 + C_6H_5 \cdot CH_2Cl = (C_6H_5 \cdot CH_2)_2NH, HCl,$$
$$(C_6H_5 \cdot CH_2)_2NH + C_6H_5 \cdot CH_2Cl = (C_6H_5 \cdot CH_2)_3N, HCl.$$

When, therefore, benzyl chloride is heated with alcoholic ammonia, the product contains all three amines and some quaternary base.

*β-Amino-*n*-propylbenzene*, $C_6H_5 \cdot CH_2 \cdot CH(NH_2) \cdot CH_3$, may be prepared by the reduction of phenylacetoneoxime; it is used in medicine, for inhalation,[f] in cases of hay fever and asthma (*amphetamine*, *benzedrine*). Its sulphate, administered orally, is said to have a stimulating effect on the central nervous system, causing wakefulness and promoting mental activity and self-confidence.

CHAPTER 29

DIAZONIUM SALTS AND RELATED COMPOUNDS

It has already been stated that when the amino-compounds, in the form of their salts, are treated with nitrous acid in *warm* aqueous solution, they yield phenols; when, however, a *well-cooled*, dilute aqueous solution of aniline hydrochloride is treated with nitrous acid, phenol is *not* produced, and the solution contains an unstable substance, *phenyldiazonium chloride* (*diazobenzene chloride*),

$$C_6H_5 \cdot NH_2, HCl + NO_2H = C_6H_5 \cdot N_2Cl + 2H_2O.$$

In this very important respect, then, aniline, and all those amino-compounds which contain the amino-group directly united with carbon of the *nucleus*, differ from aliphatic primary amines; the latter are directly converted into alcohols by nitrous acid in the cold, whereas the former are first transformed into diazonium salts, which, usually only at higher temperatures, decompose more or less readily, with the formation of phenols (p. 478).

The *diazo-* or *diazonium* salts were discovered in 1858 by P. Griess, and may be regarded as salts of *phenyldiazonium hydroxide*, $C_6H_5 \cdot N_2 \cdot OH$, and its derivatives.

The bases or hydroxides from which these salts are derived are only known in aqueous solution; they cannot be isolated, because they immediately change into highly explosive, very unstable products, which seem to be their anhydrides.

The diazonium *salts* may be isolated without much difficulty, and are crystalline compounds, very readily soluble in water; in the dry state, most of them are *highly explosive*, and should be handled only with the greatest caution.

Diazonium salts may be obtained *in crystals* by treating a well-cooled solution of an amino-compound in alcohol or acetic acid with amyl nitrite and a mineral acid, so far as possible in the absence of water,

$$C_6H_5 \cdot NH_2, HCl + C_5H_{11} \cdot O \cdot NO = C_6H_5 \cdot N_2Cl + C_5H_{11} \cdot OH + H_2O.$$

Phenyldiazonium sulphate, $C_6H_5 \cdot N_2 \cdot SO_4H$, for example, is obtained as follows: Aniline (5 g.) is dissolved in anhydrous acetic acid (20 g.), concentrated sulphuric acid (5 g.) is added, the solution

is cooled to 20° and amyl nitrite (7 g.) is cautiously dropped into the well-agitated mixture. As the reaction proceeds, the temperature is lowered to about 10°, and when all the nitrite has been added, the product is kept during 5–10 minutes. On the addition of ether (20–30 c.c.), phenyldiazonium sulphate is precipitated in crystals, which are separated, washed with alcohol and ether, and dried in the air at ordinary temperatures. It is very *explosive*.

Amyl nitrite is used instead of sodium nitrite as it is miscible with acetic acid or alcohol and is decomposed by sulphuric acid giving nitrous acid.

The diazonium salts are of very great importance in synthetical chemistry and in the preparation of dyes, because they undergo a number of important reactions; for nearly all purposes for which they are required, however, it is quite unnecessary to isolate the salts, and their aqueous solutions are directly employed.

The *preparation of a solution of a diazonium salt*, therefore, is a very common and a very simple operation, which is carried out as follows: The amino-compound is dissolved in an excess ($2\frac{1}{2}$–3 equivalents) of a dilute mineral acid, the solution is cooled in ice, and an aqueous solution of sodium or potassium nitrite (1 equivalent) is very slowly added; this process is known as *diazotisation*, and further details are given later (p. 457).

The more important *reactions* of the diazonium salts are the following:

When heated with formic acid, or treated with an alkaline solution of sodium stannite, they yield hydrocarbons,

$$C_6H_5\cdot N_2Cl+H\cdot COOH = C_6H_6+N_2+HCl+CO_2,$$
$$C_6H_5\cdot N_2Cl+NaOH+Sn(ONa)_2 = C_6H_6+N_2+Na_2SnO_3+NaCl,$$

whereas when warmed with alcohol they give an ether and a hydrocarbon, the proportions of which vary with different diazonium compounds,

$$C_6H_5\cdot N_2Cl+C_2H_5\cdot OH = C_6H_5\cdot O\cdot C_2H_5+N_2+HCl,$$
$$C_6H_5\cdot N_2Cl+C_2H_5\cdot OH = C_6H_6+N_2+HCl+CH_3\cdot CHO;$$

in the decomposition with formic acid or with alcohol, the *anhydrous* salt, prepared as described above, must be used. They also give hydrocarbons, often in better yields, with an aqueous solution of hypophosphorous acid,

$$C_6H_5\cdot N_2Cl+H_3PO_2+H_2O = C_6H_6+H_3PO_3+HCl+N_2.$$

Another method for their conversion into the corresponding hydrocarbons is given later (p. 460).

When warmed, in aqueous solution, diazonium salts decompose rapidly, with the evolution of nitrogen and the formation of phenols,

$$C_6H_5 \cdot N_2 \cdot SO_4H + H_2O = C_6H_5 \cdot OH + N_2 + H_2SO_4,$$
$$C_6H_4(CH_3) \cdot N_2Cl + H_2O = C_6H_4(CH_3) \cdot OH + N_2 + HCl,$$

but if warmed with concentrated halogen acids they give aryl halides,

$$C_6H_5 \cdot N_2 \cdot SO_4H + HI = C_6H_5I + N_2 + H_2SO_4;$$

the latter reaction is made use of principally for the preparation of iodo-derivatives (p. 457), because when the other halogen acids are used the product contains a large proportion of the corresponding phenol.

The diazonium salts behave in a very remarkable way when they are treated with certain cuprous salts; when, for example, a solution of phenyldiazonium chloride is warmed with a solution of cuprous chloride in hydrochloric acid, nitrogen is evolved, but instead of phenol, chlorobenzene is produced. In this reaction the diazonium salt combines with the cuprous chloride to form a brownish additive compound, which is decomposed at higher temperatures,

$$C_6H_5 \cdot N_2Cl, 2CuCl = C_6H_5Cl + N_2 + 2CuCl.$$

If, instead of the two chlorides, the corresponding bromides are employed, bromobenzene is produced,

$$C_6H_5 \cdot N_2Br, 2CuBr = C_6H_5Br + N_2 + 2CuBr,$$

but the use of a cuprous salt is *unnecessary* in the displacement of the diazonium group by iodine (p. 457). With a solution of potassium cuprous cyanide, a diazonium salt gives a cyanide (or nitrile, compare p. 516),

$$C_6H_5 \cdot N_2Cl, 2CuCN = C_6H_5 \cdot CN + N_2 + CuCl + CuCN.$$

By means of these very important reactions, which were discovered by Sandmeyer in 1884, it is possible to displace the *diazonium* group by Cl, Br, CN (and indirectly by —COOH, —CHO, and $—CH_2 \cdot NH_2$, into which the —CN group may be converted), and by other atoms or groups. Later it was shown by Gattermann that similar decompositions of the diazonium salts may be brought

about by the addition of copper powder, instead of a cuprous salt, to the cold acid solution of the diazonium salt.

As the diazonium salts are readily obtainable from amino-compounds, and the latter from nitro-derivatives, Sandmeyer's reaction (as modified if desirable) is very much used in the preparation of halogen, cyanogen, and other derivatives of aromatic compounds.

Fluorobenzene may be prepared by the action of fluoroboric acid on phenyldiazonium chloride,

$$C_6H_5 \cdot N_2Cl + HBF_4 = C_6H_5 \cdot N_2 \cdot BF_4 + HCl,$$
$$C_6H_5 \cdot N_2 \cdot BF_4 = C_6H_5F + N_2 + BF_3.$$

It will be seen from the above that the production of various derivatives from the amino-compound involves two distinct reactions: firstly, the preparation of a *solution* of the diazonium salt, and, secondly, the decomposition of this salt in a suitable manner.

As an example of the method employed in preparing a solution of the diazonium salt, the following may serve: Aniline (10 g.) is dissolved in a mixture of concentrated hydrochloric acid (sp. gr. 1·17, 25 g.) and water (about 75 g.), and the solution is cooled externally with coarsely powdered ice (in some cases by the addition of ice); when the temperature has fallen to about 5°, sodium nitrite (7·5 g.) in aqueous solution is slowly run in from a tap-funnel, the solution being stirred constantly and the temperature kept below 10°. The solution now contains *phenyldiazonium chloride*; if sulphuric is used instead of hydrochloric acid, *phenyldiazonium sulphate*, $C_6H_5 \cdot N_2 \cdot SO_4H$, is formed. The aniline is said to have been *diazotised*; diazotisation is complete when the solution contains free nitrous acid (as shown by potassium iodide paper) after it has been stirred well and *left for a short time*. The formation of a *coloured* precipitate of diazoaminobenzene (p. 461) at any stage indicates that insufficient acid is present.

If, now, the solution of the diazonium salt is warmed *alone* nitrogen is evolved and phenol is produced; if treated with potassium iodide, iodobenzene is formed. With a solution of cuprous chloride in hydrochloric acid, or with copper powder, *chlorobenzene* is produced (p. 426), whereas with an aqueous solution of potassium cuprous cyanide, *cyanobenzene* is formed (p. 515). In all these cases the final product is usually separated by distillation in steam.

The diazonium salts react with phenols (p. 478) in alkaline solution and with salts of tertiary aromatic amines (p. 463) giving

highly coloured *azo*-compounds, many of which are used in the dyeing industry; when, for example, a solution of a phenyldiazonium salt is added to an alkaline solution of β-naphthol (p. 549) a scarlet precipitate is formed by the displacement of a nuclear hydrogen atom of the naphthol molecule by the phenyldiazo-group (p. 675),

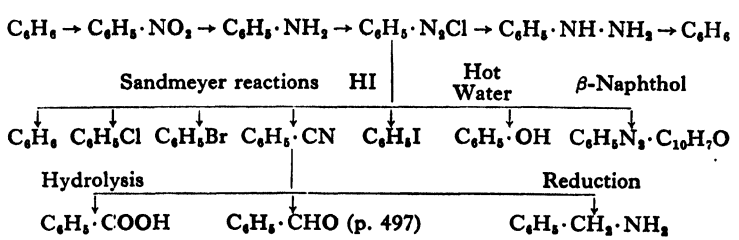
$$C_6H_5\cdot N_2\cdot SO_4H+C_{10}H_7\cdot ONa=C_6H_5\cdot N{:}N\cdot C_{10}H_6\cdot OH+NaHSO_4.$$

The last reaction is often used to prove that a given substance is a primary aromatic amino-compound: the substance is treated with sodium nitrite in acid solution and the product is added to a solution of β-naphthol in an excess of alkali.

The diazonium salts also serve for the preparation of an important class of compounds known as the *hydrazines*; these substances are obtained by reducing the diazonium salts with stannous chloride and hydrochloric acid or some other suitable reagent (p. 459), such as sulphurous acid,

$$\underset{\text{Diazonium chloride}}{R\cdot N_2Cl}+4H = \underset{\text{Hydrazine hydrochloride}}{R\cdot NH\cdot NH_2, HCl}.$$

The following scheme summarises some of the principal uses of the diazonium salts and some general reactions of aromatic compounds; it should be noted that although benzene is shown here as the parent substance, derivatives of toluene and other aromatic hydrocarbons (such as naphthalene, p. 538) would undergo similar transformations:



Constitution of Diazonium Salts. The state of combination of the two nitrogen atoms and of the acid radical in diazonium salts has formed the subject of much discussion.

That only *one* of the two nitrogen atoms is directly united to the nucleus is clearly shown by many facts—as, for example, by the

conversion of the diazonium salts into *mono*-halogen derivatives, *mono*hydric phenols, etc., and by their reduction to hydrazines, such as $C_6H_5 \cdot NH \cdot NH_2$.

Like salts of strongly basic hydroxides they are not hydrolysed in aqueous solution; the extent of their ionisation is comparable with that of alkali metal salts. Their partial structure, therefore, is $[C_6H_5 \cdot N_2]X$ (X = an acid radical), and the cation is possibly a mesomeric form of the contributing structures, $C_6H_5 \cdot N \rightleftarrows N^+$ and $C_6H_5 \cdot N^+ \equiv N$, in which the ionic charge is not confined to either nitrogen atom.

The diazonium (or diazo-) group may therefore be represented by $-N_2X$, without indicating further how these atoms are combined with one another.

The diazonium salts are often called diazo-salts, while phenyldiazonium chloride is termed *diazobenzene* chloride, and so on.

Hydrazines and Hydrazones

Phenylhydrazine, $C_6H_5 \cdot NH \cdot NH_2$, a compound of great importance, is easily prepared by the reduction of phenyldiazonium chloride (E. Fischer), usually with stannous chloride and hydrochloric acid or with sulphur dioxide,

$$C_6H_5 \cdot N_2Cl + 4H = C_6H_5 \cdot NH \cdot NH_2, HCl.$$

Aniline (9 g.) is dissolved in concentrated hydrochloric acid (170 c.c.), and diazotised in the usual way (p. 457); to the *well-cooled* solution of phenyldiazonium chloride a solution of stannous chloride ($SnCl_2, 2H_2O$: 45 g.) in concentrated hydrochloric acid (100 c.c.) is then slowly added. The precipitate of phenylhydrazine hydrochloride is separated on a suction-filter, washed with a little concentrated hydrochloric acid, and decomposed with an excess of concentrated alkali; the base is extracted with benzene, the extract is dried over solid caustic alkali, and the benzene is distilled. The product may then be purified by distillation under reduced pressure (b.p. about 137°, 18 mm.).

Phenylhydrazine crystallises in colourless prisms, melts at 23°, and boils at 242°, with slight decomposition; it readily undergoes atmospheric oxidation and darkens in colour. It is sparingly soluble in cold water, freely so in organic liquids; it is a strong base, and forms well-characterised salts, such as the hydrochloride, $C_6H_5 \cdot NH \cdot NH_2, HCl$, which is readily soluble in hot water; it

reduces Fehling's solution in the cold. Phenylhydrazine is very *poisonous*; its vapour should not be inhaled and the liquid should not touch the skin.

The *constitution* of phenylhydrazine is established by the fact that, when heated with zinc-dust and hydrochloric acid, the base is reduced to aniline and ammonia.

Phenylhydrazine is converted into benzene, with the evolution of nitrogen, when it is heated with a solution of copper sulphate or ferric chloride,

$$C_6H_5\cdot NH\cdot NH_2+2CuSO_4+H_2O = C_6H_6+N_2+Cu_2O+2H_2SO_4.$$

This important reaction may be used in order to change nitrobenzene, aniline, or a diazonium salt into benzene, since all these compounds may be transformed into phenylhydrazine by the methods already given,

$$C_6H_5\cdot NO_2 \longrightarrow C_6H_5\cdot NH_2 \longrightarrow C_6H_5\cdot N_2X \longrightarrow C_6H_5\cdot NH\cdot NH_2 \longrightarrow C_6H_6.$$

Similar transformations may be brought about in the case of many corresponding aromatic compounds; bromonitrobenzene, for example, may be thus converted into bromobenzene. Further, since the evolution of nitrogen takes place quantitatively when a hydrazine is decomposed with a solution of copper sulphate, this reaction may be employed for the estimation of hydrazines.

Phenylhydrazine reacts readily with aldehydes and ketones, with the formation of water and a *phenylhydrazone* (hydrazone); as these compounds are usually sparingly soluble and generally crystallise well, they are frequently employed for the identification and isolation of aldehydes and ketones,

$$\underset{\text{Benzaldehyde}}{C_6H_5\cdot CHO}+C_6H_5\cdot NH\cdot NH_2 = \underset{\text{Benzylidenephenylhydrazone}}{C_6H_5\cdot CH{:}N\cdot NH\cdot C_6H_5}+H_2O,$$

$$\underset{\text{Acetophenone}}{C_6H_5\cdot CO\cdot CH_3}+C_6H_5\cdot NH\cdot NH_2 = \underset{\text{Acetophenonephenylhydrazone}}{\begin{matrix}C_6H_5\\CH_3\end{matrix}\!\!>\!C{:}N\cdot NH\cdot C_6H_5}+H_2O.$$

Many phenylhydrazones are decomposed by strong mineral acids, with the regeneration of an aldehyde or ketone, and formation of a salt of phenylhydrazine,

$$C_6H_5\cdot CH{:}N\cdot NH\cdot C_6H_5+H_2O+HCl = C_6H_5\cdot CHO+C_6H_5\cdot NH\cdot NH_2,HCl;$$

on reduction with zinc-dust and acetic acid, they yield primary amines,

$$C_6H_5\cdot CH{:}N\cdot NH\cdot C_6H_5+4H = C_6H_5\cdot CH_2\cdot NH_2+C_6H_5\cdot NH_2.$$

The use of phenylhydrazine for the detection and isolation of the sugars has already been mentioned.

Various derivatives of phenylhydrazine, such as *p*-bromo-, *p*-nitro-, and 2:4-dinitro-phenylhydrazine are often used instead of the simple compound, as the phenylhydrazones formed from them crystallise more readily and are more sparingly soluble than the unsubstituted compounds.

In the preparation of a phenylhydrazone a slight excess of phenylhydrazine is directly added to the aldehyde or ketone ; or the two substances are separately dissolved in *dilute* acetic acid, and the solutions are mixed. Very often a reaction takes place spontaneously and in the absence of solvent its occurrence is recognised by the development of heat and separation of water ; in the second case, by the separation of an oily, or solid, sparingly soluble precipitate. Sometimes the application of heat is necessary. The phenylhydrazone is separated, washed with dilute acetic acid, and, if a solid, purified by recrystallisation. Phenylhydrazine hydrochloride may be used, instead of the free base, in dilute acetic acid solution, but an excess of sodium acetate must also be added.

The occurrence of a reaction, when a *neutral* substance is treated with phenylhydrazine as above, is a very important qualitative test for aldehydes and ketones.

Osazones are prepared by heating a *dilute* aqueous solution of a sugar with an excess of phenylhydrazine acetate ; after some time the osazone usually begins to separate in yellow crystals, and the heating is continued until no further precipitation occurs.

Diazoamino- and Azo-compounds

Although some of the more characteristic reactions of the diazonium salts have already been mentioned, these substances undergo many other changes of great interest and commercial importance. They react readily with primary, secondary, and tertiary amino-compounds ; when, for example, phenyldiazonium chloride is treated with aniline, diazoaminobenzene is formed,

$$C_6H_5 \cdot N_2Cl + NH_2 \cdot C_6H_5 = C_6H_5 \cdot N_2 \cdot NH \cdot C_6H_5 + HCl,$$

and with a secondary base a similar change occurs. With tertiary aromatic amino-compounds, such as dimethylaniline, diazonium salts react quite differently and give aminoazo-compounds, as shown below.

Diazoaminobenzene, $C_6H_5 \cdot N_2 \cdot NH \cdot C_6H_5$, may be described as a typical *diazoamino*-compound.

It is conveniently prepared by treating aniline hydrochloride (5 mol.) with sodium nitrite (about 2 mol.) in very dilute aqueous solution ; a part of the aniline is converted into the diazonium salt, which then reacts with the unchanged aniline, as shown above. The precipitate is separated, washed with water, dried and recrystallised from petroleum ether.

If the precipitate is left in contact with the aqueous solution at 30–40°, it slowly changes into a very dark, pasty or crystalline mass of impure *aminoazobenzene hydrochloride.*

Diazoaminobenzene forms brilliant yellow needles, melting at 98°, and is almost insoluble in water, but readily so in alcohol and ether; it is only very feebly basic, and does not form stable salts with acids.

Aminoazobenzene, $C_6H_5 \cdot N{:}N \cdot C_6H_4 \cdot NH_2$, is formed when diazoaminobenzene is warmed with a small quantity of aniline hydrochloride at 40°,

$$C_6H_5 \cdot N{:}N \cdot NH \cdot C_6H_5 \longrightarrow C_6H_5 \cdot N{:}N \cdot C_6H_4 \cdot NH_2.$$

This remarkable reaction, which is a general one, may be compared with that which occurs in the transformation of methylaniline into *p*-toluidine (p. 450) ; the group, $-N_2 \cdot C_6H_5$, leaves the nitrogen atom and *migrates* to the *para*-position of the nucleus,

$$\underset{\text{Diazoaminobenzene}}{C_6H_5 \cdot NH \cdot N_2 \cdot C_6H_5} \longrightarrow \underset{\text{p-Aminoazobenzene}}{C_6H_4 < \begin{matrix} NH_2 \\ N_2 \cdot C_6H_5 \end{matrix}}$$

$$\underset{\text{Methylaniline}}{C_6H_5 \cdot NH \cdot CH_3} \longrightarrow \underset{\text{p-Toluidine}}{C_6H_4 < \begin{matrix} NH_2 \\ CH_3 \end{matrix}}$$

In this diazoamino-transformation the presence of hydrochloric or some other strong acid is essential, and the change takes place in two stages, as follows :

$$C_6H_5 \cdot N_2 \cdot NH \cdot C_6H_5 + HCl = C_6H_5 \cdot N_2Cl + C_6H_5 \cdot NH_2,$$
$$C_6H_5 \cdot N_2Cl + C_6H_5 \cdot NH_2 = C_6H_5 \cdot N_2 \cdot C_6H_4 \cdot NH_2, HCl.$$

That the group, $-N_2 \cdot C_6H_5$, displaces hydrogen from the *p*-position to the $-NH_2$ group is proved by the fact that the aminoazobenzene thus produced is converted into *p*-phenylenediamine and aniline, on reduction with tin and hydrochloric acid,

$$NH_2 \cdot C_6H_4 \cdot N_2 \cdot C_6H_5 + 4H = NH_2 \cdot C_6H_4 \cdot NH_2 + NH_2 \cdot C_6H_5.$$

Aminoazobenzene may also be prepared by nitrating azobenzene (p. 464), and then reducing with alcoholic ammonium sulphide the

p-nitroazobenzene, $C_6H_5 \cdot N_2 \cdot C_6H_4 \cdot NO_2$, which is thus produced; aminoazobenzene, therefore, is an amino-derivative of azobenzene.

It crystallises from alcohol in brilliant orange-red plates, and melts at 126°. Its salts are intensely coloured; the hydrochloride, $C_6H_5 \cdot N_2 \cdot C_6H_4 \cdot NH_2$, HCl, for example, forms steel-blue needles.

Many substituted aminoazo-compounds may be obtained *directly* by treating tertiary alkylanilines (p. 450) with diazonium salts; dimethylaniline, for example, reacts with phenyldiazonium chloride, yielding *p*-dimethylaminoazobenzene hydrochloride,

$$C_6H_5 \cdot N_2Cl + C_6H_5 \cdot N(CH_3)_2 = C_6H_5 \cdot N{:}N \cdot C_6H_4 \cdot N(CH_3)_2, HCl,$$

and a diazoamino-compound is not formed as an intermediate product because dimethylaniline does not contain an $NH<$ or NH_2— group.

That the group, $C_6H_5 \cdot N_2$—, takes up the *p*-position to the —$N(CH_3)_2$ group, is shown by the fact that, on reduction, dimethylaminoazobenzene is converted into aniline and dimethyl-*p*-phenylenediamine, and the latter is identical with the base which is produced by reducing *p*-nitrosodimethylaniline (p. 451).

Diazonium salts, as previously stated, react very readily with phenols in alkaline solution, giving *hydroxyazo*-compounds, many of which are highly coloured dyes (p. 672). Azo-derivatives formed in this way, and by the interaction of diazonium salts with tertiary amino-compounds, etc., in a similar manner, are the products of what is termed a *coupling* process; coupling is a very important operation in the manufacture of azo-dyes.

Azoxybenzene, $C_6H_5 \cdot N{:}NO \cdot C_6H_5$, may be prepared by heating nitrobenzene with sodium arsenite or a methyl alcoholic solution of sodium methoxide,

$$4C_6H_5 \cdot NO_2 + 3CH_3 \cdot ONa = 2C_{12}H_{10}N_2O + 3H \cdot COONa + 3H_2O.$$

Sodium (1 part) is dissolved in methyl alcohol (25 parts) and nitrobenzene (3 parts) is added; the solution is heated (with reflux condenser) during about 5 hours, the alcohol is distilled, and water added. When sufficiently hard, the pasty product is pressed on porous earthenware, left to dry, and crystallised from petroleum ether.

It forms yellow needles, melting at 36°, and is insoluble in water, but readily soluble in most organic liquids.

The constitution of azoxybenzene was at one time represented by the formula (I); it was found, however, that an unsymmetrical azo-compound, $R \cdot N{:}N \cdot R'$, oxidised with hydrogen peroxide in glacial acetic acid solution, gives structurally isomeric azoxy-compounds, which therefore must be represented by (II) and (III) respectively, the oxygen and the nitrogen atoms being united by a co-ordinate covalency,

(I) $C_6H_5 \cdot \overset{O}{\diagup\!\diagdown} N - N \cdot C_6H_5$ (II) $R \cdot NO{:}N \cdot R'$ (III) $R \cdot N{:}NO \cdot R'$

Azobenzene, $C_6H_5 \cdot N{:}N \cdot C_6H_5$, may be prepared by heating an intimate mixture of azoxybenzene (1 part) and iron filings (3 parts).

The mixture is carefully heated in a small retort, and the solid distillate is purified in the same way as the azoxy-compound.

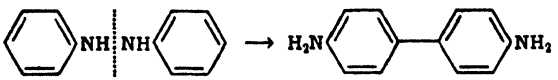
Azobenzene crystallises in red plates, melts at 68°, and distils at 293°; it is readily soluble in ether and alcohol, but practically insoluble in water. Alkaline reducing agents, such as ammonium sulphide, zinc dust and caustic soda, etc., convert azobenzene into *hydrazobenzene* (below), whereas a mixture of zinc dust and acetic acid decomposes it, with the formation of aniline,

$$C_6H_5 \cdot N{:}N \cdot C_6H_5 + 4H = 2C_6H_5 \cdot NH_2.$$

On oxidation with hydrogen peroxide in glacial acetic acid solution, it is converted into azoxybenzene.

Although azobenzene is of little importance, many azo-compounds are manufactured for use as dye stuffs (p. 672).

Hydrazobenzene, $C_6H_5 \cdot NH \cdot NH \cdot C_6H_5$, symmetrical *diphenyl-hydrazine*, is prepared as above from azobenzene, or directly from nitrobenzene by reduction with zinc dust and alcoholic sodium hydroxide. It is a colourless, crystalline substance, melting at 127°; it is readily converted into azobenzene by mild oxidising agents, such as mercuric oxide, and slowly even when air is passed through its alcoholic solution. When treated with strong acids, it undergoes a very remarkable isomeric change (the *benzidine transformation*), and is converted into *pp'*-diaminodiphenyl or *benzidine*, a base which is largely used in the preparation of azo-dyes (p. 678),



Benzidine may be produced in one operation by reducing azobenzene with tin and concentrated hydrochloric acid. It melts at

128° and is very sparingly soluble even in boiling water, but it dissolves readily in diluted (1:1) hydrochloric acid; from this solution its *sulphate* may be precipitated in lustrous scales, very sparingly soluble in boiling water, a behaviour which may serve for the identification of the base.

Other simple azo-compounds behave just like azobenzene; *o-azotoluene*, $CH_3 \cdot C_6H_4 \cdot N{:}N \cdot C_6H_4 \cdot CH_3$, for example, may be converted into the corresponding hydrazo-compound, and then, by the benzidine transformation, into *dimethylbenzidine* (tolidine),

$$\begin{matrix} {}^{(4)}NH_2 \\ {}^{(3)}CH_3 \end{matrix} > {}^{(1)}C_6H_3 \cdot {}^{(1)}C_6H_3 < \begin{matrix} NH_2{}^{(4)} \\ CH_3{}^{(3)} \end{matrix}$$

***N*-Phenylhydroxylamine**, $C_6H_5 \cdot NH \cdot OH$ (m.p. 82°), is obtained when nitrobenzene is cautiously reduced with zinc dust and an aqueous solution of ammonium chloride; like hydroxylamine, it is a mono-acidic base. Its hydrochloride, treated with sodium nitrite at 0° in aqueous solution, gives **phenylnitrosohydroxylamine**, $C_6H_5 \cdot N(OH) \cdot NO$ (m.p. 59°), the ammonium salt of which is known as *cupferron*; this salt forms compounds with metals (such as copper and iron), which may differ very considerably in solubility, and is therefore useful in analytical work.

When oxidised with dichromate and dilute sulphuric acid, phenylhydroxylamine yields **nitrosobenzene**, $C_6H_5 \cdot NO$, a crystalline, volatile substance, which melts at 68° to a green liquid; on oxidation it is converted into nitrobenzene, and on reduction, into aniline.

It has been shown that on reduction, nitrobenzene and, indeed, any aromatic nitro-compound, may yield various products according to the reducing agent employed, and the conditions under which the operation is carried out. Thus, with *acid*, and *certain* alkaline reducing agents (alcoholic ammonium sulphide), nitrobenzene is reduced first to nitrosobenzene, (I), then to phenylhydroxylamine, (II), and finally to aniline, (III),

$C_6H_5 \cdot NO_2 \longrightarrow$ (I) $C_6H_5 \cdot NO \longrightarrow$ (II) $C_6H_5 \cdot NH \cdot OH \longrightarrow$ (III) $C_6H_5 \cdot NH_2$;

the intermediate compounds (I) and (II) can only be isolated under special conditions. With other *alkaline* reducing agents, however, the phenylhydroxylamine and the nitrosobenzene react to form azoxybenzene, (IV),

$$C_6H_5 \cdot NH \cdot OH + C_6H_5 \cdot NO = \text{(IV) } C_6H_5 \cdot N{:}NO \cdot C_6H_5 + H_2O,$$

which may then undergo further reduction successively to azobenzene, (V), hydrazobenzene, (VI), and finally to aniline,

(V) $C_6H_5 \cdot N{:}N \cdot C_6H_5 \longrightarrow$ (VI) $C_6H_5 \cdot NH \cdot NH \cdot C_6H_5 \longrightarrow 2C_6H_5 \cdot NH_2$.

Many of these reactions may also be carried out by electrolytic reduction, the nature of the product depending on the experimental conditions. On the commercial scale azoxybenzene, azobenzene, and hydrazobenzene are all obtained by the graded reduction of nitrobenzene with iron borings and caustic soda.

Arsenobenzene Derivatives

Some aliphatic arsenic compounds have already been mentioned, but these are of minor importance compared with certain aromatic derivatives related to azobenzene and of great medicinal value.

***p*-Aminophenylarsinic acid,** $NH_2 \cdot C_6H_4 \cdot AsO(OH)_2$ (*arsanilic acid*), first prepared by Béchamp in 1863 by heating aniline with arsenic acid, was used later in the form of its sodium salt, *atoxyl*, in cases of sleeping sickness. About 1906 it was found that particular aromatic arsenic derivatives were of value in the treatment of diseases of protozoal origin, and Ehrlich began a comprehensive series of researches on such compounds. He showed that Béchamp's acid was not $C_6H_5 \cdot NH \cdot AsO(OH)_2$, as was then supposed, but had the above constitution ; also that other aromatic bases and phenols yielded substituted *arsinic acids* when they were heated with arsenic acid. In such reactions the arsenic-containing radical displaces hydrogen of the aromatic nucleus in the *p*-position to the amino- or phenolic group, if such a position is vacant ; if, however, the *p*-position is occupied, an *o*-derivative is formed, and the yield is poor, except with *p*-nitroaniline, which affords an exceptionally good yield of 2-*amino*-5-*nitrophenylarsinic acid.*

Another method for the preparation of aromatic arsinic acids (*Bart reaction*) consists in the treatment of a solution of a diazonium salt with sodium arsenite,

$$C_6H_5 \cdot N_2Cl + Na_3AsO_3 = C_6H_5 \cdot AsO(ONa)_2 + NaCl + N_2.$$

The *arsinic* acids are crystalline dibasic acids of which the aromatic radicals exhibit their usual properties. Amino-groups, if any, can be acetylated, methylated, or diazotised in the usual manner ; if the amino-group is protected (p. 446), a side chain may be oxidised to carboxyl, and nitro-derivatives may be obtained in the usual way. Nuclear halogen derivatives may be prepared with the aid of sodium hypochlorite or hypobromite, but free halogens usually displace the arsenic-containing radical ; p-*aminophenylarsinic acid*, for example, with bromine, yields tribromoaniline.

The arsinic acids can be reduced to derivatives of tervalent arsenic by treatment, for example, with sulphurous acid in the presence of a little iodine,

$$NH_2 \cdot C_6H_4 \cdot AsO(OH)_2 + 2HI = NH_2 \cdot C_6H_4 \cdot AsO + 2H_2O + I_2.$$

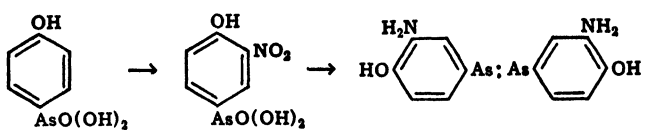
The substituted arsenious oxides thus formed can be further reduced with sodium amalgam and alcohol, giving substances analogous to azobenzene,

$$2NH_2 \cdot C_6H_4 \cdot AsO + 4H = NH_2 \cdot C_6H_4 \cdot As{:}As \cdot C_6H_4 \cdot NH_2 + 2H_2O;$$

such compounds can also be prepared directly from the arsinic acids by reduction with sodium hydrosulphite.

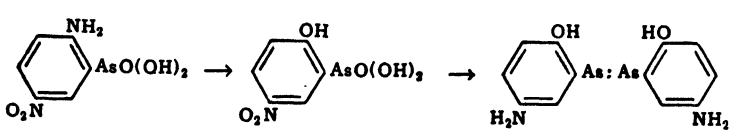
The *arsenobenzene* derivatives are solids, which oxidise easily in the air; they are not crystalline and cannot be distilled. They have a much higher toxicity towards trypanosomes, but a smaller human toxicity, than derivatives of ' quinquevalent ' arsenic.

3:3'-**Diamino-4:4'-dihydroxyarsenobenzene** is prepared from p-*hydroxyphenylarsinic acid* by nitration, followed by reduction with sodium hydrosulphite,



The dihydrochloride of this base is known as **salvarsan,** (606),[1] and has proved of very great value in the treatment of protozoal diseases (syphilis); its curative action is entirely due to its conversion, after injection, into the substituted arsenious oxide, HCl, $NH_2 \cdot C_6H_3(OH) \cdot AsO$.

2-Amino-5-nitrophenylarsinic acid (p. 466) may be converted into 2-*hydroxy*-5-*nitrophenylarsinic acid* with nitrous acid, and this compound, on reduction, gives a base, the hydrochloride of which is isomeric with salvarsan,



[1] It was the six hundred and sixth arsenic compound prepared and studied by Ehrlich. Salvarsan is also called *arsphenamine.*

Many simple derivatives of salvarsan have been obtained, of which *neosalvarsan* (*neoarsphenamine*) is important; it is produced by the condensation of sodium formaldehydesulphoxylate [1] with salvarsan, one amino-group of the latter being converted into $—NH \cdot CH_2 \cdot SO_2Na$. Aqueous solutions of neosalvarsan are neutral, whilst those of salvarsan are acidic and must be neutralised carefully before injection.

Simple aromatic arsines such as *triphenylarsine*, $(C_6H_5)_3As$, *diphenylarsenic chloride*, $(C_6H_5)_2AsCl$, and *phenylarsenic dichloride*, $C_6H_5AsCl_2$, may be prepared by the interaction of arsenic trichloride with a nuclear aromatic halide and sodium, with an aromatic hydrocarbon and aluminium chloride, or with an aromatic Grignard reagent. Owing to their highly toxic action, some of these compounds have been used in chemical warfare, but they are otherwise unimportant.

Aliphatic Diazo-compounds and Azides

Although aliphatic amino-compounds cannot be transformed into diazonium salts, corresponding with those of the aromatic series, the esters of aliphatic amino-acids may be converted into highly reactive diazo-derivatives (Curtius). When, for example, ethyl aminoacetate, in the form of its hydrochloride, is treated with sodium nitrite in aqueous solution, *ethyl diazoacetate* separates as a yellow oil (b.p. 143°),

$$HCl,NH_2 \cdot CH_2 \cdot COOEt + NaNO_2 = N_2CH \cdot COOEt + NaCl + 2H_2O.$$

Similar diazo-compounds may be obtained from the esters of other aliphatic amino-acids; most of them have a penetrating odour, and explode when they are heated. In spite of their name, these compounds are not analogues of the diazonium salts, but, like the the latter, they are readily decomposed, with the elimination of nitrogen.

They are transformed into esters of hydroxy-acids when they are boiled with dilute acids or even with water,

$$N_2CH \cdot COOEt + H_2O = HO \cdot CH_2 \cdot COOEt + N_2,$$

and they give alkyl or acyl derivatives of the hydroxy-esters when they are heated with alcohols and organic acids respectively,

$$N_2CH \cdot COOEt + CH_3 \cdot OH = CH_3O \cdot CH_2 \cdot COOEt + N_2,$$
$$N_2CH \cdot COOEt + CH_3 \cdot COOH = CH_3 \cdot CO \cdot O \cdot CH_2 \cdot COOEt + N_2.$$

[1] Sodium formaldehydesulphoxylate, $CH_2(OH) \cdot SO_2Na$, is obtained when formaldehyde sodium bisulphite is reduced with zinc dust and acetic acid.

They yield esters of dihalogen substituted acids when they are treated with halogens (even with iodine), and the corresponding monohalogen substitution products with concentrated halogen acids,

$$N_2CH\cdot COOEt+I_2 = CHI_2\cdot COOEt+N_2,$$
$$N_2CH\cdot COOEt+HBr = CH_2Br\cdot COOEt+N_2.$$

Ethyl diazoacetate gives aminoacetic acid (glycine) and ammonia when it is reduced with zinc dust and acetic acid, but with ferrous sulphate and caustic soda, or with sodium amalgam and water, it yields a salt of *glyoxylic acid hydrazone* (*hydraziacetic acid*),

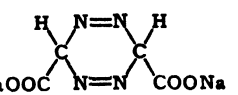
$$N_2CH\cdot COOEt+2H+H_2O = NH_2\cdot N{:}CH\cdot COOH+C_2H_5\cdot OH\ ;$$

this acid is stable only in the form of its salts, and when the latter are treated with a mineral acid, hydrazine and glyoxylic acid are formed,

$$NH_2\cdot N{:}CH\cdot COOH+H_2O = NH_2\cdot NH_2+CHO\cdot COOH.$$

Ethyl diazoacetate is hydrolysed by concentrated caustic soda, but the sodium diazoacetate undergoes polymerisation, giving the sodium salt of a *dihydrotetrazinedicarboxylic acid* (*bis-diazoacetic acid*),

$$2N_2CH\cdot COONa =$$



and the acid, liberated from this salt, is decomposed by boiling water, giving hydrazine and oxalic acid,

$$C_2H_2N_4(COOH)_2+4H_2O = 2NH_2\cdot NH_2+2C_2H_2O_4.$$

It was in this way that hydrazine was first obtained (Curtius and Jay).

Diazomethane, N_2CH_2, may be obtained by treating *methylurethane* (p. 224) with nitrous acid in ethereal solution, and then warming the product (*nitrosomethylurethane*) with caustic potash (Pechmann),

$$CH_3\cdot N(NO)\cdot COOEt+2KOH = N_2CH_2+C_2H_5\cdot OH+K_2CO_3+H_2O\ ;$$

it is more easily prepared from the nitroso-derivative of *methylurea*,

$$CH_3\cdot N(NO)\cdot CO\cdot NH_2+KOH = N_2CH_2+KOCN+2H_2O,$$

which is produced by the interaction of methylamine hydrochloride and potassium cyanate, and is readily converted into its nitroso-derivative by nitrous acid in aqueous solution.

It is a yellow, odourless, very poisonous gas, and like the aliphatic

diazo-esters it is very reactive; although it is hardly attacked by water or by methyl alcohol, it reacts with iodine, hydrochloric acid, and hydrogen cyanide, with the evolution of nitrogen, giving methylene di-iodide, methyl chloride, and methyl cyanide respectively, and reducing agents convert it into *methylhydrazine*, $NH_2 \cdot NH \cdot CH_3$. Diazomethane is sometimes used as a *methylating* agent, instead of methyl iodide or dimethyl sulphate, since it reacts with many compounds containing the group, —OH or >NH, giving —OMe or >NMe respectively, with the evolution of nitrogen; with aldehydes it gives ketones,

$$H \cdot CHO + 2CH_2N_2 = CH_3 \cdot CO \cdot CH_3 + 2N_2,$$
$$C_6H_5 \cdot CHO + CH_2N_2 = C_6H_5 \cdot CO \cdot CH_3 + N_2,$$

$$\begin{matrix} CHO \\ CHO \end{matrix} + 2CH_2N_2 = \begin{matrix} CO \cdot CH_3 \\ CO \cdot CH_3 \end{matrix} + 2N_2,$$

and it converts acids into their methyl esters.

It is also used in an important method (Arndt-Eistert) for preparing an acid from its lower homologue: an acid chloride with diazomethane gives a diazoketone, which, with water, in the presence of colloidal silver or silver oxide, gives the next higher acid,

$$R \cdot CO \cdot Cl + 2CH_2N_2 = R \cdot CO \cdot CHN_2 + CH_3Cl + N_2,$$
$$R \cdot CO \cdot CHN_2 + H_2O = R \cdot CH_2 \cdot COOH + N_2.$$

The structures of diazomethane and other aliphatic diazo-compounds are considered in Part III.

Azides. Organic derivatives of hydrazoic acid may be obtained from organic derivatives of hydrazine, just as hydrazoic acid may be prepared from hydrazine, namely, with the aid of nitrous acid.

Phenyl azide, $C_6H_5 \cdot N_3$ (*phenylazoimide, azidobenzene*), for example, is formed when sodium nitrite is added to an aqueous solution of phenylhydrazine hydrochloride,

$$C_6H_5 \cdot NH \cdot NH_2 + HO \cdot NO \rightarrow C_6H_5 \cdot N(NO) \cdot NH_2 \rightarrow C_6H_5 \cdot N_3$$

It is also produced by the interaction of phenylhydrazine and phenyldiazonium sulphate,

$$C_6H_5 \cdot NH \cdot NH_2 + C_6H_5 \cdot N_2 \cdot SO_4H = C_6H_5 \cdot N_3 + C_6H_5 \cdot NH_2, H_2SO_4,$$

or of phenyldiazonium sulphate and hydroxylamine,

$$C_6H_5 \cdot N_2 \cdot SO_4H + NH_2 \cdot OH = C_6H_5 \cdot N_3 + H_2SO_4 + H_2O.$$

Other azides may be prepared by these general reactions, and also by treating aliphatic halides with sodium or silver azide.

Phenyl azide is a yellow oil (b.p. 59° at 14 mm.), having a very disagreeable and penetrating odour; it may be distilled under greatly reduced pressure, but it explodes when it is heated under the ordinary pressure. It is very reactive; when boiled with dilute sulphuric acid it gives p-*aminophenol*, and with hydrochloric acid, p-*chloroaniline*, nitrogen being evolved in both cases. It combines with Grignard reagents to give products which are hydrolysed to diazoamino-compounds,

$$C_6H_5\cdot N_3+Ph\cdot MgBr = \begin{matrix}C_6H_5\\BrMg\end{matrix}\!\!>N\cdot N{:}NPh,$$

$$\begin{matrix}C_6H_5\\BrMg\end{matrix}\!\!>N\cdot N{:}NPh+H_2O = C_6H_5\cdot NH\cdot N_2\cdot C_6H_5+MgBr\cdot OH.$$

Methyl azide, $CH_3\cdot N_3$, may be obtained by treating sodium azide with dimethyl sulphate; it boils at 20–21°, and explodes when it is strongly heated. When treated with methyl magnesium iodide it gives **diazoaminomethane,** $CH_3\cdot N{:}N\cdot NH\cdot CH_3$, a very reactive liquid (b.p. 92°), which is decomposed by acids, giving methylamine, methyl alcohol, and nitrogen.

Ethyl azidoacetate, $N_3\cdot CH_2\cdot COOEt$, prepared from ethyl chloroacetate and sodium azide, **azidoacetic acid,** $N_3\cdot CH_2\cdot COOH$, and many other aliphatic derivatives of hydrazoic acid are known.

CHAPTER 30

SULPHONIC ACIDS AND THEIR DERIVATIVES

WHEN benzene is heated with concentrated sulphuric acid it gradually dissolves, and *benzenesulphonic acid* is formed by the substitution of the *sulphonic* group, $-SO_3H$ or $-SO_2 \cdot OH$, for an atom of hydrogen,

$$C_6H_6 + H_2SO_4 = C_6H_5 \cdot SO_3H + H_2O.$$

The homologues of benzene, and aromatic compounds in general, behave in a similar manner, and this property of yielding sulphonic derivatives (by the displacement of hydrogen of the *nucleus*), is one of the important characteristics of aromatic, as distinct from aliphatic compounds.

The sulphonic acids are *not* analogous to the alkylsulphuric acids, which are hydrogen esters of sulphuric acid.

Preparation. Sulphonic acids are prepared by treating an aromatic compound with sulphuric acid, or with anhydrosulphuric acid,

$$C_6H_5 \cdot CH_3 + H_2SO_4 = C_6H_4 < \begin{matrix} CH_3 \\ SO_3H \end{matrix} + H_2O,$$

$$C_6H_5 \cdot NH_2 + H_2SO_4 = C_6H_4 < \begin{matrix} NH_2 \\ SO_3H \end{matrix} + H_2O,$$

$$C_6H_6 + 2H_2SO_4 = C_6H_4(SO_3H)_2 + 2H_2O.$$

The number of hydrogen atoms displaced by sulphonic groups depends (as in the case of nitro-groups) on the temperature, on the concentration of the acid, and on the nature of the substance undergoing *sulphonation.*

The substance to be *sulphonated* is cautiously added to an excess of the acid, and, if necessary, heat is then applied, until the desired change is complete. After having been cooled, the product is carefully poured into water, and the acid is isolated, as described later (p. 474). In the case of a substance which is not readily soluble in water or dilute sulphuric acid, it is easy to ascertain when its sulphonation is complete by taking out a small portion of the mixture and adding water; unless the whole is soluble, unchanged substance is still present.

Sometimes chlorosulphonic acid is employed as a sulphonating agent, and in such cases chloroform or carbon tetrachloride may be used as a solvent to moderate the action; the product is either the sulphonic acid or the sulphonyl chloride,

$$C_6H_6+SO_2(OH)Cl = C_6H_5\cdot SO_3H+HCl,$$
$$C_6H_5\cdot CH_3+SO_2(OH)Cl = C_6H_4(CH_3)\cdot SO_2Cl+H_2O.$$

Sulphonic acids are also prepared by the oxidation of *thiophenols* (p. 494).

Aromatic hydrocarbons, like olefinic or acetylenic compounds, may thus be separated from paraffins by treating the mixture with sulphuric or anhydrosulphuric acid, with which the paraffins do not react.

Properties. Sulphonic acids, as a rule, are crystalline, readily soluble in water, and often very hygroscopic; they have seldom a definite melting-point, and gradually decompose when heated, so they cannot be distilled. They have a sour taste, a strongly acid reaction, and show, in fact, all the properties of strong acids, their basicity depending on the number of sulphonic groups in the molecule; their metallic salts (including the barium salts), as a rule, are readily soluble in water.

Although, generally speaking, the sulphonic acids are very stable, and are not decomposed by boiling aqueous alkalis or mineral acids, they undergo certain changes of great importance. When *fused* with alkalis they yield alkali derivatives of *phenols* (p. 478), and when their salts are strongly heated with potassium cyanide or ferrocyanide, they are converted into *cyanides*, which distil, leaving a residue of potassium sulphite,

$$C_6H_5\cdot SO_3K+KCN = C_6H_5\cdot CN+K_2SO_3.$$

The sulphonic group may also be displaced by hydrogen, by strongly heating the acids alone, or with hydrochloric acid, in sealed tubes, or by passing superheated steam into the acids or their solutions in concentrated sulphuric acid.

The $-SO_2\cdot OH$ group may be easily transformed into $-SO_2Cl$, $-SO_2\cdot NH_2$, $-SO_2\cdot OR$, etc., by methods similar to those used in preparing the corresponding derivatives of a $-CO\cdot OH$ group. When, for example, a sulphonic acid (or its alkali salt) is treated with phosphorus pentachloride, the hydroxyl group is displaced by chlorine, and a *sulphonyl chloride* is obtained,

$$3C_6H_5\cdot SO_2\cdot ONa+PCl_5 = 3C_6H_5\cdot SO_2Cl+2NaCl+NaPO_3.$$

All sulphonic acids behave in this way, and the sulphonyl chlorides are of great value, not only because they are often useful for the isolation and identification of the ill-characterised acids, but also because, like the chlorides of the carboxylic acids (acyl chlorides), they react readily with many other compounds.

The sulphonyl chlorides are slowly decomposed by water, more rapidly by alkalis, giving the sulphonic acids or their salts; they react with alcohols at high temperatures, yielding esters such as *ethyl benzenesulphonate*,

$$C_6H_5 \cdot SO_2Cl + C_2H_5 \cdot OH = C_6H_5 \cdot SO_2 \cdot OC_2H_5 + HCl,$$

and when shaken with concentrated ammonia they are converted into *sulphonamides*, which are usually crystalline, have definite melting-points, and often serve for the identification of the acids,

$$C_6H_5 \cdot SO_2Cl + NH_3 = C_6H_5 \cdot SO_2 \cdot NH_2 + HCl.$$

They also react with primary and secondary amines, yielding substituted sulphonamides,

$$R \cdot NH_2 + C_6H_5 \cdot SO_2Cl = R \cdot NH \cdot SO_2 \cdot C_6H_5 + HCl,$$
$$R_2NH + CH_3 \cdot C_6H_4 \cdot SO_2Cl = R_2N \cdot SO_2 \cdot C_6H_4 \cdot CH_3 + HCl;$$

the reaction is often carried out in the presence of alkali (p. 514), and the product is usually a well-defined crystalline substance which may serve to identify the amine. Mixtures of amines may also be separated with the aid of their sulphonyl derivatives (p. 228).

Sulphonyl chlorides, as a class, have a characteristic smell: they may be reduced with zinc dust and water to *sulphinic acids*, $R \cdot SO_2H$.

The isolation of sulphonic acids is very often a matter of some difficulty, because they are readily soluble in water and non-volatile, and cannot be extracted from their aqueous solutions with ether, etc., or separated from inorganic matter by steam distillation. The first step usually consists in their separation from the excess of sulphuric acid employed in their preparation; this may be done as follows: The aqueous solution of the product of sulphonation (above) is boiled with an excess of barium (or calcium) carbonate, filtered from the precipitated sulphate, and the filtrate—which contains the barium (or calcium) salt of the sulphonic acid—is treated with sulphuric acid so long as a precipitate is produced; an aqueous solution of the sulphonic acid is thus obtained, and when the filtered solution is evaporated to dryness, the acid remains as a syrup or in a crystalline form. If calcium carbonate has been

used, the acid will contain some calcium salt, which may be removed by adding a little alcohol, filtering and again evaporating.

Lead carbonate is sometimes employed instead of barium or calcium carbonate ; in such cases the filtrate from the lead sulphate is treated with hydrogen sulphide, filtered from lead sulphide, and then evaporated. These methods, of course, are only applicable provided that the barium, calcium, or lead salt of the acid is soluble in water ; if not, the separation is much more troublesome.

The alkali salts are easily prepared from the barium, calcium, or lead salts by treating a solution of the latter with the alkali carbonate so long as a precipitate is produced, filtering from the insoluble carbonate, and then evaporating the filtrate.

When two or more sulphonic acids are present in the product, they may often be separated by the fractional crystallisation of their salts ; if not, their sulphonyl chlorides are prepared. These compounds are soluble in ether, chloroform, etc., may often be distilled (under reduced pressure), and sometimes crystallise well, so that they may be isolated by the usual methods. (Compare saccharin, p. 518).

Benzenesulphonic acid, $C_6H_5 \cdot SO_3H$, may be prepared by gently boiling a mixture of equal volumes of benzene and concentrated sulphuric acid on a sand-bath (reflux condenser) during 20–30 hours.

When all the benzene has disappeared the *calcium* (or barium) salt is first prepared, and from the latter the *potassium* salt or the free acid may be isolated as just described.

The acid crystallises with water ($1\frac{1}{2}$ mol.) in plates, and dissolves freely in alcohol ; when fused with alkali it yields phenol (p. 483). *Benzenesulphonyl chloride*, $C_6H_5 \cdot SO_2Cl$, melts at 14·5°, the *sulphonamide*, $C_6H_5 \cdot SO_2 \cdot NH_2$, at 150°.

Benzene-*m*-disulphonic acid, $C_6H_4(SO_3H)_2$, is also prepared by heating the hydrocarbon with concentrated sulphuric acid, but a larger proportion (two volumes) of the acid is employed, and the mixture is heated more strongly (or anhydrosulphuric acid is used) ; when fused with alkalis it yields resorcinol (p. 490).

The three (*o.m.p.*) **toluenesulphonic acids,** $C_6H_4(CH_3) \cdot SO_3H$, are crystalline, and their barium salts are soluble in water ; the *o*- and *p*-acids are prepared by sulphonating toluene. ***p*-Toluenesulphonamide,** $C_6H_4(CH_3) \cdot SO_2 \cdot NH_2$ (m.p. 137°), is prepared from the sulphonyl chloride (m.p. 71°), which is a by-product in the manufacture of saccharin (p. 518) ; with a solution of sodium hypochlorite

and sodium hydroxide it gives a salt, $C_6H_4(CH_3)\cdot SO_2\cdot NNaCl$, known as *chloramine*-T, which is a very important antiseptic, used principally for the dressing of wounds; also as a decontaminant for mustard gas.

Sulphanilic acid, $C_6H_4(NH_2)\cdot SO_3H$ (aminobenzene-*p*-sulphonic acid, or aniline-*p*-sulphonic acid), is very easily prepared by heating aniline hydrogen sulphate at about 200° during some time.

A slight excess of the theoretical quantity of sulphuric acid is slowly added to aniline, contained in a porcelain basin, and the mixture is constantly stirred as it becomes solid; the basin is then *cautiously* heated on a sand-bath, the contents being stirred, and care being taken to prevent charring. The process is at an end as soon as a small portion of the product, dissolved in water, gives no oily precipitate of aniline on the addition of an excess of alkali. When it has cooled, a little water is added to the product, and the sparingly soluble sulphonic acid is separated by filtration, and purified by recrystallisation from boiling water, with the addition of animal charcoal if necessary.

Sulphanilic acid crystallises with water (1 or 2 mol.), and is readily soluble in hot, but only sparingly so in cold, water. It forms salts with bases, but it does not combine with acids; in this respect, therefore, it differs from glycine, which forms salts both with acids and bases. Heated strongly with soda-lime it gives aniline, the sulphonic group being displaced by hydrogen, and *not* by —ONa, as is usually the case.

When sulphanilic acid is dissolved in dilute alkali, and the solution is mixed with a slight excess of sodium nitrite and poured into well-cooled, dilute sulphuric acid, *diazosulphanilic acid* separates in crystals,

$$HSO_3\cdot C_6H_4\cdot NH_2+HNO_2 = {}^-SO_3\cdot C_6H_4\cdot N_2^+ + 2H_2O.$$

This compound shows the characteristic properties of a diazonium salt; when it is boiled with water it is converted into phenol-*p*-sulphonic acid and it couples with dimethylaniline, giving *helianthin* (p. 676).

Sulphanilamide, $C_6H_4(NH_2)\cdot SO_2\cdot NH_2$ (p-*aminobenzene-sulphonamide*) is prepared by sulphonating acetanilide with chlorosulphonic acid, treating the product with ammonia, and then displacing the acetyl group by hydrolysis,

$$C_6H_5\cdot NHAc \longrightarrow C_6H_4(NHAc)\cdot SO_2Cl \longrightarrow C_6H_4(NHAc)\cdot SO_2\cdot NH_2 \longrightarrow C_6H_4(NH_2)\cdot SO_2\cdot NH_2.$$

It is very sparingly soluble in water and melts at 165° ; as well as many of its derivatives, it is of very great importance in medicine. The first compound of the ' sulpha ' type to be used as a drug (in 1933) was an azo-dye, $NH_2 \cdot SO_2 \cdot C_6H_4 \cdot N{:}N \cdot C_6H_3(NH_2)_2$[2:4], *Prontosil*, the antibacterial value of which was shown to be due to its reduction to *p*-aminobenzenesulphonamide (sulphanilamide) in the body. Since this discovery was made, hundreds, if not thousands, of substituted sulphanilamides have been prepared and tested for their therapeutic value. Among these, the 2-*pyridyl* derivative (*sulphapyridine*, M & B 693), $C_6H_4(NH_2) \cdot SO_2 \cdot NH \cdot C_5H_4N$, as also the 2-*thiazole* derivative (*sulphathiazole*, M & B 760), $C_6H_4(NH_2) \cdot SO_2 \cdot NH \cdot C_3H_2NS$, are extensively used in cases of pneumonia, meningitis, peritonitis and many other bacterial diseases.

Aminobenzene-m-*sulphonic acid* (*metanilic acid*) may be obtained by reducing m-*nitrobenzenesulphonic acid*, $C_6H_4(NO_2) \cdot SO_3H$, which is formed by nitrating benzenesulphonic acid or sulphonating nitrobenzene.

Many other sulphonic acids are described later.

Sodium salts of some of the higher alkyl substituted sulphonic acids are important detergents : like the salts of the alkyl hydrogen sulphates (p. 195), they are unaffected by hard water as their calcium, etc. salts are soluble.

CHAPTER 31

PHENOLS

HYDROXY-COMPOUNDS of the aromatic series, such as *phenol* or *hydroxy-benzene*, $C_6H_5 \cdot OH$, the *cresols* or *hydroxy-toluenes*, $C_6H_4(CH_3) \cdot OH$, and *benzyl alcohol*, $C_6H_5 \cdot CH_2 \cdot OH$, are derived from the aromatic hydrocarbons by the substitution of hydroxyl groups for atoms of hydrogen, just as the aliphatic alcohols are derived from the paraffins. It will be seen, however, from the examples just given, that, whereas in the case of benzene, hydrogen atoms of the nucleus only can be displaced, in that of toluene and all the higher homologues this is not so, since a hydroxyl group may displace hydrogen either of the *nucleus* or of the *side chain*. Now the hydroxy-derivatives of benzene, and all other *nuclear* hydroxy-compounds, differ in many respects, not only from aliphatic alcohols, but also from those aromatic compounds, which contain the hydroxyl group in the side chain ; it is convenient, therefore, to distinguish between the two kinds of hydroxy-compounds, and to divide them into two groups: (*a*) the **phenols,** and (*b*) the **aromatic alcohols** (p. 495).

The *phenols*, or nuclear hydroxy-compounds, may then be classed as monohydric, dihydric, trihydric phenols, etc., according to the number of hydroxyl groups which they contain. *Phenol*, or *carbolic acid*, $C_6H_5 \cdot OH$, for example, is a monohydric phenol, as are also the three isomeric *cresols* or *hydroxytoluenes*, $C_6H_4(CH_3) \cdot OH$; the three isomeric *dihydroxybenzenes*, $C_6H_4(OH)_2$, are dihydric, whereas *phloroglucinol*, $C_6H_3(OH)_3$, is an example of a trihydric compound.

Many phenols are easily obtainable, well-known compounds ; phenol and the cresols are prepared from coal-tar in large quantities ; *carvacrol* and *thymol* occur in various plants ; and *catechol*, *pyrogallol*, etc., may be obtained by the destructive distillation of certain vegetable products.

Preparation. (1) Phenols may be prepared by treating salts of amino-compounds with nitrous acid in aqueous solution, and then heating the solutions until nitrogen ceases to be evolved,

$$C_6H_5 \cdot NH_2, HCl + HO \cdot NO = C_6H_5 \cdot OH + N_2 + H_2O + HCl,$$

$$C_6H_4 < \begin{matrix} CH_3 \\ NH_2, HCl \end{matrix} + HO \cdot NO = C_6H_4 < \begin{matrix} CH_3 \\ OH \end{matrix} + N_2 + H_2O + HCl.$$

It is possible, therefore, to prepare phenols, not only from the amino-compounds themselves, but also indirectly from the corresponding nitro-derivatives and hydrocarbons, since these substances may be converted into amino-compounds,

$$\underset{\text{Benzene}}{C_6H_6} \longrightarrow \underset{\text{Nitrobenzene}}{C_6H_5\cdot NO_2} \longrightarrow \underset{\text{Aminobenzene}}{C_6H_5\cdot NH_2} \longrightarrow \underset{\text{Phenol}}{C_6H_5\cdot OH}.$$

The conversion of an amino-compound into a phenol really takes place in two stages; at low temperatures the salt of the amino-compound is transformed into a diazonium salt, which decomposes when its aqueous solution is heated, yielding a phenol,

$$C_6H_5\cdot NH_2, HCl + HCl + KNO_2 = C_6H_5\cdot N_2Cl + KCl + 2H_2O,$$
$$C_6H_5\cdot N_2Cl + H_2O = C_6H_5\cdot OH + HCl + N_2.$$

In this last reaction a considerable proportion of tarry matter may be formed.

The amino-compound, aniline, for example, is dissolved in dilute hydrochloric acid or sulphuric acid, and *diazotised* in the usual manner (p. 457). The solution of the diazonium salt is then gradually heated to boiling (reflux condenser) until the brisk evolution of nitrogen is at an end and the phenol is afterwards separated from the tarry matter, if possible, by distillation in steam. In other cases the phenol is extracted with a suitable solvent, and the solution is shaken with caustic alkali, which dissolves the phenol, leaving most of the impurities in the organic solvent; an excess of an acid is then added to the alkaline solution and the liberated phenol is isolated by the usual methods.

Dihydric phenols may also be prepared from the monohydric compounds by a corresponding series of changes,

$$\underset{\text{Phenol}}{C_6H_5\cdot OH} \quad \underset{\text{Nitrophenol}}{C_6H_4{<}^{NO_2}_{OH}} \quad \underset{\text{Aminophenol}}{C_6H_4{<}^{NH_2}_{OH}} \quad \underset{\text{Diazonium salt}}{C_6H_4{<}^{N_2Cl}_{OH}} \quad \underset{\text{Dihydric phenol}}{C_6H_4{<}^{OH}_{OH}}$$

(2) Another important general method for the preparation of phenols consists in *fusing* a salt of a sulphonic acid with a caustic alkali and then liberating the phenol with a mineral acid; in this case, also, their preparation from the hydrocarbons is often easily accomplished, since the latter are usually converted into sulphonic acids without difficulty,

$$C_6H_5\cdot SO_3K + 2KOH = C_6H_5\cdot OK + K_2SO_3 + H_2O,$$
$$C_6H_4{<}^{CH_3}_{SO_3Na} + 2NaOH = C_6H_4{<}^{CH_3}_{ONa} + Na_2SO_3 + H_2O.$$

The alkali salt of the sulphonic acid is placed in an iron—or, better, nickel or silver—basin,[1] together with the solid caustic alkali (about 8 mol.) and a little water, and the basin is heated over a free flame, while the mixture is constantly stirred with a nickel or silver spatula, or with a thermometer, the bulb of which is encased in a glass ignition tube, or coated with a film of silver. As the mixture is very liable to spit, the eyes of the operator must be protected by spectacles or by a sheet of glass suitably placed. After the alkali and the salt have dissolved, the temperature is slowly raised ; as a rule, a temperature considerably above 200° is required, so that if the sulphonic acid is merely boiled with concentrated alkali, the desired change does not occur. When the operation is finished, the fused mass is allowed to cool, dissolved in water, and treated with an *excess* of dilute sulphuric acid ; the liberated phenol is then isolated in some suitable manner (p. 479).

Dihydric phenols may often be obtained in a similar manner from the disulphonic acids,

$$C_6H_4(SO_3K)_2+4KOH = C_6H_4(OK)_2+2K_2SO_3+2H_2O.$$

Owing to the high temperature at which these reactions must be carried out, secondary changes very frequently occur. When the sulphonic acid contains halogens, the latter are usually displaced by hydroxyl groups, especially if certain other acid radicals, such as $—NO_2$, are also present in the molecule ; when, for example, *chlorobenzenesulphonic acid*, $C_6H_4Cl\cdot SO_3H$, is fused with potash, a dihydric phenol, $C_6H_4(OH)_2$, is produced, as the halogen as well as the sulphonic group is displaced. For a similar reason, compounds such as *o*- and *p*-chloronitrobenzene may be converted into the corresponding nitrophenols (p. 484) even by a boiling solution of caustic potash, the presence of the nitro-group facilitating the displacement of the halogen atom ; m-*chloronitrobenzene*, on the other hand, is not attacked under these conditions.

In some fusions the process is not one of direct substitution only —that is to say, the hydroxyl groups in the product are not united with the same carbon atoms as those with which the displaced atoms or groups were united ; the three (o.m.p.) *bromobenzenesulphonic acids*, for example, all yield some of the *m*-compound, *resorcinol*, $C_6H_4(OH)_2$.

[1] Caustic alkalis readily attack platinum and porcelain at high temperatures, but have little action on nickel and none on silver.

It seems possible that in the case of the *o*- and *p*-di-derivatives one of the substituents is displaced by —ONa, and the other by hydrogen, which is formed as the result of a secondary reaction (compare phloroglucinol, p. 492); the sodium phenate thus produced, in the presence of atmospheric oxygen, might then be converted into the sodium derivative of resorcinol.

$$2C_6H_5\cdot ONa+O_2+2NaOH = 2C_6H_4(ONa)_2+2H_2O.$$

(3) Phenols may also be obtained by heating phenolic acids, such as salicylic acid, with soda-lime,

$$C_6H_4(OH)\cdot COONa+NaOH = C_6H_5\cdot OH+Na_2CO_3,$$

a reaction which is similar to that which occurs in the preparation of the hydrocarbons from the acids.

(4) They may be formed by treating aryl Grignard reagents with oxygen,

$$2C_6H_5\cdot MgBr+O_2 = 2C_6H_5\cdot O\cdot MgBr,$$

and then decomposing the products with mineral acids.

When phenols are heated with certain aliphatic alcohols at a high temperature (about 200°) in the presence of zinc chloride, the alkyl group displaces hydrogen of the nucleus,

$$C_6H_5\cdot OH+R\cdot OH = C_6H_4{<}^{R}_{OH}+H_2O.$$

A phenol may thus be transformed into its higher homologues.

Properties. Most phenols are crystalline and readily soluble in alcohol and ether; their solubility in water usually increases with the number of hydroxyl groups in the molecule, while their volatility diminishes; phenol and cresol, for example, are rather sparingly soluble, distil without decomposition, and are readily volatile in steam, whereas the three dihydric phenols are readily soluble and volatilise very slowly in steam. Alcoholic and aqueous solutions of most monohydric phenols give a violet colouration with ferric salts. The di- and poly-hydric compounds also give colour reactions which vary with the relative positions of the hydroxyl groups (pp. 490-493).

Most phenols give *Liebermann's* reaction: when dissolved in concentrated sulphuric acid and treated with a nitrosoamine or a nitrite,[1] they yield (red, brown, etc.) solutions which, on the addition

[1] Phenols give with nitrous acid *p*-nitroso-derivatives, which condense with the unchanged phenols to form complex coloured compounds.

of water and an excess of alkali, assume an intense blue or green colour. This reaction, therefore, affords a convenient test for phenols, as well as for nitrosoamines (p. 449).

Most phenols reduce potassium permanganate solution, and when the alkaline solutions of most di- and poly-hydric phenols are shaken in the air they turn brown or black, owing to the formation of complex oxidation products.

Although the phenols resemble the aliphatic and aromatic alcohols in many respects, they differ from both in several important particulars. The character of the hydroxyl group (like that of the amino-group, p. 441) is in fact greatly modified by its union with carbon of the benzene nucleus, just as it is altered by combination with acid-forming atoms or radicals, such as Cl—, NO_2—, etc.; in other words, the phenolic hydroxyl group has a much more pronounced acidic character than that in alcohols, and for this reason the radicals *phenyl*, C_6H_5—, *phenylene*, $C_6H_4<$, etc., may be regarded as acid-forming.

The acidic character of the phenolic hydroxyl groups is shown by their behaviour towards solutions of the alkali hydroxides, in which phenols dissolve freely, owing to the formation of metallic salts, such as *sodium phenate* or *phenoxide*, $C_6H_5 \cdot ONa$, and *potassium cresate*, $C_6H_4(CH_3) \cdot OK$; these compounds, unlike the metallic derivatives of the alcohols, can exist in the presence of water, but are decomposed by carbonic acid and by other acids, with the regeneration of the phenols. For these reasons phenols dissolve readily in aqueous alkalis, but are not more soluble in alkali carbonates than in water, unless their molecules contain other acid-forming groups or atoms; *nitrophenol*, $C_6H_4(NO_2) \cdot OH$, and *picric acid*, $C_6H_2(NO_2)_3 \cdot OH$, for example, are so acidic in character that they decompose the alkali carbonates and dissolve in their aqueous solutions.

The *metallic* derivatives of the phenols, like those of the alcohols, react with alkyl halides and with dimethyl sulphate, yielding phenolic ethers,

$$C_6H_5 \cdot OK + CH_3I = C_6H_5 \cdot O \cdot CH_3 + KI,$$

$$C_6H_4 < \begin{matrix} CH_3 \\ ONa \end{matrix} + (CH_3)_2SO_4 = C_6H_4 < \begin{matrix} CH_3 \\ OCH_3 \end{matrix} + CH_3NaSO_4,$$

which are *not* decomposed by boiling alkalis.

With phosphorus pentachloride and other halides of phosphorus, phenols give, mainly, derivatives of phosphoric or phosphorous acid (p. 424); towards acid chlorides and anhydrides, they behave in the same way as the alcohols,

$$C_6H_4<^{CH_3}_{OH}+CH_3\cdot COCl = C_6H_4<^{CH_3}_{O\cdot CO\cdot CH_3}+HCl,$$

$$C_6H_5\cdot OH+(CH_3\cdot CO)_2O = C_6H_5\cdot O\cdot CO\cdot CH_3+C_2H_4O_2.$$

When heated with organic or halogen acids, however, the phenols are not changed to any appreciable extent, because, being less basic in character than the alcohols, they do not form esters so readily.

When acyl derivatives of phenols are heated with aluminium chloride, *o*- and *p*-phenolic ketones are formed (*Fries* reaction):

$$C_6H_5\cdot O\cdot CO\cdot R \longrightarrow C_6H_4(OH)\cdot CO\cdot R.$$

In constitution the phenols may be regarded as somewhat similar to the *tertiary* alcohols, and, like the latter, many of them undergo complex changes on oxidation.

Monohydric Phenols

Phenol, $C_6H_5\cdot OH$ (*carbolic acid* or *hydroxybenzene*), occurs in very small proportions in human urine and also in that of the ox; it may be obtained from benzene, nitrobenzene, aniline, phenyldiazonium chloride, benzenesulphonic acid, and salicylic acid (p. 533) by the methods already given; but the phenol of commerce is prepared either from coal-tar, in which it was discovered by Runge in 1834, or by the hydrolysis of chlorobenzene with water or dilute caustic soda at about 300° under high pressure.

Phenol crystallises in deliquescent prisms, which melt at 43°, and turn pink on exposure to air and light; it boils at 182°, and is volatile in steam. It has a very characteristic smell, is highly *poisonous*, and has a strong caustic action on the skin, quickly causing blisters. It dissolves freely in most organic liquids, but is only moderately soluble (1 part in about 15) in cold water; its neutral *aqueous* solution gives a violet colouration with ferric chloride, and a precipitate of *tribromophenol*, $C_6H_2Br_3\cdot OH$ (m.p. 92°), with bromine water; both these reactions may serve for its detection. Owing to its poisonous and antiseptic properties, phenol is extensively used as a disinfectant; it is also employed for the manufacture of picric acid, salicylic acid, phenacetin (p. 485), etc.

When phenol (or cresylic acid, p. 374) is heated with formalin in the presence of ammonia, liquid condensation products are obtained; these mixtures, heated under pressure, change into a *plastic* solid, and finally into a hard infusible and insoluble resin, *Bakelite*, which is employed as a substitute for celluloid, shellac, etc., and for the manufacture of a great many useful and ornamental articles (Part III).

Phenylmethyl ether, $C_6H_5 \cdot O \cdot CH_3$ (*anisole*),[1] may be prepared by heating potassium phenate with methyl iodide or by gradually adding dimethyl sulphate [2] to a solution of sodium phenate in an excess of caustic soda; it has a pleasant smell, boils at 155°, and is practically insoluble in water. When warmed with concentrated hydriodic acid, it yields phenol and methyl iodide,

$$C_6H_5 \cdot O \cdot CH_3 + HI = C_6H_5 \cdot OH + CH_3I.$$

Phenylethyl ether, $C_6H_5 \cdot O \cdot C_2H_5$ (*phenetole*), can be obtained from potassium phenate and ethyl iodide; it boils at 172°.

Anisole, phenetole, and other phenolic *ethers* are *not* hydrolysed by boiling alkalis, but, like aliphatic ethers, are decomposed by concentrated mineral acids.

Phenyl acetate, $CH_3 \cdot CO \cdot OC_6H_5$, prepared by heating phenol with acetic anhydride, boils at 196°, and is readily hydrolysed even by boiling water.

Nitrophenols, $C_6H_4(NO_2) \cdot OH$, are formed very readily when phenol is treated even with dilute nitric acid; the presence of the hydroxyl group not only facilitates the introduction of the nitro-group, but also determines the position taken up by the latter. The o- and p-*nitrophenols* are thus produced.

Phenol (1 part, say 10 g.), just liquefied by the addition of a small proportion of water, is gradually added to a mixture of sodium nitrate (1·6 parts), sulphuric acid (2·5 parts), and water (4 parts), which is kept below 20° and well agitated. The dark brown, oily product is left to settle, the acid layer is decanted, and the residue is washed with a little water by decantation; it is then submitted to distillation in steam, whereon *o*-nitrophenol passes over as a yellow oil, which crystallises as it cools. The receiver is changed when the distillate ceases to give crystals (or oil), but the operation

[1] The names of phenolic ethers in general end in *ole*, but this termination is not restricted to such compounds.

[2] As previously stated (p. 196), dimethyl sulphate is very poisonous.

is continued until the distillate becomes practically colourless. The boiling solution of the residue is filtered from tarry matter, and the *p*-nitrophenol, which separates when the solution cools, is purified by recrystallisation from boiling water, with the addition of animal charcoal. The *o*-compound may be crystallised from aqueous alcohol.

m-*Nitrophenol* is prepared by reducing *m*-dinitrobenzene to *m*-nitroaniline (p. 447), and then treating a solution of the latter in an excess of dilute sulphuric acid with nitrous acid ; the solution of the diazonium salt is slowly heated to about 100°, and the *m*-nitrophenol, which is thus produced, may be purified by recrystallisation from water.

The melting-points of the three compounds are :

o-Nitrophenol	*m*-Nitrophenol	*p*-Nitrophenol
45°	96°	114°

The *o*- and the *m*-compounds are yellow, but the *p*-derivative is colourless ; the *o*-compound is readily volatile in steam. The three nitrophenols are all sparingly soluble in cold water, but dissolve freely in alkalis and also in alkali carbonates, forming (*p*-) yellow or (*o*- and *m*-) red salts, which are not decomposed by carbonic acid ; they have, therefore, a more marked acidic character than phenol, owing to the presence of the nitro-group.

The *ethyl* derivative of *p*-nitrophenol gives on reduction p-*aminophenetole*, $NH_2 \cdot C_6H_4 \cdot OC_2H_5$ (*phenetidine*), which is converted into its acetyl derivative when it is treated with acetic anhydride. The product, *acetyl*-p-*phenetidine* (acetyl-*p*-aminophenetole), $Ac \cdot NH \cdot C_6H_4 \cdot OC_2H_5$, melts at 137°, is only very sparingly soluble in water, and is used in medicine, under the name, *phenacetin*, in cases of neuralgia, and as an antipyretic.

Picric acid (Gr. *pikros*, bitter) or trinitrophenol, $C_6H_2(NO_2)_3 \cdot OH$, is formed when materials such as wood, silk, leather, and some resins are heated with concentrated nitric acid, very complex reactions taking place ; it may be prepared by heating phenol, or the *o*- and *p*-nitrophenols, with nitric and sulphuric acids.

Phenol (1 part) is dissolved in concentrated sulphuric acid (5 parts), water (4 parts) is added, the solution is cooled, and nitric acid of sp. gr. 1·4 (4 parts) is cautiously dropped into the flask which is carefully agitated ; after the first energetic action has subsided, the solution is carefully heated on a water-bath during about two hours, and then allowed to cool. The product solidifies

to a mass of crystals ; it is mixed with a little water, separated by filtration, washed, and recrystallised from hot water.

When phenol is dissolved in sulphuric acid, it is converted into a mixture of o- and p-*phenolsulphonic acids*, $C_6H_4(OH)\cdot SO_3H$ (below); on subsequent treatment with nitric acid, the sulphonic group, as well as two atoms of hydrogen, are displaced by nitro-groups,

$$C_6H_4(OH)\cdot SO_3H+3HO\cdot NO_2 = C_6H_2(NO_2)_3\cdot OH+H_2SO_4+2H_2O.$$

Picric acid is a yellow crystalline compound, melting at 122·5°.[1] It is only very sparingly soluble in cold, but is moderately easily soluble in hot water, and its solutions impart to silk and wool, but not to cotton, a yellow colour ; it is, in fact, one of the earlier known artificial organic dyes. It has very marked acidic properties, and readily decomposes carbonates. The *potassium* derivative, $C_6H_2(NO_2)_3\cdot OK$, and the *sodium* derivative, $C_6H_2(NO_2)_3\cdot ONa$, are yellow and crystalline, the former being sparingly, the latter readily, soluble in cold water. These compounds, and also the ammonium derivative, *explode* violently on percussion or when heated ; picric acid itself burns quietly when it is ignited on a spatula, but can be caused to explode violently with a detonator, and has been used in warfare under the name of *Melinite* or *Lyddite*. When warmed with an aqueous suspension of bleaching powder, picric acid is decomposed, giving chloropicrin (p. 78).

Picric acid may be produced by oxidising 1:3:5-*trinitrobenzene*, $C_6H_3(NO_2)_3$, with potassium ferricyanide, the presence of the nitro-groups facilitating the substitution of hydroxyl for hydrogen ; the constitution of picric acid, therefore, may be written

$$C_6H_3(NO_2)_3\cdot OH[3NO_2 = 2{:}4{:}6].$$

Picric acid forms crystalline compounds with benzene, naphthalene, anthracene, and other hydrocarbons, and also salts with amines, so that it may be used for the detection and purification of such substances. The compound which it forms with benzene, for example, crystallises in yellow needles, is decomposed by water, and has the composition, $C_6H_2(NO_2)_3\cdot OH, C_6H_6$; *ethylamine picrate*, $C_2H_5\cdot NH_2, C_6H_2(NO_2)_3\cdot OH$, and the picrates of many other bases may be recrystallised from water.

Phenol-o-sulphonic acid, $C_6H_4(OH)\cdot SO_3H$, is formed, together with a comparatively small quantity of the *p*-acid, when a solution of phenol in concentrated sulphuric acid is kept for some time at

[1] Picric acid and all picrates should be handled with the greatest care as they may detonate very readily even in a melting-point tube.

ordinary temperatures; when, however, the solution is heated at 100–110°, the *o*-acid is decomposed into phenol and sulphuric acid, which then react to give *phenol*-p-*sulphonic acid.*

Phenol-m-*sulphonic acid* is prepared by carefully heating benzene-*m*-disulphonic acid with alkali at 170–180°; under these conditions only one of the sulphonic groups is displaced,

$$C_6H_4<^{SO_3K}_{SO_3K}+2KOH = C_6H_4<^{OK}_{SO_3K}+K_2SO_3+H_2O.$$

The *o*-acid is used as an antiseptic under the name, *aseptol.*

The three (*o.m.p.*) **cresols,** $C_6H_4(CH_3)\cdot OH$ (hydroxytoluenes), the next homologues of phenol, occur in coal-tar, from which the *o*-compound can be isolated by fractional distillation; for the separation of the *m*- and *p*-isomerides from one another, chemical methods are used.

All three compounds may be prepared by diazotising the corresponding *toluidines* (aminotoluenes), $C_6H_4(CH_3)\cdot NH_2$, or by fusing the corresponding *toluenesulphonic acids* with potash,

$$C_6H_4<^{CH_3}_{SO_3K}+2KOH = C_6H_4<^{CH_3}_{OK}+K_2SO_3+H_2O.$$

Their melting- and boiling-points are:

	o-Cresol	*m*-Cresol	*p*-Cresol
M.p.	30°	11°	34°
B.p.	191°	202°	202°

The cresols resemble phenol in most of their ordinary properties, as, for example, in being only moderately soluble in water, and in forming potassium and sodium derivatives, which are decomposed by carbonic acid; they also yield alkyl derivatives, etc., by the displacement of the hydrogen of the hydroxyl group. They all give a violet colouration with ferric chloride, and on distillation with zinc-dust, they are all converted into toluene,

$$C_6H_4<^{CH_3}_{OH}+Zn = C_6H_5\cdot CH_3+ZnO.$$

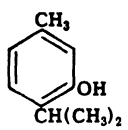
Like phenol, the cresols are poisonous and are used as antiseptics (*lysol*), as are also *amyl*-m-*cresol* and *hexylresorcinol* (p. 491). *Dettol* is a mixture of chloroxylenols.

A very interesting fact regarding the three cresols is that they are not oxidised by chromic acid, although toluene, as already stated, is slowly converted into benzoic acid; the hydroxyl group,

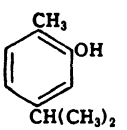
therefore, protects the methyl group from the attack of acid oxidising agents, and this is true also in the case of other phenols of similar constitution. If, however, the hydrogen of the hydroxyl group is displaced by an alkyl, or by an acyl radical, then the protection is withdrawn, and the methyl is converted into the carboxyl group in the usual manner; the *methylcresols*, $C_6H_4(OCH_3)\cdot CH_3$, for example, are oxidised by chromic acid, and are converted into the corresponding *methoxybenzoic acids*, $C_6H_4(OCH_3)\cdot COOH$.

2-Methyl-4-chlorophenoxyacetic acid, $C_6H_3Cl(Me)\cdot O\cdot CH_2\cdot COOH$, a derivative of *o*-cresol, is used as a weed-killer (*methoxone*, *agroxone*); it kills plants such as yellow and white charlock, pennycress and corn buttercups without any damage to cereals and thus increases the yield of grain. It does not harm grass and can be used on lawns.

Of the higher monohydric phenols, **thymol** and **carvacrol** may be mentioned; these two compounds are isomeric monohydroxy-derivatives of *cymene*, $C_6H_4(CH_3)\cdot C_3H_7$ (p. 419), and their constitutions are respectively represented below:



Thymol



Carvacrol

Thymol occurs in oil of thyme, together with cymene; it crystallises in large plates, melts at 51·5°, and has a characteristic smell, like that of thyme. It is only very sparingly soluble in water, and does *not* give a colouration with ferric chloride; when heated with phosphorus pentoxide it yields propylene and *m*-cresol,

$$C_6H_3(OH)<\begin{matrix}CH_3\\C_3H_7\end{matrix} = C_6H_4(OH)\cdot CH_3+C_3H_6.$$

Carvacrol occurs in the oil of *Origanum hirtum*, and may be prepared by heating camphor with iodine,

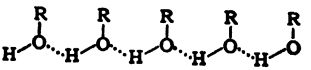
$$C_{10}H_{16}O+I_2 = C_{10}H_{14}O+2HI;$$

it boils at 237°, and its alcoholic solution gives a green colouration with ferric chloride. When heated with phosphorus pentoxide, it is decomposed into propylene and *o*-cresol.

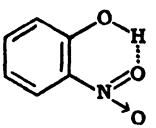
It has already been mentioned that alcohols are associated; the same phenomenon is shown by phenols. When, however, the

hydroxylic hydrogen atoms in such compounds are displaced by alkyl radicals, the resulting ethers do not show any association. Association therefore is dependent on the hydroxylic hydrogen atoms which must be capable in some way of linking the molecules.

Such *hydrogen bonding* is assumed to occur between the hydroxylic hydrogen atom and an oxygen atom of another molecule, giving a chain-like structure,



When the structures of the isomeric nitrophenols are examined it will be seen that in the *o*-, but not in the *m*- and *p*-compounds, the hydrogen atom of the phenolic group is suitably situated in space with regard to an oxygen atom of the nitro-group to permit of hydrogen bonding,

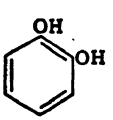


As the hydrogen atom is here employed in hydrogen bonding within *one* molecule it will not be available for linking different molecules and *o*-nitrophenol should not associate; that it does not, is shown by the high volatility of the *o*- as compared with that of the *m*- and *p*-compounds, a difference which extends to all *o*-nitro-hydroxy-compounds. A difference in volatility is not shown by the ethers of the isomeric nitrophenols.

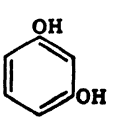
Hydrogen bonding of this kind which gives rise to a ring structure is known as *chelation* and is very common, particularly among suitable *o*-disubstituted derivatives of benzene.

Dihydric Phenols

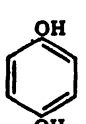
The isomeric dihydric phenols—*catechol*, *resorcinol*, and *quinol* (hydroquinone)—are well-known compounds of considerable importance, and are respectively represented by the formulae,



Catechol
(*o*-dihydroxybenzene)



Resorcinol
(*m*-dihydroxybenzene)



Quinol (hydroquinone)
(*p*-dihydroxybenzene)

Catechol, $C_6H_4(OH)_2$, occurs in *catechu*, a substance obtained in India from *Acacia catechu* and other trees, and was first produced by the destructive distillation of this vegetable product. It may be prepared by fusing *phenol-o-sulphonic acid* with potash, and by heating *guaiacol* or *methylcatechol* (see below) with concentrated hydriodic or hydrobromic acid,

$$C_6H_4(OH)\cdot OCH_3+HI = C_6H_4(OH)_2+CH_3I\,;$$

also by oxidising salicylaldehyde with a dilute aqueous alkaline solution of hydrogen peroxide,

$$C_6H_4{<}\begin{matrix}CHO\\ONa\end{matrix}+H_2O_2 = C_6H_4{<}\begin{matrix}OH\\OH\end{matrix}+H\cdot COONa.$$

It is prepared commercially by heating *o*-chlorophenol with 20% alkali and a trace of copper sulphate at about 190° under pressure.

It melts at 105°, is readily soluble in water, and its solutions in aqueous alkalis darken on exposure to the air ; its aqueous solution gives, with ferric chloride, a *green* colouration, which, on the addition of sodium bicarbonate, changes first to violet and then to red, a reaction which is common to many *ortho*-dihydric phenols (p. 493).

Guaiacol, $C_6H_4(OMe)\cdot OH$, is obtained from the tar produced during the destructive distillation of beech-wood and from the resin *guaiacum* ; it melts at 32°, has a pleasant smell, and gives a green colouration with ferric chloride in alcoholic solution.

Resorcinol, $C_6H_4(OH)_2$, is prepared on a large scale by fusing benzene-*m*-disulphonic acid with sodium hydroxide,

$$C_6H_4(SO_3Na)_2+4NaOH = C_6H_4(ONa)_2+2Na_2SO_3+2H_2O.$$

It is also obtained when the *p*-disulphonic acid and many other *o*- and *p*-di-derivatives of benzene are treated in the same way, but how such remarkable changes occur, it is difficult to say (compare p. 481). Resorcinol melts at 110°, and dissolves freely in water, alcohol, and ether ; its aqueous solution gives a dark-violet colouration with ferric chloride, and a crystalline precipitate of *tribromoresorcinol*, $C_6HBr_3(OH)_2$, with bromine water. When resorcinol is strongly heated for a few minutes with phthalic anhydride (p. 521), and the brown or red mass is then dissolved in caustic soda, there results a brownish-red solution, which, when poured into a large volume of water, shows a beautiful green fluorescence ; this phenomenon is due to the formation of *fluorescein*. Other *m*-dihydric phenols give this *fluorescein reaction*, which, therefore, affords a con-

venient and very delicate test for such compounds; this reaction may also be employed as a test for *inner* anhydrides of *dicarboxylic acids*.

Resorcinol is used in large quantities in preparing *fluorescein*, *eosin*, and various azo-dyes (p. 676).

Styphnic acid (2:4:6-*trinitroresorcinol*) is prepared by the nitration of resorcinol with nitric and sulphuric acids. It is yellow and strongly acidic and, like picric acid, gives unstable crystalline products with certain hydrocarbons. It melts at 180°.

4-n-*Hexylresorcinol*, $C_6H_3(OH)_2 \cdot C_6H_{13}$, is prepared by condensing resorcinol with caproic acid in the presence of zinc chloride and reducing the resulting ketone by Clemmensen's method; it is an important disinfectant.

Quinol, $C_6H_4(OH)_2$ (hydroquinone), is formed, together with glucose, when the glucoside (pp. 316, 354), *arbutin*, which occurs in the leaves of the bear-berry, is boiled with dilute sulphuric acid,

$$C_{12}H_{16}O_7 + H_2O = C_6H_4(OH)_2 + C_6H_{12}O_6.$$

It is usually prepared by reducing quinone (p. 506) with sulphurous acid in aqueous solution,[1] but about 20% of the quinone is converted into *quinolsulphonic acid*,

$$C_6H_4O_2 + H_2SO_3 = C_6H_3(OH)_2 \cdot SO_3H.$$

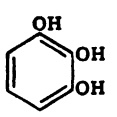
It melts at 170°, is readily soluble in water, and when treated with ferric chloride or other mild oxidising agents, it is converted into quinone,

$$C_6H_4(OH)_2 + O = C_6H_4O_2 + H_2O.$$

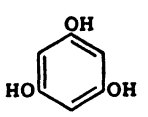
Its solutions in aqueous alkalis darken on exposure to the air.

Trihydric Phenols

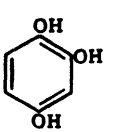
The three trihydric phenols, $C_6H_3(OH)_3$, are respectively represented by the following formulae:



Pyrogallol
(1:2:3-trihydroxybenzene)



Phloroglucinol
(1:3:5-trihydroxybenzene)



Hydroxyquinol
(1:2:4-trihydroxybenzene)

[1] The name *hydroquinone*, by which this dihydroxybenzene is still known, recalls its relation to quinone; it was changed to quinol, in conformity with the rule that the name of a hydroxy-compound should end in *ol*.

Pyrogallol, $C_6H_3(OH)_3$, sometimes called pyrogallic acid, is prepared by heating gallic acid (p. 536) alone or with glycerol, at about 210°, until the evolution of carbon dioxide ceases,

$$C_6H_2(OH)_3 \cdot COOH = C_6H_3(OH)_3 + CO_2.$$

It melts at 133°, and is readily soluble in water, but more sparingly soluble in alcohol and ether (the effect of hydroxyl groups); its aqueous solution gives, with ferric chloride, a red, and with ferrous sulphate containing a trace of ferric chloride, a deep, dark-blue colouration. It dissolves freely in alkalis, giving solutions which rapidly absorb oxygen and turn black on exposure to the air, a fact which is made use of in gas analysis, for the estimation of oxygen. Pyrogallol has strong reducing properties, and precipitates gold, silver, and mercury from solutions of their salts, which oxidise it to oxalic acid and other products; many other phenols, such as *catechol*, *resorcinol*, and *quinol*, are also reducing agents, especially in alkaline solution, but the monohydric compounds are much less readily oxidised. Pyrogallol and quinol are used in photography as developers, as are also aminomonohydric phenols and their derivatives; *metol*, for example, is the sulphate of p-*methylaminophenol*, $C_6H_4(OH) \cdot NH \cdot CH_3$, and *amidol* the sulphate of *diaminophenol* [OH:2NH$_2$ = 1:2:4].

Pyrogallol forms mono-, di-, and tri-alkyl derivatives; a *dimethyl* derivative, $C_6H_3(OCH_3)_2 \cdot OH$, occurs in beech-wood tar.

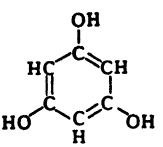
Phloroglucinol, $C_6H_3(OH)_3$ (1:3:5 or symmetrical tri-hydroxybenzene), is produced when phenol, resorcinol, and many resins, such as gamboge, dragon's-blood, etc., are fused with alkali; it is prepared by the hydrolysis of 1:3:5-triaminobenzene (p. 437) or triamino-benzoic acid.

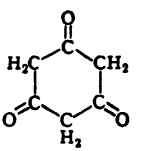
It may also be prepared by fusing resorcinol (1 part) with caustic soda (6 parts) during about 25 minutes, or until the vigorous evolution of hydrogen has ceased. The chocolate-coloured melt is dissolved in water, and the solution is treated with an excess of dilute sulphuric acid and repeatedly extracted with ether; the extract is evaporated, and the residue recrystallised from water.

It crystallises in prisms with $2H_2O$, melts at about 218°, and is very soluble in water; the solution has a sweet taste, gives with ferric chloride a bluish-violet colouration, and when mixed with caustic alkali, rapidly turns brown in contact with the air, owing to the absorption of oxygen. When warmed with acetyl chloride,

phloroglucinol yields a *triacetate*, $C_6H_3(O\cdot CO\cdot CH_3)_3$, melting at 106°, and in many other reactions its behaviour points to the conclusion that it contains three *hydroxyl* groups; on the other hand, when treated with hydroxylamine, it gives a *trioxime*, $C_6H_6(:N\cdot OH)_3$, and in this and certain other respects it behaves as though it were a *triketone*.

For these reasons phloroglucinol may be represented by either of the following formulae,





and it may be assumed that the *trihydroxy*-compound is readily convertible into the *triketone* and *vice versa* by tautomeric change.

Hydroxyquinol, or 1:2:4-trihydroxybenzene, is formed when quinol is fused with potash. It melts at 140°, is very soluble in water, and its aqueous solution is coloured greenish-brown by ferric chloride, but on the addition of sodium bicarbonate the colour changes to blue and then to red (p. 490).

Mercuration of Aromatic Compounds

It has already been pointed out that certain derivatives of benzene, such as aniline and phenol may be very rapidly converted into tri-halogen substitution products at the ordinary temperature. Certain di- and tri-hydric phenols also react readily when they are heated with an aqueous solution of ammonium hydrogen carbonate, giving phenolic acids (p. 531). Another interesting case of substitution, brought about by a seemingly very inert reagent, was discovered by Dimroth (1898), who found that benzene and many of its derivatives reacted with mercuric acetate. The hydrocarbon, heated with the salt at 110°, gives *phenylmercuriacetate*, $C_6H_5\cdot Hg\cdot O\cdot CO\cdot CH_3$, and acetic acid, and toluene reacts in a corresponding manner; after prolonged heating benzene is converted into *phenylene-dimercuriacetate*, $C_6H_4(Hg\cdot O\cdot CO\cdot CH_3)_2$. The process is known as *mercuration* and is an important general reaction.

Phenol reacts with mercuric acetate in aqueous solution at the ordinary temperature, giving a crystalline precipitate of a

dimercuriacetate, $HO \cdot C_6H_3(Hg \cdot O \cdot CO \cdot CH_3)_2$, the *o*- and *p*-monomercuriacetates remaining in solution. Various other types of aromatic compounds such as amines, amino-acids, phenolic acids, etc., are also converted into mercuriacetates at ordinary temperatures; but others such as nitrobenzene and benzoic acid react only at higher temperatures.

The mercuriacetates are generally crystalline, more or less soluble in water and organic solvents. When boiled with a solution of sodium chloride, they give *mercurichlorides*, such as $HO \cdot C_6H_4 \cdot HgCl$, but with boiling hydrochloric acid, the —Hg·OAc group is displaced by hydrogen. Halogens displace the mercuri-group even at ordinary temperatures, giving the corresponding halogen derivative, so that in this way the orientation of the compound may be easily accomplished. Thus the mercuri-derivative of nitrobenzene gives *o*-bromonitrobenzene, a fact which shows that in mercuration the nitro-group is *o*-orientating; similarly the mercuration of benzoic acid gives an *o*-derivative. These results are entirely contrary to what might have been expected, since both nitrobenzene and benzoic acid normally give *m*-derivatives. Toluene gives *o*-, *m*-, and *p*-derivatives in the proportion 43:13:34.

Thiophenols and Sulphides

Thiophenol, *phenyl mercaptan*, $C_6H_5 \cdot SH$, may be obtained by heating sodium benzenesulphonate with sodium hydrogen sulphide,

$$C_6H_5 \cdot SO_3Na + NaHS = C_6H_5 \cdot SNa + NaHSO_3,$$

or by treating phenol with phosphorus pentasulphide,

$$5C_6H_5 \cdot OH + P_2S_5 = 5C_6H_5 \cdot SH + P_2O_5;$$

it is usually prepared by reducing benzenesulphonyl chloride with zinc and dilute sulphuric acid,

$$C_6H_5 \cdot SO_2Cl + 6H = C_6H_5 \cdot SH + 2H_2O + HCl.$$

It boils at 169° and has a most unpleasant smell; it resembles ethyl mercaptan in forming a mercury derivative, $(C_6H_5 \cdot S)_2Hg$, and in being oxidised to a sulphonic acid (p. 130).

Diphenyl sulphide, $(C_6H_5)_2S$, is formed, together with thiophenol, by treating phenol with phosphorus pentasulphide. It boils at 296° and has a smell of leeks. It can be oxidised to *diphenyl sulphoxide*, $(C_6H_5)_2SO$, and *diphenyl sulphone*, $(C_6H_5)_2SO_2$. Other mercaptans and sulphides can be obtained by similar reactions and have similar properties.

CHAPTER 32

ALCOHOLS, ALDEHYDES, KETONES, AND QUINONES

Alcohols

THE aromatic alcohols are derived from the hydrocarbons by the substitution of hydroxyl groups for hydrogen atoms of the *side chain*: *benzyl alcohol* $C_6H_5 \cdot CH_2 \cdot OH$, for example, is derived from *toluene*; *tolyl carbinol*, $C_6H_4(CH_3) \cdot CH_2 \cdot OH$, from *xylene*; and so on. The compounds of this type are very closely related to the aliphatic alcohols, although, of course, they show at the same time the general behaviour of aromatic substances.

They may be obtained by methods exactly analogous to those employed in the case of the aliphatic alcohols—namely, by heating the corresponding halogen derivatives with water, weak alkalis, or moist silver oxide,

$$C_6H_5 \cdot CH_2Cl + H_2O = C_6H_5 \cdot CH_2 \cdot OH + HCl,$$

and by reducing the corresponding aldehydes and ketones,

$$C_6H_5 \cdot CHO + 2H = C_6H_5 \cdot CH_2 \cdot OH,$$
$$C_6H_5 \cdot CO \cdot CH_3 + 2H = C_6H_5 \cdot CH(OH) \cdot CH_3.$$

Those compounds which, like benzyl alcohol, contain the carbinol group, $-CH_2 \cdot OH$, directly united with the nucleus, may also be prepared by treating the corresponding aldehydes with alcoholic or aqueous caustic potash; this important general reaction is described later (p. 496).

The aromatic alcohols are usually liquids, very sparingly soluble in water; their behaviour with alkali metals, phosphorus pentachloride, and acids, is similar to that of the aliphatic compounds, as will be seen from a consideration of the properties of benzyl alcohol, one of the better-known aromatic alcohols.

Benzyl alcohol, $C_6H_5 \cdot CH_2 \cdot OH$ (phenylcarbinol), an isomeride of the three *cresols*, occurs in storax (a resin obtained from the tree, *Styrax officinalis*), and also in balsam of Peru and balsam of Tolu, either in the free state, or as an ester of cinnamic or benzoic acid.

It may be obtained by reducing benzaldehyde (p. 499) with sodium amalgam and water,

$$C_6H_5 \cdot CHO + 2H = C_6H_5 \cdot CH_2 \cdot OH,$$

and by passing anhydrous formaldehyde into an ethereal solution of phenyl magnesium bromide and then decomposing the additive compound with acids,

$$CH_2O+C_6H_5\cdot MgBr = C_6H_5\cdot CH_2\cdot OMgBr,$$
$$C_6H_5\cdot CH_2\cdot O\cdot MgBr+HCl = C_6H_5\cdot CH_2\cdot OH+MgClBr.$$

It is conveniently prepared in the laboratory by treating benzaldehyde with cold caustic potash (*Cannizzaro's* reaction),

$$2C_6H_5\cdot CHO+KOH = C_6H_5\cdot CH_2\cdot OH+C_6H_5\cdot COOK.$$

The aldehyde (10 parts) is shaken with a solution of potash (9 parts) in water (10 parts) until the whole forms an emulsion; after the lapse of 24 hours, water is added to dissolve the potassium benzoate, the solution is extracted with ether, the dried ethereal extract is evaporated, and the benzyl alcohol is purified by distillation.

In this reaction *benzyl benzoate*, $C_6H_5\cdot CH_2\cdot O\cdot CO\cdot C_6H_5$, is probably formed in the first place, and can in fact be obtained by using sodium benzylate instead of sodium hydroxide.

Benzyl alcohol is produced commercially by boiling benzyl chloride with milk of lime or a solution of sodium carbonate. It boils at 205° and is only sparingly soluble in water, but is miscible with organic solvents. It is readily attacked by sodium and by potassium, with the evolution of hydrogen, yielding metallic derivatives, which are decomposed by water; when treated with phosphorus pentachloride, it is partly converted into *benzyl chloride*,

$$C_6H_5\cdot CH_2\cdot OH+PCl_5 = C_6H_5\cdot CH_2Cl+POCl_3+HCl.$$

When heated with concentrated acids, or treated with anhydrides or acid chlorides, it gives esters; with hydrobromic acid, for example, it yields *benzyl bromide*, $C_6H_5\cdot CH_2Br$ (b.p. 198°), and with acetyl chloride or acetic anhydride it gives *benzyl acetate*, $C_6H_5\cdot CH_2\cdot O\cdot CO\cdot CH_3$ (b.p. 216°). On oxidation with dilute nitric acid, it is first converted into benzaldehyde and then into benzoic acid,

$$C_6H_5\cdot CH_2\cdot OH+O = C_6H_5\cdot CHO+H_2O,$$
$$C_6H_5\cdot CH_2\cdot OH+2O = C_6H_5\cdot COOH+H_2O.$$

All these changes are strictly analogous to those undergone by the aliphatic alcohols.

A great many alcohols containing both aliphatic (alkyl) and

aromatic (aryl) hydrocarbon radicals have been prepared with the aid of the Grignard reagents. *Phenyldimethyl carbinol*, $C_6H_5 \cdot C(CH_3)_2OH$, for example, is easily obtained from acetone and phenyl magnesium bromide; *phenylethyl carbinol*, $C_6H_5 \cdot CH(C_2H_5) \cdot OH$, from benzaldehyde and ethyl magnesium bromide, and so on. In all such compounds the hydroxyl group shows much the same behaviour as that in aliphatic tertiary and secondary alcohols respectively.

A few other alcohols are described later (pp. 525, 535).

Aldehydes

The relation between the aromatic aldehydes and the aromatic alcohols is the same as that between the corresponding classes of aliphatic compounds; *benzaldehyde*, $C_6H_5 \cdot CHO$, for example, corresponds with *benzyl alcohol*, $C_6H_5 \cdot CH_2 \cdot OH$; *salicylaldehyde*, $C_6H_4(OH) \cdot CHO$, with *salicyl alcohol*, $C_6H_4(OH) \cdot CH_2 \cdot OH$; *phenylacetaldehyde*, $C_6H_5 \cdot CH_2 \cdot CHO$, with *β-phenylethyl alcohol* (benzyl carbinol), $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot OH$, and so on.

Now those compounds, which contain a nuclear aldehyde group, are of far greater importance than those in which this group is combined with a carbon atom of the *side chain*; whereas, moreover, the latter resemble aliphatic aldehydes very closely in general character, and do not therefore require a detailed description, the former differ from the aliphatic compounds in several important particulars, as below.

Preparation. Aromatic aldehydes containing a *nuclear* aldehyde group may be prepared by the following reactions:

(1) The corresponding alcohol, usually obtained from a chloride, $R \cdot CH_2Cl$, is gently oxidised.

(2) The calcium salt of the corresponding acid is heated with calcium formate,

$$(C_6H_5 \cdot COO)_2Ca + (H \cdot COO)_2Ca = 2C_6H_5 \cdot CHO + 2CaCO_3.$$

(3) A cyanide, obtained from a diazonium salt, is reduced to an aldimine with a solution of anhydrous stannous chloride in ether, saturated with hydrogen chloride; the precipitated stannichloride of the aldimine is readily decomposed by warm water, giving the aldehyde (Stephen),

$$R \cdot CN \longrightarrow R \cdot CCl{:}NH \longrightarrow R \cdot CH{:}NH \longrightarrow [R \cdot CH{:}NH,HCl]_2SnCl_4 \longrightarrow R \cdot CHO.$$

These three methods are analogous to those used in the preparation of aliphatic aldehydes.

(4) A mixture of carbon monoxide and hydrogen chloride is passed into a hydrocarbon, in the presence of anhydrous cuprous chloride and aluminium chloride (Gattermann). This method seems to depend on the formation of the very unstable chloride of formic acid, $H \cdot CO \cdot Cl$, which, in the presence of the catalysts, reacts with the benzene, with the elimination of hydrogen chloride.

Properties. Aromatic aldehydes *resemble* aliphatic aldehydes in the following respects: They readily undergo oxidation, sometimes merely on exposure to the air, yielding the corresponding acids,

$$C_6H_5 \cdot CHO + O = C_6H_5 \cdot COOH,$$

and they reduce ammoniacal solutions of silver hydroxide, but in some cases only very slowly. On reduction they are converted into the corresponding alcohols,

$$C_6H_5 \cdot CHO + 2H = C_6H_5 \cdot CH_2 \cdot OH.$$

When treated with phosphorus pentachloride, they give dihalogen derivatives, such as *benzal chloride*, $C_6H_5 \cdot CHCl_2$, two atoms of chlorine being substituted for one atom of oxygen. They react with hydroxylamine, yielding aldoximes, and with phenylhydrazine, giving phenylhydrazones,

$$C_6H_5 \cdot CHO + NH_2 \cdot OH = H_2O + C_6H_5 \cdot CH{:}N \cdot OH,$$

Benzaldoxime (m.p. 35°) [1]

$$C_6H_5 \cdot CHO + NH_2 \cdot NH \cdot C_6H_5 = H_2O + C_6H_5 \cdot CH{:}N \cdot NH \cdot C_6H_5.$$

Benzylidenephenylhydrazone (m.p. 159°) [2]

They also react with semicarbazide. *Benzaldehyde semicarbazone*, $NH_2 \cdot CO \cdot NH \cdot N{:}CH \cdot C_6H_5$ (m.p. 214°), for example, separates at once in crystals when benzaldehyde is shaken with an aqueous solution of semicarbazide hydrochloride and sodium acetate. Like some phenylhydrazones, the semicarbazones are decomposed by acids, yielding the aldehyde or ketone and a salt of semicarbazide.

They show Schiff's reaction, combine directly with sodium bisulphite, forming crystalline compounds, and with hydrogen cyanide they yield hydroxycyanides (cyanohydrins), such as *mandelonitrile*, $C_6H_5 \cdot CH(OH) \cdot CN$.

[1] There are two stereoisomeric benzaldoximes (Part III).
[2] This compound is also called benzalphenylhydrazone.

Those aldehydes which contain the —CHO group directly united with the nucleus, *differ* from the fatty aldehydes in the following respects: They do not reduce Fehling's solution, and do not readily undergo polymerisation. When shaken with concentrated potash (or soda), they yield a mixture of the corresponding alcohol and acid (Cannizzaro's reaction).

They also undergo the benzoin transformation (p. 501) and the Perkin reaction (p. 526).

They do not readily form additive compounds with ammonia, but yield complex products, such as *hydrobenzamide*, $(C_6H_5 \cdot CH)_3N_2$, which is obtained when benzaldehyde is treated with ammonia.

Aromatic aldehydes of both types readily undergo *condensation* with many other fatty and aromatic compounds. When, for example, a mixture of benzaldehyde and acetone is treated with a few drops of caustic soda at ordinary temperatures, *benzylidene-acetone*, $C_6H_5 \cdot CH{:}CH \cdot CO \cdot CH_3$ (m.p. 45°), is formed; a similar reaction occurs with acetaldehyde (p. 529), and with ketones, aldehydes and esters in general condensation takes place with the $>CH_2$ group in an α-position to the carbonyl radical (Claisen).

When benzaldehyde is warmed with aniline, it gives *benzylidene-aniline*, $C_6H_5 \cdot CH{:}N \cdot C_6H_5$ (m.p. 45°), a type of compound, which is known as a *Schiff's* base.

Benzaldehyde, $C_6H_5 \cdot CHO$, sometimes called 'oil of bitter almonds,' was formerly obtained from the glycoside, *amygdalin* (p. 354), which occurs in the almonds accompanied by, but apart from, the enzyme, emulsin; when the almonds are macerated with water, the emulsin gradually decomposes the amygdalin into benzaldehyde, hydrogen cyanide, and glucose.

Benzaldehyde may be prepared in the laboratory by boiling benzyl chloride with an aqueous solution of lead nitrate, or copper nitrate, the benzyl alcohol which is first formed being oxidised to the aldehyde by the metallic nitrate,

$$2C_6H_5 \cdot CH_2 \cdot OH + Cu(NO_3)_2 + 2HCl = 2C_6H_5 \cdot CHO + CuCl_2 + N_2O_3 + 3H_2O.$$

Benzyl chloride (5 parts), water (25 parts), and copper nitrate (4 parts) are boiled together in a flask provided with a reflux condenser, during 6–8 hours, and a stream of carbon dioxide is passed into the liquid all the time, in order to expel the oxides of nitrogen, which would otherwise oxidise the benzaldehyde to benzoic acid. The process is at an end when the oil contains not more than traces of chlorine, as ascertained by washing a small portion with

water, and boiling it with silver nitrate and nitric acid. The benzaldehyde is then extracted with ether, the ethereal extract is shaken with a concentrated solution of sodium bisulphite, and the crystals of the bisulphite compound, $C_6H_5 \cdot CH(OH) \cdot SO_3Na$, are separated by filtration and washed with ether; the benzaldehyde is then regenerated, with the aid of dilute sulphuric acid, extracted with ether, dried, and distilled.

It is usually prepared on the large scale by (*a*) the direct oxidation of toluene or (*b*) the hydrolysis of benzal chloride, $C_6H_5 \cdot CHCl_2$.

(*a*) Toluene is cautiously oxidised at about 40° with 65% sulphuric acid and precipitated manganese dioxide. (*b*) Crude benzal chloride (benzylidene dichloride), which contains benzotrichloride, is heated at 30° and stirred with about 0·3% of iron powder; after the elapse of about 30 minutes, 15% of water is added and the temperature is carefully raised, whereon the dichloride undergoes hydrolysis. The benzoic acid, formed from the trichloride, is neutralised with milk of lime, the benzaldehyde is distilled in steam, agitated with a 35% solution of sodium bisulphite until it has all dissolved, and then liberated from the clarified solution by the addition of sodium carbonate.

Benzaldehyde is a highly refractive liquid of sp. gr. 1·05 at 15°; it boils at 179°, and is volatile in steam. It has a pleasant smell, like that of bitter almonds, and is only sparingly soluble in water, but is miscible with organic liquids. It is extensively used for flavouring purposes, and is employed, on the large scale, in the manufacture of various dyes.

Nitrobenzaldehydes, $C_6H_4(NO_2) \cdot CHO$. When treated with a mixture of nitric and sulphuric acids, benzaldehyde yields *m*-nitrobenzaldehyde (m.p. 58°) as the principal product, and small proportions of *o*-nitrobenzaldehyde (m.p. 41°).

p-Nitrobenzaldehyde (m.p. 106°), and also the *o*-compound, are conveniently prepared by the oxidation of the corresponding nitrocinnamic acids (p. 528) with alkaline permanganate,

$$C_6H_4{<}^{NO_2}_{CH:CH \cdot COOH} + 4O = C_6H_4{<}^{NO_2}_{CHO} + 2CO_2 + H_2O.$$

During the operation the mixture is shaken with benzene in order to extract the aldehyde as it is formed, and thus prevent its further oxidation. The benzene solution is then evaporated, and the aldehyde is purified by recrystallisation.

The nitrobenzaldehydes are colourless, crystalline substances; when reduced with ferrous sulphate and ammonia, they are

readily converted into the corresponding *aminobenzaldehydes*, $C_6H_4(NH_2)\cdot CHO$.

o-*Nitrobenzaldehyde* is a particularly interesting substance, as, when its solution in acetone is mixed with a few drops of dilute caustic soda, a precipitate of *indigo-blue* (*indigotin*) gradually forms (Baeyer),

$$2C_6H_4\langle^{NO_2}_{CHO}+2CH_3\cdot CO\cdot CH_3 = C_6H_4\langle^{NH}_{CO}\rangle C{:}C \langle^{CO}_{NH}\rangle C_6H_4$$
Indigo-blue
$$+2CH_3\cdot COOH+2H_2O.$$

Benzoin, $C_6H_5\cdot CO\cdot CH(OH)\cdot C_6H_5$, a *ketonic alcohol*, is formed and separates in crystals, when benzaldehyde (5 parts) is heated with a solution of potassium cyanide (1 part) in aqueous alcohol during about an hour, and the solution is then cooled,

$$2C_6H_5\cdot CHO = C_6H_5\cdot CO\cdot CH(OH)\cdot C_6H_5;$$

it melts at 137°, reduces Fehling's solution and forms an osazone with phenylhydrazine; on oxidation with boiling concentrated nitric acid, it gives a yellow *diketone*, **benzil,** $C_6H_5\cdot CO\cdot CO\cdot C_6H_5$, which melts at 95°.

Many other aromatic (and certain aliphatic) aldehydes give products corresponding with benzoin when they are treated with potassium cyanide; this transformation, known as the *benzoin reaction*, depends on the intermediate formation of a hydroxy-cyanide (mandelonitrile),

$$C_6H_5\cdot CH(OH)\cdot CN+C_6H_5\cdot CHO = C_6H_5\cdot CH(OH)\cdot CO\cdot C_6H_5+HCN,$$

the necessary hydrogen cyanide having been produced by the hydrolysis of the potassium cyanide.

Hydrobenzoin, $C_6H_5\cdot CH(OH)\cdot CH(OH)\cdot C_6H_5$, is formed, together with benzyl alcohol by the reduction of benzaldehyde, just as a pinacol is formed from a ketone (p. 155); its molecule contains two structurally identical asymmetric groups, and like dihydroxy-succinic acid (tartaric acid) it exists in *d*-, *l*-, and *meso*-forms, also as a conglomerate (p. 299).

Phenolic or Hydroxy-aldehydes

The hydroxy-derivatives of the aldehydes, such as the *hydroxy-benzaldehydes*, $C_6H_4(OH)\cdot CHO$, in which the hydroxyl group is united with the *nucleus*, combine the properties of phenols and aldehydes, and are classed as *phenolic aldehydes*.

Preparation. (1) By the oxidation of the corresponding phenolic alcohols ; *saligenin* (p. 535), or o-*hydroxybenzyl alcohol*, for example, yields *salicylaldehyde* or o-*hydroxybenzaldehyde*,

$$C_6H_4<\begin{matrix}OH\\CH_2\cdot OH\end{matrix}+O = C_6H_4<\begin{matrix}OH\\CHO\end{matrix}+H_2O.$$

Such alcohols, however, are not easily obtained, and indeed in many cases have only been produced by the reduction of the phenolic aldehydes.

(2) By heating phenols with chloroform in alkaline solution (*Tiemann* and *Reimer* reaction),

$$C_6H_5\cdot OH+CHCl_3+4KOH = C_6H_4(OK)\cdot CHO+3KCl+3H_2O.$$

The changes which occur in this reaction are not understood ; possibly the phenol reacts with the chloroform, in the presence of the alkali, yielding an intermediate product containing halogen,

$$C_6H_5\cdot OH+CHCl_3 = C_6H_4(OH)\cdot CHCl_2+HCl,$$

which, by the further action of the alkali, is converted into a hydroxybenzaldehyde, just as *benzal chloride* is transformed into *benzaldehyde*,

$$C_6H_4(OH)\cdot CHCl_2 \longrightarrow C_6H_4(OH)\cdot CH(OH)_2\,[1] \longrightarrow C_6H_4(OH)\cdot CHO.$$

As a rule, the principal product is the *o*-hydroxyaldehyde, small quantities of the *p*-compound being produced at the same time.

(3) By treating phenols, dissolved in benzene or ether, with hydrogen cyanide and hydrogen chloride in the presence of anhydrous aluminium chloride (Gattermann ; p. 498). Probably the two acids unite and form a compound, CHCl:NH, which then gives with the phenol an *aldimine* (p. 497),

$$C_6H_5\cdot OH+CHCl{:}NH = HO\cdot C_6H_4\cdot CH{:}NH+HCl\,;$$

this product is readily hydrolysed by acids or alkalis, with the formation of the *p*-hydroxyaldehyde and ammonia.[2]

Ethers of phenolic aldehydes may be obtained from phenolic ethers in a similar manner and the reaction has also been used for the preparation of aldehydes from hydrocarbons, but the yields are often very poor.

[1] An intermediate product, $C_6H_4(OH)\cdot CH(OC_6H_5)_2$, may also be formed.

[2] The reactions are in fact more complicated than this simple explanation would suggest.

When an alkyl cyanide is substituted for hydrogen cyanide, a phenol gives a ketone in the place of an aldehyde (Hoesch),

$$C_6H_4(OH)_2 \longrightarrow C_6H_3(OH)_2 \cdot CR{:}NH \longrightarrow C_6H_3(OH)_2 \cdot CO \cdot R.$$

The phenolic aldehydes combine the reactions of both phenols and aldehydes.

Salicylaldehyde, $C_6H_4(OH) \cdot CHO$ (*o*-hydroxybenzaldehyde), may be obtained by oxidising saligenin with chromic acid (p. 502), but it is usually prepared from phenol by the Tiemann-Reimer reaction.

Phenol (25 g.) and caustic soda (80 g.) are dissolved in water (80 g.), the solution is heated to 65–70° in a flask provided with a reflux condenser, and chloroform (60 g.) is added in small quantities at a time from a tap-funnel, cooling if necessary at first, and later boiling the liquid. At the end of about 2 hours any unchanged chloroform is distilled, and the alkaline solution is mixed with an excess of dilute sulphuric acid and distilled in steam, when phenol and salicylaldehyde pass over. (The residue in the flask contains p-*hydroxybenzaldehyde*, which may be extracted from the filtered liquid with ether, and purified by recrystallisation.) The distillate is extracted with ether, the extract evaporated, and agitated with 2 volumes of a strong solution of sodium bisulphite. The crystalline bisulphite compoundis separated by filtration with the aid of a suction-pump, and decomposed with warm dilute sulphuric acid ; the regenerated *salicylaldehyde* is extracted with ether, dried over anhydrous sodium sulphate, and purified by distillation.

Salicylaldehyde boils at 197°, and has a penetrating, aromatic odour ; it dissolves readily in alkalis, giving yellow solutions, and its aqueous solution shows a violet colouration with ferric chloride. When reduced with sodium amalgam and water it yields *saligenin*, $C_6H_4(OH) \cdot CH_2 \cdot OH$ (p. 535), whereas oxidising agents convert it into *salicylic acid*, $C_6H_4(OH) \cdot COOH$.

p-*Hydroxybenzaldehyde* (m.p. 116°) dissolves readily in hot water, and gives, with ferric chloride, a slight violet colouration.

m-*Hydroxybenzaldehyde* is obtained by converting *m*-nitrobenzaldehyde into *m*-aminobenzaldehyde, and then displacing the amino-group by hydroxyl, with the aid of nitrous acid. It crystallises from water in needles, and melts at 108°.

Anisaldehyde, $C_6H_4(OCH_3) \cdot CHO$ (*p*-methoxybenzaldehyde), is prepared from oil of aniseed. This essential oil contains *anethole*, $C_6H_4(OCH_3) \cdot CH{:}CH \cdot CH_3$, a crystalline substance (m.p. 22°),

which on oxidation with potassium dichromate and sulphuric acid is converted into *anisaldehyde*.

Anisaldehyde may be prepared synthetically by warming p-*hydroxybenzaldehyde* with alcoholic potash and methyl iodide or dimethyl sulphate,

$$C_6H_4(OK)\cdot CHO+CH_3I = C_6H_4(OCH_3)\cdot CHO+KI.$$

It boils at 248°, and has a characteristic, aromatic odour; on reduction with sodium amalgam it yields *anisyl alcohol*, $C_6H_4(OCH_3)\cdot CH_2\cdot OH$ (p. 535), and on oxidation it gives *anisic acid*, $C_6H_4(OCH_3)\cdot COOH$ (p. 536).

Ketones

The ketones of the aromatic, like those of the aliphatic, series have the general formula, R—CO—R′, where R and R′ represent different or identical radicals, one of which, of course, must be aromatic.

Preparation. (1) A calcium salt or a suitable mixture of calcium salts is heated,

$$(C_6H_5\cdot COO)_2Ca = C_6H_5\cdot CO\cdot C_6H_5+CaCO_3,$$
$$(C_6H_5\cdot COO)_2Ca+(CH_3\cdot COO)_2Ca = 2C_6H_5\cdot CO\cdot CH_3+2CaCO_3.$$

(2) A secondary alcohol, conveniently prepared from an aldehyde and Grignard reagent, is oxidised.

(3) An aromatic hydrocarbon is treated with an acid chloride or anhydride in the presence of aluminium chloride (Friedel and Crafts),

$$C_6H_6+CH_3\cdot CO\cdot Cl = C_6H_5\cdot CO\cdot CH_3+HCl,$$
$$C_6H_6+C_6H_5\cdot CO\cdot Cl = C_6H_5\cdot CO\cdot C_6H_5+HCl,$$
$$C_6H_6+(CH_3\cdot CO)_2O = C_6H_5\cdot CO\cdot CH_3+CH_3\cdot COOH.$$

(4) An unsaturated ketone, prepared by condensing an aldehyde with a ketone (p. 499), is reduced to the saturated ketone,

$$C_6H_5\cdot CHO+CH_3\cdot CO\cdot C_6H_5 \longrightarrow C_6H_5\cdot CH{:}CH\cdot CO\cdot C_6H_5 \longrightarrow C_6H_5\cdot CH_2\cdot CH_2\cdot CO\cdot C_6H_5.$$

(5) A side chain halogen compound is condensed with ethyl sodioacetoacetate and the product is submitted to ketonic hydrolysis,

$$C_6H_5\cdot CH_2Cl \longrightarrow C_6H_5\cdot CH_2\cdot CH(CO\cdot CH_3)\cdot COOEt \longrightarrow C_6H_5\cdot CH_2\cdot CH_2\cdot CO\cdot CH_3.$$

Phenolic ketones may be prepared by the Fries reaction (p. 483) and the Hoesch synthesis (p. 503): also by condensing phenols with acids or acid anhydrides in the presence of zinc chloride (p. 491).

Acetophenone, $C_6H_5 \cdot CO \cdot CH_3$ (phenylmethyl ketone, acetylbenzene), is formed, and distils, when a mixture of calcium benzoate and calcium acetate is heated, but it is most conveniently prepared by dropping acetyl chloride into well-cooled benzene, in the presence of anhydrous aluminium chloride.

Benzene (15 parts, in c.c.) and aluminium chloride (7 parts) are placed in a flask, fitted with a reflux condenser and cooled in ice, and acetyl chloride (5 parts, in c.c.) is gradually added from a tap-funnel. When the evolution of hydrogen chloride ceases, the flask is taken out of the ice, and after about an hour's time the contents are *cautiously* added to crushed ice. The benzene solution is separated, washed with water and dilute alkali successively, dried with calcium chloride and distilled. The portion collected from about 196–204° should solidify at ordinary temperatures.

Acetophenone melts at 20·5°, and boils at 202°; it is used as a hypnotic in medicine, under the name of *hypnone*. Its chemical behaviour is very similar to that of the aliphatic ketones and most of its reactions, or at any rate those which are determined by the carbonyl group, might be foretold from those of acetone. On reduction with sodium amalgam and aqueous alcohol, it is converted into *phenylmethyl carbinol*, $C_6H_5 \cdot CH(OH) \cdot CH_3$, just as acetone is transformed into *iso*propyl alcohol; like acetone, and other aliphatic ketones, it reacts with hydroxylamine, giving the *oxime*, $C_6H_5 \cdot C(:N \cdot OH) \cdot CH_3$ (m.p. 60°), and with phenylhydrazine, giving the *phenylhydrazone*, $C_6H_5 \cdot C(:N_2HC_6H_5) \cdot CH_3$ (m.p. 106°). It forms a cyanohydrin (hydroxycyanide), $C_6H_5 \cdot CMe(OH) \cdot CN$, with hydrogen cyanide, but does not combine with sodium hydrogen sulphite. On oxidation it is resolved into benzoic acid and carbon dioxide, just as acetone is oxidised to acetic acid and carbon dioxide,

$$C_6H_5 \cdot CO \cdot CH_3 + 4O = C_6H_5 \cdot COOH + CO_2 + H_2O.$$

Acetophenone shows also the general behaviour of aromatic compounds and may be converted into a nitro-derivative, mainly the *m*-compound, by the displacement of *nuclear* hydrogen.

Halogens displace hydrogen of the methyl group very readily giving compounds such as *ω-chloroacetophenone* and *ω-bromoacetophenone*; with amyl nitrite and sodium ethoxide *iso*nitrosoacetophenone, $C_6H_5 \cdot CO \cdot CH{:}NOH$, is formed. Just as acetone gives mesityl oxide and mesitylene, so acetophenone gives the ketone, $C_6H_5 \cdot C(CH_3){:}CH \cdot CO \cdot C_6H_5$ (*dypnone*) and 1:3:5-*triphenylbenzene* under appropriate conditions.

The homologues of acetophenone, such as *propionophenone*, $C_6H_5 \cdot CO \cdot C_2H_5$, *butyrophenone*, $C_6H_5 \cdot CO \cdot C_3H_7$, etc., are of little importance, but *benzophenone*, an aromatic ketone of a different series, may be briefly described.

Benzophenone, $C_6H_5 \cdot CO \cdot C_6H_5$ (diphenyl ketone or benzoylbenzene), may be obtained by heating calcium benzoate, and by treating benzene with benzoyl chloride, or with carbonyl chloride, in the presence of aluminium chloride,

$$2C_6H_6 + COCl_2 = C_6H_5 \cdot CO \cdot C_6H_5 + 2HCl.$$

It melts at 49°, and, like aromatic ketones in general, does not combine with sodium hydrogen sulphite ; when distilled over zinc-dust or reduced with amalgamated zinc and hydrochloric acid, it gives *diphenylmethane*, just as acetophenone gives ethylbenzene.

Aromatic ketones in general react normally with Grignard reagents.

Quinones

When quinol is oxidised with an excess of ferric chloride in aqueous solution, a yellowish colouration is produced ; the solution then darkens (p. 507), acquires a very penetrating odour, and, if sufficiently concentrated, deposits yellow crystals.

The substance formed in this way is named *quinone* (benzoquinone), and is the simplest member of a very interesting class of compounds ; its formation may be expressed by the equation,

$$C_6H_4(OH)_2 + O = C_6H_4O_2 + H_2O.$$

Quinone, $C_6H_4O_2$, was first obtained by the oxidation of quinic acid, from which it derives its name ; it is usually prepared by oxidising aniline with potassium dichromate and sulphuric acid.

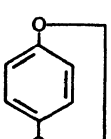
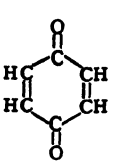
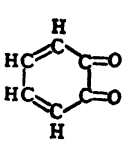
Aniline (20 g.) is dissolved in water (500 c.c.) and sulphuric acid (87 c.c.), and finely powdered potassium dichromate (70 g.) is gradually added in small quantities at a time to the solution, which is kept at 0–5° and constantly stirred. When in the course of 2 hours one-third of the dichromate has been used, the mixture is left overnight, cooled again as before, and the rest of the dichromate gradually added. After the elapse of about 8 hours, the crude quinone is separated by filtration, and purified by distillation in steam. The reactions which occur during the oxidation of aniline to quinone are very complex ; aniline black is possibly an intermediate product.

Quinone crystallises in golden-yellow prisms, melts at 116°, sublimes very readily, and is volatile in steam ; it has a peculiar, irritating, and very characteristic smell, and is only sparingly soluble in water, but dissolves freely in many organic solvents. It is reduced by sulphurous acid giving quinol.

Quinhydrone, $C_6H_4O_2, C_6H_4(OH)_2$, a dark green, crystalline additive compound of quinone and quinol, is formed as an intermediate product in this reaction, and also during the oxidation of quinol to quinone with ferric chloride.

The component molecules of quinhydrone are probably united by hydrogen bonds.

Constitution of Quinone. It is known that the two oxygen atoms in the molecule of quinone are in the *para*-position to one another, because when quinone is reduced it gives *quinol* (*para*dihydroxybenzene), from which it may be produced by oxidation ; further, when quinone is treated with phosphorus pentachloride, it is converted into *p*-dichlorobenzene. From these facts it would also seem that each of the oxygen atoms is combined with a carbon atom by one bond only, and that the structure of quinone should be expressed by the formula (I). But in some respects quinone behaves as if its molecule contained two $>C=O$ groups, each of which has properties similar to those of the carbonyl radical in compounds such as acetone, acetophenone, etc. ; when treated with a solution of a hydroxylamine salt, for example, quinone yields a *monoxime*, $O:C_6H_4:NOH$ (p-*nitrosophenol*, p. 451),[1] and also a *dioxime*, $HON:C_6H_4:NOH$.

I  II  III 

If, from this evidence, it were concluded that quinone is a diketone, then its structure would be expressed by the formula (II) which is fundamentally different from that of any aromatic compound so far described ; in (II) the closed chain of six carbon atoms does not represent a benzene nucleus, but contains two pairs of *unsaturated* carbon atoms, united together in the same way as those

[1] Quinone monoxime and *p*-nitrosophenol are tautomeric.

in the molecules of olefines. This view is strongly supported by the fact that quinone combines *directly* with bromine, at ordinary temperatures, in the absence of direct sunlight, giving a di- and a tetra-bromide, $C_6H_4Br_2O_2$ and $C_6H_4Br_4O_2$, whereas aromatic (benzenoid) compounds as a class do *not* form such additive products. The constitution of quinone, therefore, is represented by formula (II); the compound is *not* benzenoid, but is a diketone derived from a cyclic *di-olefine*, and its formation from, and conversion into, quinol, as well as its transformation into *p*-dichlorobenzene involve various stages.

Benzoquinone and many other *para*-quinones may be produced by the oxidation, with chromic acid or ferric chloride, of many hydroxy- and amino-compounds, which contain these substituents in the *para*-position; quinone, for example, is formed not only from aniline and quinol, but also by oxidising *p*-aminophenol, $C_6H_4(OH)\cdot NH_2$, and *p*-phenylenediamine, $C_6H_4(NH_2)_2$; *p-toluquinone*, [O:O:CH_3 = 1:4:2], is obtained in a similar manner by the oxidation of *p*-toluylenediamine, $C_6H_3(NH_2)_2\cdot CH_3$[NH_2:NH_2:CH_3 = 1:4:2], as well as from *o*-toluidine. All *para*-quinones resemble (benzo-) quinone in smell, in having a yellow colour, and in being readily volatile (p. 551).

***o*-Benzoquinone,** $C_6H_4O_2$ (III, p. 507), is a light-red, crystalline substance, which is obtained when catechol is oxidised with silver oxide in dry ethereal solution (in the presence of anhydrous sodium sulphate). It has no smell, is not volatile in steam, and decomposes when it is heated at 60–70°; it is reduced to catechol by sulphurous acid in aqueous solution.

m-Quinones are not known (and apparently cannot exist); this fact affords further evidence in favour of the formulae given to the *o*- and *p*-compounds, because a corresponding formula for a *m*-quinone cannot be written.

When bleaching-powder is used in oxidising amino-compounds, such as those mentioned above, *quinone chloroimines* and *quinone dichlorodiimines* are formed in the place of quinones,

$$NH_2\cdot C_6H_4\cdot OH + 4Cl = \underset{\text{Quinone chloroimine}}{NCl:C_6H_4:O} + 3HCl,$$

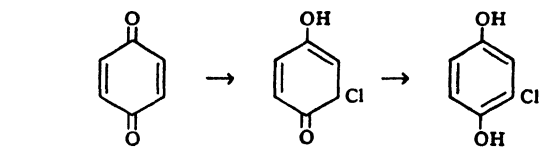
$$NH_2\cdot C_6H_4\cdot NH_2 + 6Cl = \underset{\text{Quinone dichlorodiimine}}{NCl:C_6H_4:NCl} + 4HCl.$$

The quinone chloroimines and dichlorodiimines resemble quinone in many respects; they are crystalline, readily volatile in steam,

and are respectively converted into *p*-aminophenol and *p*-phenylenediamine, or their derivatives, on reduction.

Chloranil, $O{:}C_6Cl_4{:}O$ (tetrachloroquinone), is produced by treating phenol with hydrochloric acid and potassium chlorate, oxidation and chlorination taking place; it crystallises in yellow plates, sublimes without melting, and is sparingly soluble in alcohol, nearly insoluble in water. It is readily reduced to *tetrachloroquinol*, $HO \cdot C_6Cl_4 \cdot OH$, and is sometimes used as an oxidising agent in the preparation of dyes, when the use of inorganic reagents is undesirable.

p-Quinones combine directly with various compounds giving, finally, substituted quinols; with dry hydrogen chloride, for example, quinone gives *chloroquinol* and with acetic anhydride and sulphuric acid (*Thiele* reaction) *hydroxyquinol*, as its triacetyl derivative,



Further additive reactions of quinones are described in Part III. Many substituted and complex quinones occur naturally.

CHAPTER 33

CARBOXYLIC ACIDS

THE carboxylic acids of the aromatic series are derived from the aromatic hydrocarbons, just as those of the aliphatic series are derived from the paraffins—namely, by the substitution of one or more carboxyl groups for a corresponding number of hydrogen atoms. In this, as in other cases, however, one of two classes of compounds may be obtained, according as substitution takes place in the *nucleus* or in the *side chain*; benzene, of course, yields only acids of the former type, such as *benzoic acid*, $C_6H_5 \cdot COOH$, the three (o.m.p.) *phthalic acids*, $C_6H_4(COOH)_2$, the three tricarboxylic acids, $C_6H_3(COOH)_3$, etc., but toluene (and all the higher homologues) may give rise to derivatives of both kinds—as, for example, the three *toluic acids*, $C_6H_4(CH_3) \cdot COOH$, and *phenylacetic acid*, $C_6H_5 \cdot CH_2 \cdot COOH$.

Although there are no very important differences in the properties of these two classes of acids, it is convenient to describe them separately, and to consider first those compounds in which the carboxyl groups are directly united with carbon of the *nucleus*.

Preparation. (1) By oxidising the alcohols or aldehydes,

$$C_6H_5 \cdot CH_2 \cdot OH + 2O = C_6H_5 \cdot COOH + H_2O,$$
$$C_6H_5 \cdot CHO + O = C_6H_5 \cdot COOH.$$

(2) By hydrolysing the nitriles (p. 516) with alkalis or mineral acids,

$$C_6H_5 \cdot CN + 2H_2O = C_6H_5 \cdot COOH + NH_3,$$
$$C_6H_4(CH_3) \cdot CN + 2H_2O = C_6H_4(CH_3) \cdot COOH + NH_3,$$

reactions which are exactly similar to those employed in the case of the fatty acids.

(3) By treating aryl Grignard reagents with dry carbon dioxide, and then decomposing the products with a mineral acid.

(4) Perhaps, however, the most important method, and one which has no counterpart in the aliphatic series, is by oxidising the homologues of benzene with dilute nitric acid, chromic acid, or potassium permanganate,

$$C_6H_5 \cdot CH_3 + 3O = C_6H_5 \cdot COOH + H_2O,$$
$$C_6H_5 \cdot CH_2 \cdot CH_3 + 6O = C_6H_5 \cdot COOH + CO_2 + 2H_2O.$$

As a rule, only those acids which contain *nuclear* carboxyl groups can be obtained in this way, because a saturated side chain is oxidised to —COOH, no matter how many —CH_2— groups it may contain ; in other words, all homologues of benzene which contain only one alkyl group yield *benzoic acid*, whereas those containing two, give one of the *phthalic acids*, and so on.

The reason for this seems to be that when the side chain contains more than one carbon atom, the —CH_2— group, which is united to carbon of the nucleus, is attacked first, and the product, an alcohol or a ketone, then undergoes further oxidation in the usual way. When, however, the side chain is unsaturated, it may be possible to restrict oxidation to the —CH:CH— group ; from *phenylbutylene*, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH{:}CH_2$ (p. 541), for example, β-phenylpropionic acid, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot COOH$ (p. 526), might be obtained.

When two or more side chains are present, one may be oxidised before the other is attacked, in which case an alkyl substituted acid is obtained (compare mesitylenic acid, p. 396),

$$C_6H_4(CH_3)_2 + 3O = C_6H_4(CH_3) \cdot COOH + H_2O,$$
$$C_6H_3(CH_3)_3 + 3O = C_6H_3(CH_3)_2 \cdot COOH + H_2O.$$

Oxidation is frequently carried out by boiling the hydrocarbon with nitric acid (1 vol.), diluted with water (2–4 vol.), until brown fumes are no longer formed. The mixture is then made slightly alkaline, and any unchanged hydrocarbon and traces, if any, of nitrohydrocarbon are separated by distillation with steam, or by extraction with ether ; the solution is then strongly acidified, and the precipitated acid purified by recrystallisation.

Most hydrocarbons are only very slowly attacked by oxidising agents, and therefore it is often advantageous first to substitute chlorine or a hydroxy-group for hydrogen of the side chain as in this way oxidation is facilitated. *Benzyl chloride*, $C_6H_5 \cdot CH_2Cl$, and *benzyl acetate*, $C_6H_5 \cdot CH_2 \cdot O \cdot CO \cdot CH_3$ (p. 496), for example, are much more readily oxidised than toluene, because they undergo hydrolysis, giving benzyl alcohol, which is much more rapidly attacked.

(5) Aromatic methyl ketones, $R \cdot CO \cdot CH_3$, often readily prepared by the Friedel-Crafts reaction, are easily oxidised to acids by an alkali hypochlorite or hypobromite.

Ordinary coal is oxidised by an alkaline solution of potassium permanganate giving nearly 50% of a complex mixture of benzene-

carboxylic acids; ten of the twelve theoretically possible acids are thus obtained, the missing compounds being benzoic acid and one of the tetracarboxylic acids, $C_6H_2(COOH)_4$. The hexacarboxylic acid, $C_6(COOH)_6$ (p. 523), is also formed when graphite is oxidised with fuming nitric acid.

Properties. The monocarboxylic acids are crystalline, and mostly distil without decomposition; they are sparingly soluble in cold water, but dissolve much more readily in hot water and organic solvents. In all those properties which are determined by the carboxyl group, the aromatic are closely analogous to the aliphatic acids, and give corresponding derivatives, as shown by the following examples:

Benzoic acid	$C_6H_5\cdot COOH$	Benzoyl chloride	$C_6H_5\cdot COCl$
Sodium benzoate	$C_6H_5\cdot COONa$	Benzamide	$C_6H_5\cdot CO\cdot NH_2$
Ethyl benzoate	$C_6H_5\cdot COOC_2H_5$	Benzoic anhydride	$(C_6H_5\cdot CO)_2O$

When heated with soda-lime, they are decomposed with the loss of carbon dioxide and formation of the corresponding hydrocarbons, just as acetic acid under similar conditions yields methane,

$$C_6H_5\cdot COONa+NaOH = C_6H_6+Na_2CO_3,$$
$$C_6H_4(CH_3)\cdot COONa+NaOH = C_6H_5\cdot CH_3+Na_2CO_3.$$

Benzoic acid, $C_6H_5\cdot COOH$, occurs in the free state in many resins, especially in gum benzoin and Peru balsam, from the former of which it derives its name; it is also found in the urine of the ox and the horse (about 2%), as *hippuric acid* or *benzoylglycine*, $C_6H_5\cdot CO\cdot NH\cdot CH_2\cdot COOH$, a crystalline compound melting at 187°.

It may be obtained by heating gum benzoin and recrystallising the crude sublimate from water; or by boiling hippuric acid with concentrated hydrochloric acid during about an hour, cooling the solution, and separating the crystalline deposit,

$$C_6H_5\cdot CO\cdot NH\cdot CH_2\cdot COOH+HCl+H_2O = C_6H_5\cdot COOH+HCl, NH_2\cdot CH_2\cdot COOH.$$

It may also be prepared by oxidising toluene, benzyl alcohol, or benzaldehyde, by hydrolysing *benzonitrile* (p. 515) with acids or alkalis,

$$C_6H_5CN+2H_2O = C_6H_5\cdot COOH+NH_3,$$

and by treating benzaldehyde with caustic potash or soda (Cannizzaro reaction).

Benzoic acid may be manufactured by hydrolysing crude benzotrichloride (p. 431),

$$2C_6H_5 \cdot CCl_3 + 4Ca(OH)_2 = (C_6H_5 \cdot COO)_2Ca + 3CaCl_2 + 4H_2O ;$$

the benzoic acid is precipitated from the solution of its calcium salt with hydrochloric acid and recrystallised or distilled.

Benzoic acid separates from water in glistening crystals, melts at 122°, and boils at 249°, but it sublimes very readily even at 100°, and is volatile in steam ; it dissolves in 400 parts of water at 15°, but is readily soluble in hot water and many organic solvents. Its vapour has a characteristic odour (which may serve for the identification of the acid), and an irritating action on the throat, causing violent coughing. Most of the metallic salts of benzoic acid are soluble in water, and crystallise well, but the *silver* salt is only very sparingly soluble in cold water.

Ethyl benzoate, $C_6H_5 \cdot COOC_2H_5$, is prepared by saturating a solution of benzoic acid (1 part) in alcohol (3 parts) with hydrogen chloride, and then warming the solution (with reflux condenser) during about two hours.

The excess of alcohol is then separated by distillation, and the oily residue is shaken with a dilute solution of sodium carbonate until free from acids ; the ester is washed with water, dried with calcium chloride, and distilled. A little ether may be used to dissolve the ester, if it does not separate well from the aqueous washings.

It boils at 213°, has a pleasant aromatic odour, and is readily hydrolysed by boiling alkalis.

Methyl benzoate boils at 199°.

Phenyl benzoate, $C_6H_5 \cdot CO \cdot OC_6H_5$, obtained by treating phenol with benzoyl chloride, melts at 71°, and is readily hydrolysed by aqueous alkalis.

Benzoyl chloride, $C_6H_5 \cdot COCl$, is easily prepared by treating benzoic acid with phosphorus pentachloride.

The dry acid is placed in a distillation flask, and about 5% more than one molecular proportion of the pentachloride is added. When the reaction is finished, the mixture of phosphorus oxychloride (b.p. 107°) and benzoyl chloride is submitted to fractional distillation. The whole operation is conducted in a fume-cupboard.

It is an oil of a most irritating odour, and boils at 197° ; it is gradually decomposed by water, yielding benzoic acid and hydro-

chloric acid. Benzoyl chloride is a very important laboratory reagent (below).

Benzoic anhydride, $(C_6H_5 \cdot CO)_2O$, is produced when benzoyl chloride is treated with sodium benzoate, just as acetic anhydride is formed by the interaction of acetyl chloride and sodium acetate; also by heating benzoic acid with acetic anhydride. It melts at 42°, and resembles acetic anhydride in chemical properties, but it reacts only very slowly with cold water or sodium carbonate solution.

Benzoyl chloride and benzoic anhydride, more especially the former, are frequently used for the *benzoylation* of hydroxy- and amino-compounds, as they react with such substances, yielding *benzoyl derivatives*, the univalent *benzoyl* group, $C_6H_5 \cdot CO—$, taking the place of a hydrogen atom of the hydroxyl or amino-radical,

$$C_6H_5 \cdot COCl + C_2H_5 \cdot OH = C_6H_5 \cdot CO \cdot O \cdot C_2H_5 + HCl,$$
$$(C_6H_5 \cdot CO)_2O + C_2H_5 \cdot OH = C_6H_5 \cdot CO \cdot O \cdot C_2H_5 + C_6H_5 \cdot COOH,$$
$$C_6H_5 \cdot COCl + NH_2 \cdot C_6H_5 = C_6H_5 \cdot CO \cdot NH \cdot C_6H_5 + HCl.$$

As such benzoyl compounds usually crystallise much more readily than the corresponding acetyl derivatives, they are generally prepared in preference to the latter when it is a question of the identification or isolation of a substance.

Benzoyl derivatives may be prepared by heating the hydroxy- or amino-compound with benzoyl chloride alone, or in the presence of pyridine (p. 568), which combines with the hydrogen chloride formed in the reaction. On a small scale, however, the *Schotten-Baumann* method may be used.

Benzoyl chloride and 10% caustic alkali are added alternately, in *small* quantities at a time, to an aqueous solution or suspension of the compound, and, after each addition, the mixture is well shaken and cooled. The operation is continued until no further formation of the benzoyl derivative seems to occur. Alkali alone is then added until the disagreeable smell of benzoyl chloride is no longer noticed, and the solution remains permanently *alkaline*; unless this is done, the benzoyl derivative will contain benzoic acid. The product is finally separated by filtration or by extraction with ether, and purified in a suitable manner.

The alkali serves to convert phenols into their more reactive metallic derivatives, to prevent the formation of the less reactive salts of bases, and also to dissolve the benzoic acid which is produced.

p-Nitrobenzoyl chloride (m.p. 75°) is also frequently used in a similar manner, as the *p*-nitrobenzoyl derivatives of bases, etc., usually crystallise so well.

Benzamide, $C_6H_5 \cdot CO \cdot NH_2$, affords an example of an aromatic amide ; it may be obtained by reactions similar to those employed in the case of acetamide, as, for example, by shaking ethyl benzoate with concentrated ammonia,

$$C_6H_5 \cdot COOC_2H_5 + NH_3 = C_6H_5 \cdot CO \cdot NH_2 + C_2H_5 \cdot OH ;$$

but it is also conveniently prepared by treating benzoyl chloride with an excess of dry ' ammonium carbonate,'

$$C_6H_5 \cdot COCl + 2NH_4HCO_3 = C_6H_5 \cdot CO \cdot NH_2 + 2CO_2 + 2H_2O + NH_4Cl.$$

Ammonium carbonate (about 10 g.) is placed in a mortar, the benzoyl chloride (4–5 g.) is added, and the two substances are well mixed with a pestle ; if there is still a strong smell of the chloride at the end of about ten minutes, a little more ammonium carbonate is stirred in. The solid is extracted with a little cold water, which removes the ammonium salts, and is then recrystallised from boiling water.

Benzamide melts at 130°, and is sparingly soluble in cold, but readily soluble in hot, water ; like other amides, it is decomposed by boiling alkalis, yielding ammonia and an alkali salt,

$$C_6H_5 \cdot CO \cdot NH_2 + KOH = C_6H_5 \cdot COOK + NH_3.$$

Benzonitrile, $C_6H_5 \cdot CN$ (phenyl cyanide), may be obtained by heating benzamide with phosphorus pentoxide, a method similar to that employed in the preparation of aliphatic nitriles,

$$C_6H_5 \cdot CO \cdot NH_2 = C_6H_5 \cdot CN + H_2O.$$

It cannot be prepared by treating chloro- or bromo-benzene with potassium cyanide, because the halogen atom is so firmly held that no interaction occurs, but it may be obtained by *fusing* potassium benzenesulphonate with potassium cyanide or ferrocyanide,

$$C_6H_5 \cdot SO_3K + KCN = C_6H_5 \cdot CN + K_2SO_3.$$

It is most conveniently prepared from aniline by Sandmeyer's reaction—namely, by treating a solution of phenyldiazonium chloride with potassium cuprous cyanide,

$$C_6H_5 \cdot N_2Cl \longrightarrow C_6H_5 \cdot N_2Cl, 2CuCN \longrightarrow C_6H_5 \cdot CN.$$

Aniline (1 part) is *diazotised* in the usual way, and the solution of the diazonium chloride is then gradually added to a hot solution

of potassium cuprous cyanide; the product is distilled in steam and then extracted with ether. The extract is washed with dilute caustic soda, and dried with calcium chloride; the ether is then distilled, and the cyanide is purified by distillation.

The solution of potassium cuprous cyanide required above is prepared by slowly adding powdered potassium cyanide (3 parts) to a hot solution of hydrated cupric sulphate ($2\frac{1}{2}$ parts) in water (15 parts),

$$2CuSO_4+6KCN=2(CuCN,KCN)+(CN)_2+2K_2SO_4.$$

This and the subsequent operations, including steam distillation, must be conducted in a good draught cupboard, on account of the evolution of cyanogen and hydrogen cyanide, both of which are *highly poisonous*.

Benzonitrile boils at 191°, and smells rather like nitrobenzene. Its reactions resemble those of the aliphatic nitriles; thus, it is converted into the corresponding acid on hydrolysis with alkalis (or mineral acids),

$$C_6H_5\cdot CN+2H_2O = C_6H_5\cdot COOH+NH_3,$$

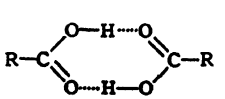
and into a primary amine or an aldimine on reduction.

Other aromatic nitriles, such as the three *tolunitriles*, $C_6H_4(CH_3)\cdot CN$, are known; also compounds such as *phenylacetonitrile* (*benzyl cyanide*, p. 525), $C_6H_5\cdot CH_2\cdot CN$, which contain the cyanogen group in the side chain.

Carboxylic acids are usually largely associated to molecules $(R\cdot COOH)_2$ and at the same time show electrolytic dissociation, which is complete in the case of some of their salts; the following equilibria are therefore possible and the proportions of the components depend on the temperature, nature and proportion of the solvent (if any), as well as on the compound,

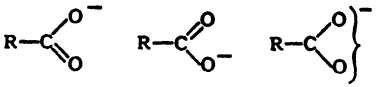
$$(R\cdot COOH)_2 \rightleftarrows 2R\cdot COOH \rightleftarrows 2R\cdot COO'+2H'.$$

Association is explained by hydrogen bonding similar to that which is assumed in alcohols, but is restricted to two molecules by ring formation:



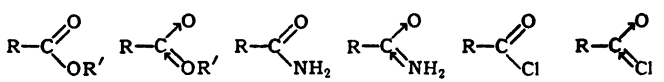
The acid ion is represented by (I) in which the two oxygen atoms are shown as differently united to the carbon atom, but the

ion may be a mesomeric form of (I) and (II), which might be roughly indicated by (III),



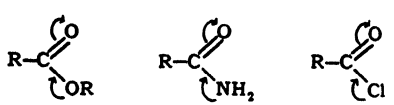
I II III

In esters, amides and acid chlorides resonance is also possible between the pairs of contributors indicated below, but the mesomeric forms of such compounds are probably structures not very different from those usually formulated; the carbonyl group is so modified, however, that it does not undergo ketonic reactions.



The theory of resonance thus affords some explanation of the great difference in behaviour between the carbonyl group of an acid and that of a ketone.

The possible resonance in these and similar cases is often indicated by expressions such as the following in which the arrows indicate electron drifts.



Substitution Products of Benzoic Acid. Benzoic acid is attacked by chlorine, bromine, nitric acid, and sulphuric acid, giving a *meta*-derivative in all cases, according to rule; when, for example, benzoic acid is heated with bromine and water at 125°, m-*bromobenzoic acid*, $C_6H_4Br \cdot COOH$ (m.p. 155°), is formed. The o- and p-*bromobenzoic acids* are obtained by oxidising the corresponding *bromotoluenes* with dilute nitric or chromic acid; the former melts at 150°, the latter at 253°. Nitric acid, in the presence of sulphuric acid, acts readily on benzoic acid, m-*nitrobenzoic acid*, $C_6H_4(NO_2) \cdot COOH$ (m.p. 141°), being the principal product; o-*nitrobenzoic acid* (m.p. 147°) and p-*nitrobenzoic acid* (m.p. 238°) are obtained by the oxidation of o- and p-*nitrotoluene* respectively (p. 437); when these acids are reduced with tin and hydrochloric acid, they yield the corresponding *aminobenzoic acids*,

$C_6H_4(NH_2)\cdot COOH$, which, like glycine, form salts with mineral acids and with bases.

Anthranilic acid, $C_6H_4(NH_2)\cdot COOH$ (*o*-aminobenzoic acid), was first obtained by the oxidation of indigo (p. 681); it is prepared by treating phthalimide (p. 521) with sodium hydroxide and sodium hypochlorite (a method analogous to Hofmann's amide reaction),

$$C_6H_4<\begin{matrix}CO\\CO\end{matrix}>NH+NaOCl+3NaOH=C_6H_4<\begin{matrix}NH_2\\COONa\end{matrix}+Na_2CO_3+NaCl+H_2O,$$

and was formerly an intermediate product in the manufacture of indigo (p. 682). It melts at 144°, decomposes at higher temperatures, giving aniline and carbon dioxide, and is sparingly soluble in water.

Methyl anthranilate is used in perfumery.

When heated with sulphuric acid, benzoic acid is converted into m-*sulphobenzoic acid*, $C_6H_4(SO_3H)\cdot COOH$, but small proportions of the *p*-acid also are produced. The *o*- and *p*-acids are obtained by oxidising the corresponding *toluenesulphonic acids*.

The sulphobenzoic acids are very soluble in water; when fused with potash they yield phenolic acids (p. 530), just as benzenesulphonic acid gives phenol,

$$C_6H_4(SO_3K)\cdot COOK+2KOH=C_6H_4(OK)\cdot COOK+K_2SO_3+H_2O.$$

Saccharin is the *imide* of *o*-sulphobenzoic acid, and is remarkable for having the sweetening effect of about 400 times its weight of sucrose. It is prepared from toluene, which is first treated with chlorosulphonic acid; the resulting o-*toluenesulphonyl chloride* is partially freed from the *p*-compound by freezing out the latter, and converted into its *amide* with ammonia. The purified amide is oxidised with alkaline potassium permanganate and the product is treated with a mineral acid; the liberated carboxylic acid then loses the elements of water yielding saccharin (m.p. 224°),

$$C_6H_4<\begin{matrix}SO_2\cdot NH_2\\CH_3\end{matrix}\longrightarrow C_6H_4<\begin{matrix}SO_2\cdot NH_2\\COOK\end{matrix}\longrightarrow C_6H_4<\begin{matrix}SO_2\\CO\end{matrix}>NH.$$

The ammonium salt of the imide, *sucramine*, is soluble in water and has an even greater sweetening power than saccharin.

p-*Carboxybenzenesulphonamide*, prepared by oxidising *p*-toluenesulphonamide, gives with chlorine an *N*-dichloro-derivative, $HOOC\cdot C_6H_4\cdot SO_2\cdot NCl_2$ (*halazone*), which is used for sterilising water.

The three (*o.m.p.*) **toluic acids,** $C_6H_4(CH_3)\cdot COOH$, may be produced by oxidising the respective *xylenes* with dilute nitric acid,

$$C_6H_4(CH_3)_2+3O = C_6H_4(CH_3)\cdot COOH+H_2O,$$

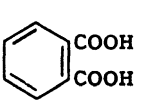
but the *o*- and *p*-acids are best prepared by converting the corresponding *toluidines* into the nitriles by Sandmeyer's reaction, and then hydrolysing the latter with acids or alkalis,

$$C_6H_4<^{CH_3}_{NH_2} \longrightarrow C_6H_4<^{CH_3}_{CN} \longrightarrow C_6H_4<^{CH_3}_{COOH}$$

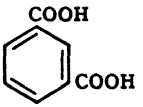
The *o*-, *m*-, and *p*-toluic acids melt at 107°, 112°, and 181° respectively, and resemble benzoic acid very closely, but since they contain a methyl group, they have also properties which are not shown by benzoic acid ; on oxidation, for example, they are converted into the corresponding *phthalic acids*, just as toluene is transformed into benzoic acid.

Dicarboxylic Acids

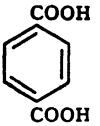
The important dicarboxylic acids are the three (*o.m.p.*) *phthalic acids*, or benzenedicarboxylic acids, which are respectively represented by the formulae,



Phthalic acid



*Iso*phthalic acid



Terephthalic acid

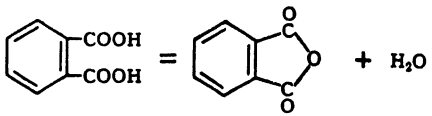
These compounds may be prepared by the oxidation of the corresponding *xylenes* (dimethylbenzenes) with dilute nitric acid, or by treating the *toluic acids* with potassium permanganate in alkaline solution,

$$C_6H_4<^{CH_3}_{CH_3}+6O = C_6H_4<^{COOH}_{COOH}+2H_2O,$$

$$C_6H_4<^{CH_3}_{COOH}+3O = C_6H_4<^{COOH}_{COOH}+H_2O.$$

They are crystalline and yield normal and hydrogen metallic salts and esters, acid chlorides, amides, etc., by reactions similar to those employed in the preparation of corresponding derivatives of aliphatic dicarboxylic acids.

Phthalic acid, like succinic acid, is converted into its anhydride when it is heated at about 200°,



but an anhydride of iso*phthalic acid* or of *terephthalic acid* cannot be produced ; it is, in fact, a general rule that the formation of an anhydride from *one* molecule of a *nuclear* dicarboxylic acid (an *inner* anhydride) takes place only when the two carboxyl groups are in the *o*-position, never when they occupy the *m*- or *p*-position (p. 395).

When cautiously heated with soda-lime, the benzenedicarboxylic acids yield benzoic acid,

$$C_6H_4<\begin{matrix}COONa\\COONa\end{matrix}+NaOH = C_6H_5\cdot COONa+Na_2CO_3,$$

but at higher temperatures both carboxyl groups are displaced by hydrogen, and benzene is formed.

When phthalic acid, or its anhydride, is strongly heated with about twice its weight of resorcinol, *fluorescein* (p. 667) is produced, and the reddish-brown product, when dissolved in caustic soda and poured into a large quantity of water, yields a solution having a green fluorescence. This *fluorescein* reaction is shown by all *o*-dicarboxylic acids of the benzene series, but not by the *m*- and *p*-dicarboxylic acids ; it is also shown by certain aliphatic acids, such as succinic acid, which give inner anhydrides, and may therefore be used for their identification. When the anhydride (unlike that of phthalic acid) is not readily formed, a drop of sulphuric acid is added before the mixture is heated.

Phthalic acid, $C_6H_4(COOH)_2$ (benzene-*o*-dicarboxylic acid), may be obtained by oxidising o-*xylene* or o-*toluic acid* ; it used to be manufactured by oxidising *naphthalene* (p. 538) with sulphuric acid, in the presence of mercuric sulphate.

Naphthalene dissolves in hot concentrated (or fuming) sulphuric acid, giving sulphonic acids. At about 295–300°, in the presence of about 3% of their weight of mercuric sulphate, these acids are rapidly oxidised, sulphur dioxide is evolved, and phthalic anhydride sublimes or distils. The crude anhydride is separated, washed with water, dried and sublimed.

In the laboratory, naphthalene (1 part), concentrated sulphuric acid (8 parts), and mercuric sulphate (0·1 part) are gradually heated together in a retort until most of the contents (except the mercuric salt) has distilled. The anhydride is separated, washed with water, and dissolved in boiling caustic soda; from the filtered solution phthalic acid is precipitated on the addition of sulphuric acid.

The acid is now obtained from its anhydride, which is manufactured by the atmospheric oxidation of naphthalene, at about 330°, in the presence of vanadium pentoxide.

Phthalic acid crystallises in prisms, and melts from about 184°, with the formation of the anhydride, so that, when the melted substance has solidified, and the melting-point is again determined, it may be about 132° (that of the anhydride).

Phthalic acid dissolves in about 100 parts of water at ordinary temperatures; it is readily soluble in many organic liquids. The *barium* salt, $C_6H_4(COO)_2Ba$, precipitated on the addition of barium chloride to a neutral solution of the ammonium salt, is very sparingly soluble in water.

Diethyl phthalate, $C_6H_4(COOC_2H_5)_2$, is readily prepared by saturating an alcoholic solution of phthalic acid (or its anhydride) with hydrogen chloride. It is a liquid, b.p. 295°.

Phthalyl (phthaloyl) chloride, $C_6H_4(COCl)_2$, is prepared by heating phthalic anhydride (1 mol.) with phosphorus pentachloride (1 mol.). It melts at 15° and is slowly decomposed by water, with the regeneration of phthalic acid. An isomeric form (m.p. 89°), $C_6H_4<\begin{matrix}CCl_2\\CO\end{matrix}>O$, is known (compare succinyl chloride, p. 278).

Phthalic anhydride, $C_6H_4<\begin{matrix}CO\\CO\end{matrix}>O$, sublimes in long needles, melting at 132° when the acid is heated; it does not dissolve immediately in a cold solution of sodium carbonate, but is readily hydrolysed by caustic alkalis. It is used in the manufacture of *glyptal* plastics and dyes.

Phthalimide, $C_6H_4<\begin{matrix}CO\\CO\end{matrix}>NH$, may be prepared by heating an intimate mixture of phthalic anhydride (5 parts) and dry ammonium carbonate (6 parts).

The mixture is heated in a small flask on a wire gauze or sand-bath; it first becomes pasty and then gradually hardens in the

course of about 15 minutes. The product is recrystallised from boiling water or aqueous alcohol.

It melts at 238° and is an intermediate product in the preparation of anthranilic acid (p. 518).

Phthalimide, like succinimide, yields a potassium derivative, $C_6H_4<\begin{matrix}CO\\CO\end{matrix}>NK$, with alcoholic potash, and this compound, as was shown by Gabriel, is very useful in the preparation of primary amines and their derivatives (p. 226).

Potassium phthalimide, or a mixture of the imide and dry potassium carbonate, reacts with alkyl halides, aliphatic di-halides, such as ethylene dibromide, etc., giving substituted phthalimides,

$$C_6H_4<\begin{matrix}CO\\CO\end{matrix}>NK+C_2H_5I = \underset{\text{Ethylphthalimide}}{C_6H_4<\begin{matrix}CO\\CO\end{matrix}>N\cdot C_2H_5}+KI,$$

$$C_6H_4<\begin{matrix}CO\\CO\end{matrix}>NK+CH_2Br\cdot CH_2Br = \underset{\text{Bromoethylphthalimide}}{C_6H_4<\begin{matrix}CO\\CO\end{matrix}>N\cdot CH_2\cdot CH_2Br}+KBr,$$

$$2C_6H_4<\begin{matrix}CO\\CO\end{matrix}>NK+CH_2Br\cdot CH_2Br = \underset{\text{Ethylenediphthalimide}}{C_6H_4<\begin{matrix}CO\\CO\end{matrix}>N\cdot CH_2\cdot CH_2\cdot N<\begin{matrix}CO\\CO\end{matrix}>C_6H_4}+2KBr.$$

These products are hydrolysed by mineral acids and by alkalis (most readily by hydrazine), giving an amine, or a bromo- or hydroxy-amine; *ethylphthalimide*, for example, gives ethylamine, whereas *bromoethylphthalimide* gives either *β-bromoethylamine*, $NH_2\cdot CH_2\cdot CH_2Br$, or *β-aminoethyl alcohol*, $NH_2\cdot CH_2\cdot CH_2\cdot OH$, according to the reagent used. *Ethylenediphthalimide* yields *ethylenediamine*, $NH_2\cdot CH_2\cdot CH_2\cdot NH_2$.

***Iso*phthalic acid**, $C_6H_4(COOH)_2$ (benzene-*m*-dicarboxylic acid), is produced by oxidising m-*xylene* with nitric acid or chromic acid; or from m-*toluic acid*, by oxidation with potassium permanganate in alkaline solution.

It crystallises in needles, melts above 300°, and when strongly heated sublimes unchanged; it is very sparingly soluble in water.

Terephthalic acid, $C_6H_4(COOH)_2$ (benzene-*p*-dicarboxylic acid), is formed by the oxidation of p-*xylene*, p-*toluic acid*, and of all di-alkyl substitution derivatives of benzene, which, like *cymene*,

$CH_3 \cdot C_6H_4 \cdot CH(CH_3)_2$, contain the alkyl groups in the *p*-position. It is best prepared by oxidising *p*-toluic acid (p. 519) in alkaline solution with potassium permanganate.

Terephthalic acid is almost insoluble in water, and, when heated, sublimes without melting.

*Iso*phthalic acid, terephthalic acid, and other acids which melt above 300° (or have an indefinite melting-point), are best identified with the aid of their methyl esters, which generally crystallise well, and melt at comparatively low temperatures; *m*-, and *p*-dimethyl phthalates, for example, melt at 67° and 140° respectively.

The acid (0·1–0·5 g.) is warmed in a test-tube with about three times its weight of phosphorus pentachloride, and the clear solution, which now contains the chloride of the acid, is poured into an excess of methyl alcohol. As soon as the vigorous reaction has subsided, the liquid is diluted with water, and the crude methyl ester is collected and recrystallised; its melting-point is then determined.

Benzenehexacarboxylic acid, $C_6(COOH)_6$, as already mentioned, is formed by the oxidation of graphite or of coal. Its *aluminium* salt, $C_6(COO)_6Al_2, 18H_2O$, occurs naturally in crystals in certain beds of brown-coal, or lignite, and from its appearance was called *honeystone*; the acid from this salt was named *mellitic acid* (Lat. *mel*, honey), and was afterwards obtained by oxidising *hexamethylbenzene*, $C_6(CH_3)_6$, with potassium permanganate. The acid crystallises in lustrous needles, is readily soluble in water, decomposes when it is heated, and gives benzene when its sodium salt is heated with soda-lime.

Side Chain Carboxylic Acids

Various aromatic compounds already described have certain properties similar to those of comparable aliphatic substances because of the presence, in the former, of groups of atoms (*side chains*) which have an aliphatic structure; benzyl chloride, benzyl alcohol and benzylamine, for example, have many reactions in common with methyl chloride, methyl alcohol and methylamine, respectively, because of their related structures. Since, moreover, nearly all aliphatic compounds may theoretically be converted into aromatic analogues by the substitution of a phenyl group for hydrogen, a homologous series of the former may have its aromatic counterpart. This is well illustrated in the case of the carboxylic

acids : corresponding with the aliphatic, there is a series of aromatic acids, which may be regarded as derived from the former in the manner just mentioned.

Formic acid, $H \cdot COOH$,
Benzoic acid, $C_6H_5 \cdot COOH$ (phenylformic acid).

Acetic acid, $CH_3 \cdot COOH$,
Phenylacetic acid, $C_6H_5 \cdot CH_2 \cdot COOH$.

Propionic acid, $CH_3 \cdot CH_2 \cdot COOH$,
β-Phenylpropionic acid, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot COOH$.

Butyric acid, $CH_3 \cdot CH_2 \cdot CH_2 \cdot COOH$,
γ-Phenylbutyric acid, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot COOH$.

With the exception of benzoic acid, these acids are derived from aromatic hydrocarbons by the substitution of carboxyl for hydrogen of the *side chain*. They have not only the characteristic properties of aromatic compounds in general, but also those of fatty acids, and, like the latter, they may be converted, in many cases, into unsaturated compounds by the loss of two or more atoms of hydrogen ; the compounds thus produced correspond with the olefinic aliphatic acids, as the following examples show :

Propionic acid, $CH_3 \cdot CH_2 \cdot COOH$,
β-Phenylpropionic acid, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot COOH$.

Acrylic acid, $CH_2{:}CH \cdot COOH$,
β-Phenylacrylic acid, $C_6H_5 \cdot CH{:}CH \cdot COOH$.

Propiolic acid, $CH{:}C \cdot COOH$,
Phenylpropiolic acid, $C_6H_5 \cdot C{:}C \cdot COOH$.

Preparation. Aromatic acids, which contain the carboxyl group in the *side chain*, may be prepared by *carefully* oxidising the corresponding alcohols and aldehydes, and by hydrolysing the corresponding nitriles with alkalis or mineral acids,

$$C_6H_5 \cdot CH_2 \cdot CN + 2H_2O = C_6H_5 \cdot CH_2 \cdot COOH + NH_3,$$

but these methods are limited in application, owing to the difficulty of obtaining the requisite substances.

The more important general methods are : (1) By the reduction of the corresponding unsaturated acids, many of which are prepared without much difficulty (p. 526),

$$C_6H_5 \cdot CH{:}CH \cdot COOH + 2H = C_6H_5 \cdot CH_2 \cdot CH_2 \cdot COOH.$$

(2) By the interaction of the sodium compound of diethyl malonate or of ethyl acetoacetate and a side chain halogen derivative of an aromatic hydrocarbon. As, in this method, the procedure is similar to that employed in preparing aliphatic acids, one example only need be given—namely, the synthesis of *β-phenylpropionic acid.*

Diethyl sodiomalonate is heated with benzyl chloride, and the *diethyl benzylmalonate* which is thus produced,

$$C_6H_5\cdot CH_2Cl+CHNa(COOC_2H_5)_2 = C_6H_5\cdot CH_2\cdot CH(COOC_2H_5)_2+NaCl,$$

is hydrolysed with alcoholic potash. The *benzylmalonic acid* is then isolated, and heated at 200°, when it is converted into *β-phenylpropionic acid*, with the loss of carbon dioxide,

$$C_6H_5\cdot CH_2\cdot CH(COOH)_2 = C_6H_5\cdot CH_2\cdot CH_2\cdot COOH+CO_2.$$

It should be remembered that *only side chain* halogen derivatives can be employed in such syntheses, because with nuclear halogen compounds, such as *monochlorotoluene*, $C_6H_4Cl\cdot CH_3$, no action takes place (p. 425).

(3) By heating an alkyl aryl ketone with a solution of yellow ammonium sulphide at 150-200° (Willgerodt): an amide of a side chain acid is produced and may then be hydrolysed,

$$C_6H_5\cdot CO\cdot CH_3 \longrightarrow C_6H_5\cdot CH_2\cdot CO\cdot NH_2,$$
$$C_6H_5\cdot CO\cdot CH_2\cdot CH_2\cdot CH_3 \longrightarrow C_6H_5\cdot CH_2\cdot CH_2\cdot CH_2\cdot CO\cdot NH_2.$$

Phenylacetic acid, $C_6H_5\cdot CH_2\cdot COOH$, is prepared by boiling an alcoholic solution of benzyl chloride with potassium cyanide during about three hours; the *benzyl cyanide* (b.p. 234°), which is thus formed, is isolated by fractional distillation and hydrolysed with boiling diluted sulphuric acid,

$$C_6H_5\cdot CH_2Cl \longrightarrow C_6H_5\cdot CH_2\cdot CN \longrightarrow C_6H_5\cdot CH_2\cdot COOH.$$

Phenylacetic acid melts at 76·5°, boils at 265°, and crystallises from water in glistening plates; it has a characteristic smell, and forms many simple derivatives just as do benzoic and acetic acids.

When oxidised with chromic acid it yields benzoic acid, a change of a different type from that undergone by the isomeric toluic acids (p. 519),

$$C_6H_5\cdot CH_2\cdot COOH+3O = C_6H_5\cdot COOH+CO_2+H_2O.$$

β-Phenylethyl alcohol, $C_6H_5\cdot CH_2\cdot CH_2\cdot OH$ (b.p. 219°), prepared by reducing ethyl phenylacetate with sodium and alcohol or from ethylene oxide and phenyl magnesium bromide; and *phenylacet-*

aldehyde, $C_6H_5 \cdot CH_2 \cdot CHO$ (b.p. 195°), obtained by oxidising the alcohol, are used in perfumery; the former smells like roses, the latter like hyacinths. The aldehyde polymerises readily, giving various products.

Phenylbromoacetonitrile or *b*romo*b*enzyl *c*yanide (known as B.B.C.), $C_6H_5 \cdot CHBr \cdot CN$, is prepared by brominating benzyl cyanide and is a potent lachrymator. It melts at 25° and boils at 242° with decomposition.

β-Phenylpropionic acid, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot COOH$ (*hydrocinnamic acid*), is conveniently prepared by reducing *cinnamic acid* (below) with sodium amalgam and water or hydrogen and a catalyst,

$$C_6H_5 \cdot CH{:}CH \cdot COOH + 2H = C_6H_5 \cdot CH_2 \cdot CH_2 \cdot COOH,$$

but may also be obtained from the product of the action of benzyl chloride on diethyl sodiomalonate as just described. It crystallises from water in needles, melts at 47°, and boils at 280°.

Cinnamic acid, $C_6H_5 \cdot CH{:}CH \cdot COOH$ (*β-phenylacrylic acid*), is closely related to β-phenylpropionic acid, and is perhaps the best-known *unsaturated* aromatic acid. It was first obtained (and derives its name) from oil of cinnamon, which contains a large proportion of the corresponding (*cinnam-*) aldehyde. The acid occurs in large proportions in storax (*Styrax officinalis*), partly in the free state, and may be obtained by gently warming this resin with caustic soda; the filtered aqueous solution of *sodium cinnamate* is treated with hydrochloric acid, and the precipitated cinnamic acid is purified by recrystallisation from light petroleum or hot water.

Cinnamic acid is prepared by heating benzaldehyde with acetic anhydride and anhydrous sodium acetate (*Perkin* reaction), the mixed anhydride initially formed being subsequently hydrolysed,

$$C_6H_5 \cdot CHO + CH_3 \cdot CO \cdot O \cdot CO \cdot CH_3 = C_6H_5 \cdot CH{:}CH \cdot CO \cdot O \cdot CO \cdot CH_3 + H_2O,$$

$$C_6H_5 \cdot CH{:}CH \cdot CO \cdot O \cdot CO \cdot CH_3 + H_2O = C_6H_5 \cdot CH{:}CH \cdot COOH + CH_3 \cdot COOH.$$

A mixture of benzaldehyde (10 parts), acetic anhydride (15 parts), and anhydrous sodium acetate (5 parts) is boiled during about 8 hours in a flask heated in an oil-bath (air condenser). The cooled mixture is poured into water, and any unchanged benzaldehyde is distilled in steam; caustic soda is then added in excess, and the hot solution, filtered from oily and resinous impurities, is strongly acidified with hydrochloric acid; the precipitated cinnamic acid is purified by recrystallisation from boiling water.

This reaction is a very important one for the preparation of unsaturated aromatic acids, as, by employing the anhydrides and sodium salts of other aliphatic acids, homologues of cinnamic acid are obtained. When, for example, benzaldehyde is heated with sodium propionate and propionic anhydride, *β-phenyl-α-methylacrylic acid* (*α-methylcinnamic acid*), $C_6H_5 \cdot CH{:}C(CH_3) \cdot COOH$, is formed; *β-benzylidenepropionic acid*, $C_6H_5 \cdot CH{:}CH \cdot CH_2 \cdot COOH$, is not obtained in this reaction, because combination always takes place between the aldehydic oxygen atom and the hydrogen atoms of the α-$CH_2<$ group of the anhydride.

β-Benzylidenepropionic acid, however, may be prepared by heating benzaldehyde with a mixture of sodium succinate and succinic anhydride, a process in which carbon dioxide is eliminated,

$$C_6H_5 \cdot CHO + COOH \cdot CH_2 \cdot CH_2 \cdot COOH = C_6H_5 \cdot CH{:}CH \cdot CH_2 \cdot COOH + CO_2 + H_2O.$$

It melts at 87°, and boils at 302°; at its boiling-point, it is gradually converted into *α-naphthol* and water (p. 542).

Other aldehydes which contain a *nuclear* aldehyde group may be used in the Perkin reaction; the three *toluic aldehydes*, $CH_3 \cdot C_6H_4 \cdot CHO$, for example, give with sodium acetate and acetic anhydride the three (o.m.p.) *methylcinnamic acids*, $CH_3 \cdot C_6H_4 \cdot CH{:}CH \cdot COOH$.

Cinnamic acid crystallises from water in needles, and melts at 133°. Its chemical behaviour, in many respects, is similar to that of acrylic acid and other unsaturated aliphatic acids; it combines directly with bromine, for example, yielding *β-phenyl-αβ-dibromopropionic acid* (*cinnamic acid dibromide*), $C_6H_5 \cdot CHBr \cdot CHBr \cdot COOH$, and with hydrogen bromide, giving *β-phenyl-β-bromopropionic acid*, $C_6H_5 \cdot CHBr \cdot CH_2 \cdot COOH$.

A solution of cinnamic acid in sodium carbonate immediately reduces a dilute solution of potassium permanganate at ordinary temperatures; all *unsaturated* acids show this behaviour, and are thus easily distinguished from saturated acids (Baeyer), but not from phenolic acids, phenols, and several other types of compounds which may reduce alkaline permanganate very readily. On reduction with sodium amalgam and water, cinnamic acid is converted into β-phenylpropionic acid, just as acrylic acid is transformed into propionic acid.

When distilled with soda-lime, cinnamic acid is decomposed into carbon dioxide, and *phenylethylene* or *styrene* (p. 419),

$$C_6H_5 \cdot CH{:}CH \cdot COONa + NaOH = C_6H_5 \cdot CH{:}CH_2 + Na_2CO_3.$$

Ethyl cinnamate may be prepared from the acid in the usual way, or by condensing benzaldehyde with ethyl acetate in the presence of sodium ethoxide, an important general reaction (Claisen),

$$C_6H_5 \cdot CHO + CH_3 \cdot COOEt = C_6H_5 \cdot CH{:}CH \cdot COOEt + H_2O.$$

Concentrated nitric acid converts cinnamic acid into a mixture of about equal quantities of *o*- and p-*nitrocinnamic acids*,

$$C_6H_4(NO_2) \cdot CH{:}CH \cdot COOH.$$

For their separation, these acids are converted into their ethyl esters, $C_6H_4(NO_2) \cdot CH{:}CH \cdot COOC_2H_5$ (with alcohol and hydrogen chloride); the sparingly soluble ester of the *p*-acid separates, while the readily soluble *ethyl* o-*nitrocinnamate* remains in solution. From the purified esters the acids are regenerated, by hydrolysis with dilute sulphuric acid. They resemble cinnamic acid closely in properties, and combine directly with bromine, yielding the corresponding *β-nitrophenyl-αβ-dibromopropionic acids*, $C_6H_4(NO_2) \cdot CHBr \cdot CHBr \cdot COOH$.

Stereoisomerism of Aromatic Olefinic Acids. Some unsaturated aromatic acids are known in stereoisomeric (*cis*- and *trans*-) forms, corresponding with those of ethylenedicarboxylic acid (maleic and fumaric acids). Allo*cinnamic acid*, $C_6H_5 \cdot CH{:}CH \cdot COOH$, for example, is a stereoisomeride of cinnamic acid, and occurs, together with the latter, in certain by-products from the preparation of cocaine; it exists in three different crystalline modifications, melting at 42°, 58°, and 68° respectively, and represents the *cis*-isomeride, in which the C_6H_5— and —COOH groups occupy positions corresponding with those of the two —COOH groups in maleic acid. *Cinnamylideneacetic acid* (p. 529) also exists in stereoisomeric forms, both of which are produced in the given reaction.

Many olefinic acids, not only of the aromatic, but also of the aliphatic series, may undergo an interesting change when they are heated with concentrated aqueous alkalis. β-Benzylidenepropionic acid, $C_6H_5 \cdot CH{:}CH \cdot CH_2 \cdot COOH$ (p. 527), for example, is partly converted into a *structural isomeride*, $C_6H_5 \cdot CH_2 \cdot CH{:}CH \cdot COOH$, owing to the migration or shifting of the double binding from the βγ- to the αβ-position. In such changes, particularly in the case of aliphatic acids, the general rule is, that the double binding

migrates towards the carboxyl group, but such reactions are usually reversible.

Cinnamaldehyde, $C_6H_5 \cdot CH{:}CH \cdot CHO$, is the principal component of oil of cinnamon, from which it may be extracted with the aid of a solution of sodium hydrogen sulphite. It may be obtained by heating a mixture of the calcium salts of cinnamic and formic acids, or by condensing benzaldehyde with acetaldehyde, in the presence of sodium ethoxide.

It boils at 252°, and has a characteristic aromatic odour; on exposure to the air, it is oxidised to cinnamic acid. Its *phenylhydrazone* melts at 168°. Cinnamaldehyde, like benzaldehyde, condenses readily with many other compounds; thus, when it is treated with malonic acid, in the presence of pyridine, it gives *cinnamylidenemalonic acid*, $C_6H_5 \cdot CH{:}CH \cdot CH{:}C(COOH)_2$, which yields *cinnamylideneacetic acid*, $C_6H_5 \cdot CH{:}CH \cdot CH{:}CH \cdot COOH$, and carbon dioxide when it is heated.

Many other unsaturated acids, both aliphatic and aromatic, are prepared by condensing an aldehyde with malonic acid.

Phenylpropiolic acid, $C_6H_5 \cdot C{\vdots}C \cdot COOH$, is obtained by treating phenyl-$\alpha\beta$-dibromopropionic acid, or its ethyl ester, with alcoholic potash,

$$C_6H_5 \cdot CHBr \cdot CHBr \cdot COOH = C_6H_5 \cdot C{\vdots}C \cdot COOH + 2HBr,$$

a method similar to that employed in preparing acetylene by the action of alcoholic potash on ethylene dibromide. It melts at 137°, and at higher temperatures, or when heated with water at 120°, it decomposes into carbon dioxide and *phenylacetylene*, a colourless liquid (b.p. 142°) closely related to acetylene in chemical properties,

$$C_6H_5 \cdot C{\vdots}C \cdot COOH = C_6H_5 \cdot C{\vdots}CH + CO_2.$$

o-*Nitrophenylpropiolic acid*, $C_6H_4(NO_2) \cdot C{\vdots}C \cdot COOH$, may be similarly prepared from o-nitrophenyldibromopropionic acid; when treated with reducing agents, such as hydrogen sulphide, or glucose and alkali, it is converted into indigo-blue (Baeyer),

$$2C_6H_4\!<\!\begin{matrix} C{\vdots}C \cdot COOH \\ NO_2 \end{matrix} + 4H = C_{16}H_{10}O_2N_2 + 2CO_2 + 2H_2O.$$

This method of preparation, however, is not of technical value.

CHAPTER 34

PHENOLIC AND HYDROXY-CARBOXYLIC ACIDS

AROMATIC hydroxy-acids are derived from benzoic acid and its homologues, by the substitution of hydroxyl groups for hydrogen atoms ; like the hydroxy-derivatives of the aromatic hydrocarbons, they may be divided into two classes, according as the HO— group is united with carbon of the nucleus or of the side chain. In the first case this radical has the same character as in phenols, and consequently hydroxy-acids of this class, as, for example, the three (o.m.p.) *hydroxybenzoic acids*, $C_6H_4(OH)\cdot COOH$, are both phenols and carboxylic acids ; in the second case, however, the hydroxyl group has the same character as in alcohols, so that the compounds of this class, such as *mandelic acid*, $C_6H_5\cdot CH(OH)\cdot COOH$, have properties resembling those of aliphatic hydroxy-acids ; in other words, the differences between the two classes of aromatic hydroxy-acids are practically the same as those between phenols and alcohols.

As those acids which contain hydroxyl united with carbon of the nucleus form by far the more important class, they are described first, and the following statements refer to the phenolic acids only.

Preparation. The phenolic acids may be prepared from the carboxylic acids, by reactions exactly similar to those employed in the preparation of phenols from hydrocarbons ; that is to say, the acids are converted into nitro-derivatives, and then into amino-compounds, and the latter are treated with nitrous acid in the usual manner,

$$C_6H_5\cdot COOH \longrightarrow C_6H_4{<}^{COOH}_{NO_2} \longrightarrow C_6H_4{<}^{COOH}_{NH_2} \longrightarrow C_6H_4{<}^{COOH}_{OH}$$

or, the acids are heated with sulphuric acid, and their sulphonic acids are fused with a caustic alkali,

$$C_6H_5\cdot COOH \longrightarrow C_6H_4{<}^{COOH}_{SO_3H} \longrightarrow C_6H_4{<}^{COOH}_{OH}$$

It must be borne in mind, however, that as the carboxyl group determines the position taken up by the nitro- and sulphonic groups, only the *m*-hydroxy-compounds are formed by these two methods.

The *o*-phenolic acids, and in some cases the *p*-compounds, are

most conveniently prepared from the phenols by one of the following methods :

The *dry* sodium compound of a phenol is heated at about 200° in a stream of carbon dioxide (Kolbe),

$$2C_6H_5\cdot ONa+CO_2 = C_6H_4<\begin{matrix}COONa\\ ONa\end{matrix}+C_6H_5\cdot OH.$$

Under these conditions half the phenol distils and is recovered ; but if the sodium phenate is saturated with carbon dioxide under pressure at about 100°, it is converted into *sodium phenylcarbonate*, which, at about 130° under pressure, is transformed into a phenolic sodium derivative,

$$C_6H_5\cdot ONa+CO_2 \longrightarrow C_6H_5\cdot O\cdot COONa \longrightarrow C_6H_4<\begin{matrix}COOH\\ ONa\end{matrix}$$

The sodium phenylcarbonate decomposes into carbon dioxide and sodium phenate, which re-unite to form the final product.

Many dihydric and trihydric phenols may be converted into phenolic acids, by merely heating them in aqueous solution with ammonium (or potassium) hydrogen carbonate ; when resorcinol, for example, is treated in this way, it yields a mixture of isomeric *resorcylic acids*, $C_6H_3(OH)_2\cdot COOH$. This reaction affords a striking illustration of the readiness with which hydrogen atoms of the nucleus may be displaced in the case of certain substitution products of benzene (compare pp. 446, 483).

The second general method for the preparation of phenolic acids from phenols consists in boiling a strongly alkaline solution of the phenol with carbon tetrachloride ; the principal product is the *p*-acid, but variable proportions of the *o*-acid are also formed,

$$C_6H_5\cdot OK+CCl_4+5KOH = C_6H_4<\begin{matrix}COOK\\ OK\end{matrix}+4KCl+3H_2O.$$

The phenol (1 mol.) is dissolved in a concentrated aqueous solution of potassium hydroxide (6 mol.), carbon tetrachloride (1 mol.), and enough alcohol to form a homogeneous solution are added, and finally a small proportion of precipitated copper. After the substances have been heated together during 8–10 hours, any unchanged carbon tetrachloride is steam-distilled, water is added, and the filtered solution is treated with an excess of acid and extracted with ether ; the ethereal extract is then shaken with a solution of sodium carbonate, which extracts the acids, leaving any phenol dissolved in the ether. The phenolic acids are then precipitated with a mineral acid, and purified by recrystallisation.

This method is an extension of that of Tiemann and Reimer (p. 502), and it may be assumed that the reaction occurs in various stages, as indicated below :

$$C_6H_5\cdot OH \longrightarrow C_6H_4<\begin{matrix}CCl_3\\OH\end{matrix} \longrightarrow C_6H_4<\begin{matrix}C(OH)_3\\OH\end{matrix} \longrightarrow C_6H_4<\begin{matrix}COOH\\OH\end{matrix}$$

Properties. The phenolic acids are crystalline, more readily soluble in water, and less volatile, than the acids from which they are derived ; many of them decompose when heated strongly, carbon dioxide being evolved ; when heated with soda-lime they are all decomposed, with the formation of (sodium derivatives of) phenols,

$$C_6H_4(ONa)\cdot COONa+NaOH = C_6H_5\cdot ONa+Na_2CO_3,$$
$$C_6H_3(ONa)_2\cdot COONa+NaOH = C_6H_4(ONa)_2+Na_2CO_3.$$

The *o*-acids, as, for example, *salicylic acid*, give, in neutral aqueous solution, a violet colouration with ferric chloride, whereas the *m*- and *p*-acids, such as m- and p-*hydroxybenzoic acids*, give no colouration.

The phenolic acids show the chemical properties of both phenols and carboxylic acids. As carboxylic acids, they form salts by the displacement of the hydrogen atom of the carboxyl group ; such salts are obtained when the acids are treated with *carbonates* or with one equivalent of a metallic hydroxide. When, however, an excess of *alkali hydroxide* is employed, the hydrogen atom of the phenolic group is also displaced, just as in the case of phenols. Phenolic acids, therefore, form both mono- and di-metallic salts ; thus *salicylic acid* yields the two sodium salts, $C_6H_4(OH)\cdot COONa$ and $C_6H_4(ONa)\cdot COONa$.

The di-metallic salts are decomposed by carbonic acid, giving mono-metallic salts, just as the phenates give phenols ; the metal in combination with the carboxyl group, however, cannot be displaced in this way.

Esters of the phenolic acids are prepared in the usual manner —namely, by saturating a solution of the acid in an excess of an alcohol with hydrogen chloride ; by this treatment the hydrogen of the carboxyl group only is displaced, salicylic acid, for example, giving *methyl salicylate*, $C_6H_4(OH)\cdot COOCH_3$. These esters still have phenolic properties, and dissolve in caustic alkalis, forming metallic derivatives, such as *potassium methyl salicylate*, $C_6H_4(OK)\cdot COOCH_3$; the latter, with alkyl halides or dimethyl sulphate, yield alkyl deriva-

tives, such as *methyl o-ethoxybenzoate*,[1] $C_6H_4(OC_2H_5)\cdot COOCH_3$. On hydrolysis with alcoholic potash, *only* the alkyl of the carboxyl group is displaced from di-alkyl compounds of this kind; methyl ethoxybenzoate, for example, yields the potassium salt of ethoxybenzoic acid,

$$C_6H_4<\begin{matrix}COOCH_3\\OC_2H_5\end{matrix}+KOH = C_6H_4<\begin{matrix}COOK\\OC_2H_5\end{matrix}+CH_3\cdot OH.$$

The other alkyl group is not eliminated even by boiling alkalis, a behaviour which corresponds with that of the alkyl group in derivatives of phenols, such as *anisole*, $C_6H_5\cdot OCH_3$. Just, however, as anisole is decomposed into phenol and methyl iodide when it is heated with hydriodic acid, so ethoxybenzoic acid, under similar conditions, yields the phenolic acid (compare p. 596),

$$C_6H_4<\begin{matrix}COOH\\OC_2H_5\end{matrix}+HI = C_6H_4<\begin{matrix}COOH\\OH\end{matrix}+C_2H_5I.$$

Salicylic acid,[2] $C_6H_4(OH)\cdot COOH$ (o-*hydroxybenzoic acid*), occurs in the blossom of *Spiraea ulmaria*, and is also found in considerable quantities, as *methyl salicylate*, in oil of wintergreen (*Gaultheria procumbens*). It used to be prepared, especially for pharmaceutical purposes, by hydrolysing this oil with potash.

Salicylic acid may be obtained by oxidising *salicylaldehyde*, or *salicyl alcohol* (saligenin, p. 535), with chromic acid, by treating o-*aminobenzoic acid* (anthranilic acid) with nitrous acid, and also by boiling *phenol* with caustic soda and carbon tetrachloride.

It is prepared on the large scale by treating *dry* sodium phenate with carbon dioxide under pressure, first at about 100° and then at about 120–140°; the product is dissolved in water, and the salicylic acid is precipitated with hydrochloric acid.

Salicylic acid is sparingly soluble in cold (1 in 400 parts at 15°), but readily so in hot, water, from which it crystallises in needles, melting at 159°; its neutral solutions give with ferric chloride an intense violet colouration. When rapidly heated it sublimes, and only slight decomposition occurs, but when distilled slowly, it decomposes to a great extent into phenol and carbon dioxide; when heated with soda-lime it gives sodium phenate.

[1] This compound might be called *methyl ethylsalicylate*, but such a name would be ambiguous, as it might also be given to the various isomerides of the formula, $C_6H_3(C_2H_5)(OH)\cdot COOCH_3$.

[2] Salicin (p. 535), related to salicylic acid, occurs in the willow tree, Lat. *salix, salicis*, from which these names are derived.

When salicylic acid is reduced with sodium and boiling amyl alcohol, it is converted into *pimelic acid*, $COOH \cdot [CH_2]_5 \cdot COOH$;[1] in a similar manner, certain other *o*-phenolic acids (but not the *m*- or *p*-compounds) may be transformed into homologues of pimelic acid.

Salicylic acid is a strong antiseptic, and, as it has no smell, it is frequently used as a disinfectant instead of phenol ; it is also employed in medicine and in the manufacture of azo-dyes.

Its mono-metallic salts, such as *potassium salicylate*, $C_6H_4(OH) \cdot COOK$, and *calcium salicylate*, $\{C_6H_4(OH) \cdot COO\}_2Ca$, are prepared by neutralising a hot aqueous solution of the acid with metallic *carbonates* ; most of them are soluble in water. The di-metallic salts, such as $C_6H_4(OK) \cdot COOK$, are obtained when an excess of the metallic *hydroxide* is used ; with the exception of those of the alkali metals, they are almost insoluble in water and are decomposed by carbonic acid, giving the mono-metallic salts.

Methyl salicylate, $C_6H_4(OH) \cdot COOCH_3$, may be prepared in the manner described above, or by distilling a mixture of salicylic acid, and methyl alcohol with sulphuric acid; it is a very pleasant-smelling oil, boiling at 223° ; **ethyl salicylate,** $C_6H_4(OH) \cdot COOC_2H_5$, boils at 231·5°. These and other esters are immediately converted into solid sodium derivatives by concentrated solutions of alkalis, but when water is then added and the solutions are boiled, the esters undergo hydrolysis.

Phenyl salicylate, $C_6H_4(OH) \cdot COOC_6H_5$, is prepared by heating a mixture of sodium salicylate and sodium phenoxide with phosphorus oxychloride,

$$2C_6H_4(OH) \cdot COONa + 2C_6H_5 \cdot ONa + POCl_3 = 2C_6H_4(OH) \cdot COOC_6H_5 + 3NaCl + NaPO_3 ;$$

it melts at 43°, is almost odourless, and is much employed in medicine and in surgery, under the name of *salol*, in the place of salicylic acid. It is practically insoluble in water and its alcoholic solution gives a violet colouration with ferric chloride.

Acetylsalicylic acid, $C_6H_4(OAc) \cdot COOH$ (*aspirin*), obtained by heating salicylic acid with acetic anhydride or acetyl chloride, is also an important drug ; it melts at 135° and is very sparingly soluble in water. Its aqueous solution gives no colouration with ferric chloride, but does so after having been boiled during some time.

[1] Tetrahydrosalicylic acid, containing the group —C(OH):C(COOH)—, is probably first formed ; this enolic compound then changes into a β-ketonic acid, which undergoes acid hydrolysis.

Methyl o-*methoxybenzoate*, $C_6H_4(OCH_3)\cdot COOCH_3$, is formed when methyl salicylate is heated with potash (1 mol.) and methyl iodide in alcoholic solution; it boils at 245°, and gives a salt of o-methoxybenzoic acid, $C_6H_4(OCH_3)\cdot COOH$ (m.p. 98·5°), when it is hydrolysed with aqueous alkali.

m-*Hydroxybenzoic acid* is prepared by fusing m-*sulphobenzoic acid* with alkali, and also by the action of nitrous acid on m-*aminobenzoic acid*. It melts at 201°.

p-*Hydroxybenzoic acid* (m.p. 213°) is formed, together with salicylic acid, by the action of carbon tetrachloride and potash on phenol; it may also be obtained from p-*sulphobenzoic acid* by fusion with alkali, or by the action of nitrous acid on p-*aminobenzoic acid*. It is prepared by heating dry potassium phenate in a stream of carbon dioxide at 220° so long as phenol distils; when, however, the temperature is kept below 150°, potassium salicylate is formed.

Saligenin, $C_6H_4(OH)\cdot CH_2\cdot OH$ (o-*hydroxybenzyl alcohol*, *salicyl alcohol*), is an example of a substance which is both a phenol and an alcohol. It is produced, together with glucose, by the action of dilute acids or enzymes on *salicin* (below), and may be prepared by reducing salicylaldehyde with sodium amalgam and aqueous alcohol.

It melts at 87°, and is readily soluble in water; the solution becomes deep blue on the addition of ferric chloride. Owing to its phenolic nature, it forms alkali salts, which, when heated with alkyl halides, give the corresponding ethers; on the other hand, it shows the properties of an alcohol, and yields salicylaldehyde and salicylic acid on oxidation.

Salicin, $C_6H_{11}O_5\cdot O\cdot C_6H_4\cdot CH_2\cdot OH$, occurs in the bark of the willow tree; it melts at 201° and chars when strongly heated. It is readily soluble in hot water, and when hydrolysed by boiling dilute acids or certain enzymes, it gives saligenin and glucose,

$$C_6H_{11}O_5\cdot O\cdot C_6H_4\cdot CH_2\cdot OH + H_2O = HO\cdot C_6H_4\cdot CH_2\cdot OH + C_6H_{12}O_6,$$

and the solution then reduces Fehling's solution. It is turned red by concentrated sulphuric acid.

The m- and p-*hydroxybenzyl alcohols* may be prepared by the reduction of the m- and p-*hydroxybenzaldehydes* (p. 503); they melt at 73° and 125° respectively.

Anisyl alcohol, $C_6H_4(OCH_3)\cdot CH_2\cdot OH$ (*p*-methoxybenzyl alcohol), is obtained by treating *anisaldehyde*, $C_6H_4(OCH_3)\cdot CHO$ (p. 503), with sodium amalgam and aqueous alcohol, or with alcoholic potash (Cannizzaro reaction); also by heating *p*-hydroxybenzyl alcohol with caustic alkali and methyl iodide in alcoholic solution.

It melts at 25°, and boils at 258° ; on oxidation, it yields *anisaldehyde* and *anisic acid.*

Anisic acid, $C_6H_4(OCH_3)\cdot COOH$ (p-*methoxybenzoic acid*), is obtained by oxidising *anethole*, $C_6H_4(OCH_3)\cdot CH:CH\cdot CH_3$ (the principal component of oil of aniseed), with chromic acid ; it may also be prepared by methylating p-*hydroxybenzoic acid.*

It melts at 184°, and when heated with soda-lime it is decomposed, with the formation of *anisole* ; when heated with fuming hydriodic acid, it yields p-*hydroxybenzoic acid* and methyl iodide.

There are six *dihydroxybenzoic acids*, $C_6H_3(OH)_2\cdot COOH$, two of which are derived from catechol, three from resorcinol, and one from quinol ; the most important of these is **protocatechuic acid** [COOH:OH:OH = 1:3:4], one of the two isomeric *catecholcarboxylic acids.* This compound is formed when many resins, such as catechu and gum benzoin, and also certain alkaloids, are fused with potash ; it may be prepared by heating catechol with water and ammonium hydrogen carbonate at 140°.

It melts at 199°, is very soluble in water, and when strongly heated, it is decomposed into catechol and carbon dioxide ; its aqueous solution gives with ferric chloride a green solution, which becomes violet and then red on the addition of sodium hydrogen carbonate.

Gallic acid, $C_6H_2(OH)_3\cdot COOH$ [3OH = 3:4:5] (*pyrogallolcarboxylic acid*), is a trihydroxybenzoic acid ; it occurs in gall-nuts, tea, and many other vegetable products, and is best prepared by boiling *tannin* (below) with dilute acids. It crystallises in needles, melts at 220°, and at the same time is resolved into pyrogallol and carbon dioxide ; it is readily soluble in water, and its aqueous solution gives with ferric chloride a bluish-black precipitate. Gallic acid is a strong reducing agent, and precipitates gold, silver, and platinum from solutions of their salts.

Tannin (tannic acid) is the name given to a vegetable product which occurs in large quantities in gall-nuts, sumach, and in many kinds of bark, from which it may be extracted with boiling water. It is an almost colourless, amorphous substance, and is readily soluble in water ; its solutions have a very astringent taste, and give with ferric chloride an intense dark-blue solution, for which reason tannin is employed in the manufacture of inks. Tannin is used in dyeing, as a mordant, owing to its property of forming insoluble coloured compounds with many dyes (p. 659). It is also exten-

sively employed in tanning. When animal skin or membrane, after certain preliminary operations, is left in a solution of tannin, or in contact with a suitable moist bark, it absorbs and combines with the tannin, and is converted into a much tougher material; such tanned skins constitute leather.

When boiled with dilute sulphuric acid, *some* tannins are completely converted into gallic acid and glucose, a fact which seems to show that these substances are probably glycosides, derived from glucose by the displacement of hydroxylic hydrogen atoms by *galloyl-*, $C_6H_2(OH)_3 \cdot CO$— (or *digalloyl-*) groups. As, however, tannins are amorphous and ill-characterised their structures have not been fully elucidated, and many of them may be mixtures of variable composition.

Mandelic acid, $C_6H_5 \cdot CH(OH) \cdot COOH$ (*phenylglycollic acid*), is an example of an aromatic hydroxy-acid in which the hydroxyl group is in the *side chain*. It may be obtained by boiling the glycoside, amygdalin (p. 354), with concentrated hydrochloric acid; it is usually prepared by treating the solid bisulphite compound of benzaldehyde with a concentrated solution of sodium cyanide and hydrolysing the resulting oily hydroxycyanide (*mandelonitrile*) with boiling concentrated hydrochloric acid,

$$C_6H_5 \cdot CH(OH) \cdot O \cdot SO_2Na + NaCN = C_6H_5 \cdot CH(OH) \cdot CN + Na_2SO_3,$$
$$C_6H_5 \cdot CH(OH) \cdot CN + 2H_2O = C_6H_5 \cdot CH(OH) \cdot COOH + NH_3.$$

Mandelic acid is moderately soluble in water, and shows the general behaviour of a hydroxy-acid; when heated with hydriodic acid, for example, it is reduced to *phenylacetic acid* (p. 525), just as lactic acid is reduced to propionic acid,

$$C_6H_5 \cdot CH(OH) \cdot COOH + 2HI = C_6H_5 \cdot CH_2 \cdot COOH + I_2 + H_2O.$$

The hydroxyl group in mandelic acid has an aliphatic character similar to that which it shows in glycollic acid, and in alcohols, so that there are many points of difference between mandelic acid and phenolic acids, such as salicylic acid, which contain nuclear hydroxyl groups. When *ethyl mandelate*, $C_6H_5 \cdot CH(OH) \cdot COOC_2H_5$, for example, is treated with caustic alkalis it does *not* yield a metallic derivative of the ester: the hydrogen of the hydroxyl group *is* displaced, however, when the ester is treated with sodium.

Mandelic acid, like lactic acid, exists in optically isomeric forms. The synthetical acid (m.p. 118°) is a *dl*-substance, but the acid (m.p. 133°) prepared from amygdalin is laevorotatory.

CHAPTER 35

NAPHTHALENE AND ITS DERIVATIVES

ALL the aromatic hydrocarbons hitherto described, with the exception of diphenyl, diphenylmethane, and triphenylmethane (p. 420), contain only *one* closed chain of six carbon atoms, and are very closely related to benzene; most of them may be prepared from and reconverted into benzene, by comparatively simple reactions, so that they are all classed and named as benzene substitution products. The exceptions just mentioned are also closely related to benzene, although diphenyl and diphenylmethane contain two, and triphenylmethane contains three, closed chains of six carbon atoms.

There are, however, other classes or types of aromatic hydrocarbons rather more distantly related to benzene, and of these *naphthalene* is perhaps second only to benzene in importance; it is the parent substance of a great number of compounds, many of which are extensively employed in the manufacture of dyes.

Naphthalene, $C_{10}H_8$, occurs in coal-tar in larger proportion than does any other hydrocarbon, and is easily isolated from this source commercially (p. 373). The crystals of crude naphthalene, which are deposited from the fraction of coal-tar passing over between 170 and 230° (*middle oil*), are first pressed to get rid of liquid impurities, then washed with caustic soda, and afterwards warmed with a small quantity of concentrated sulphuric acid, which converts most of the foreign substances into soluble sulphonic acids; the washed naphthalene is finally distilled or sublimed.

Naphthalene crystallises in lustrous plates, melts at 81°, and boils at 218°. It has a highly characteristic smell, and is extraordinarily volatile, considering its high molecular weight—so much so, in fact, that only part of the naphthalene in crude coal-gas is deposited in the condensers; the rest is carried forward into the purifiers, and even into the gas-mains, where, in very cold weather, it may be deposited in crystals and cause stoppages, particularly at the bends of the pipes. It is insoluble in water, but dissolves freely in many organic solvents. Like certain other aromatic hydro-

carbons, it crystallises with picric acid, and when concentrated benzene solutions of the two substances are mixed, *naphthalene picrate*, $C_{10}H_8, C_6H_2(NO_2)_3 \cdot OH$, is precipitated in yellow needles, which melt at 149°.

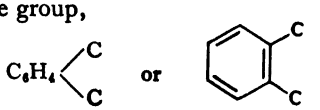
Naphthalene is employed as a disinfectant or insecticide (moth balls), and for the preparation of hydronaphthalenes, phthalic acid, and anthranilic acid, but mainly for the manufacture of a great many derivatives, which are employed in the colour industry.

Constitution. Naphthalene has the characteristic properties of an aromatic compound, as its behaviour under various conditions is similar to that of benzene and its derivatives, but different from that of aliphatic compounds. It is attacked by halogens, nitric acid, and sulphuric acid, giving substitution products: with nitric acid, for example, it yields *nitro*-derivatives, and with sulphuric acid it gives *sulphonic acids*,

$$C_{10}H_8 + HNO_3 = C_{10}H_7 \cdot NO_2 + H_2O,$$
$$C_{10}H_8 + H_2SO_4 = C_{10}H_7 \cdot SO_3H + H_2O.$$

This similarity between benzene and naphthalene at once suggests a resemblance in constitution, a view which is confirmed by the fact that naphthalene, like benzene, is a very stable compound, and is resolved into simpler substances only with difficulty. When, however, naphthalene is boiled with chromic acid or dilute nitric acid, or heated strongly with concentrated sulphuric acid (p. 520), it is slowly oxidised, yielding carbon dioxide, water, and *ortho*-phthalic acid, $C_6H_4(COOH)_2$.

Now the formation of phthalic acid in this way is a fact of very great importance, since it is evidence that the molecule of naphthalene contains the group,



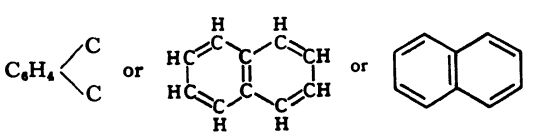
—that is to say, that it contains a benzene nucleus to which two carbon atoms are united in the *ortho*-position to one another. This fact alone, however, is insufficient to establish the constitution of the hydrocarbon, since it is still necessary to account for two atoms of carbon and four of hydrogen, and there are various ways in which these might be united with the given group.

Clearly, therefore, it is important to ascertain the structure of

that part of the naphthalene molecule, which has been oxidised to carbon dioxide and water—to obtain, if possible, some decomposition product of known constitution, in which these carbon and hydrogen atoms are retained in their original state of combination.

Now this can be done in the following way: When *nitronaphthalene*, $C_{10}H_7 \cdot NO_2$, a simple mono-substitution product of the hydrocarbon, is boiled with dilute nitric acid, it yields *nitrophthalic acid*, $C_6H_3(NO_2)(COOH)_2$; naphthalene, therefore, contains a benzene nucelus, and the nitro-group in nitronaphthalene is combined with that nucleus. If, however, the *same* nitronaphthalene is reduced to *aminonaphthalene*, $C_{10}H_7 \cdot NH_2$, and the latter is oxidised, *phthalic acid* (and not aminophthalic acid) is obtained. This last fact can only be explained on the assumption either that the benzene nucleus, which is known to be united with the amino-group, has been destroyed, or that the amino-group has been displaced by *hydrogen* during oxidation. Since, however, the latter alternative is contrary to experience, the former must be accepted, and it must be concluded that the benzene nucleus which is contained in the oxidation product of aminonaphthalene is *not the same* as that present in the oxidation product of nitronaphthalene; in other words, different parts of the naphthalene molecule have been oxidised to carbon dioxide and water in the two cases, and yet in both these reactions the group, (I), remains.

The constitution of naphthalene, therefore, may be provisionally expressed by the formula (II) or the equivalent (III),[1]

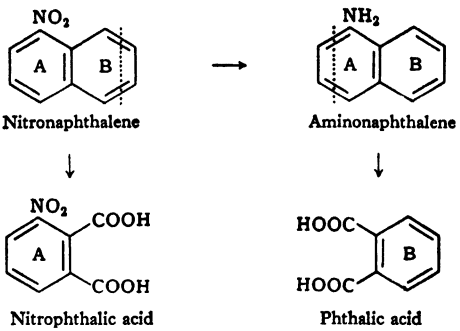


I II III

as will be obvious if the above changes are now reconsidered with the aid of such a formula. When nitronaphthalene is oxidised, the nucleus B (p. 541), which does not contain the nitro-group, is disintegrated (as indicated by the dotted lines), and the product is nitrophthalic acid; when, on the other hand, aminonaphthalene is oxidised, the nucleus A, combined with the amino-group, is attacked,

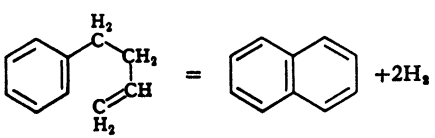
[1] As here and elsewhere, the symbols C and H are very often omitted from the formulae of benzene rings and only substituents are shown.

and, together with the amino-group, undergoes disintegration, with the production of phthalic acid :



It was in this way that Graebe determined the constitution of naphthalene in 1880 ; he proved that (as had been suggested by Erlenmeyer as early as 1866) its molecule contains two benzene nuclei which are said to be *condensed* together in the *o*-position, and have two *o*-carbon atoms in common, as shown. Further evidence which confirms this conclusion has since been obtained from syntheses of naphthalene and its derivatives, and from the results of the study of the isomerism of its substitution products.

Naphthalene may be obtained synthetically by passing the vapour of *phenylbutylene*, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH : CH_2$ [1] (or of *phenylbutylene dibromide*, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CHBr \cdot CH_2Br$), over red-hot lime ; the change involves the loss of hydrogen, as in the formation of other aromatic, from aliphatic, hydrocarbons (p. 376),



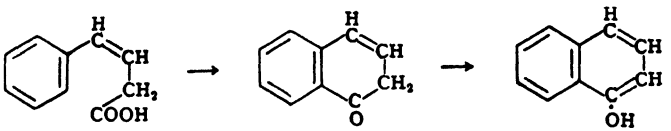
A most important synthesis of naphthalene was accomplished by Fittig, who showed that *α-naphthol* (α-hydroxynaphthalene) is

[1] *Phenylbutylene* may be obtained by treating benzyl chloride with allyl magnesium bromide.

$C_6H_5 \cdot CH_2Cl + CH_2 : CH \cdot CH_2 \cdot MgBr = C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH : CH_2 + MgClBr.$

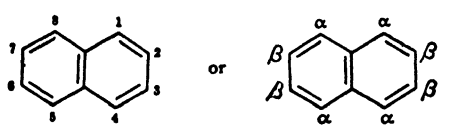
It is a liquid, boiling at 178°, and, like butylene, it combines directly with one molecule of bromine, yielding the dibromide.

formed when β-benzylidenepropionic acid (a substance of *known* constitution, p. 527) is heated at about 300°. This reaction may take place in two stages as the first product is probably a keto-derivative of naphthalene, which passes into α-naphthol by intramolecular or tautomeric change,



The α-naphthol thus obtained may be converted into naphthalene by distillation with zinc-dust, just as phenol may be transformed into benzene.

Isomerism of Naphthalene Derivatives. As in the case of benzene, the study of the isomerism of its substitution products affords the most convincing evidence as to the fundamental structure of naphthalene. In the first place, this hydrocarbon differs from benzene in yielding *two* isomeric *mono*-substitution products; there are, for example, two *monochloronaphthalenes*, two *monohydroxynaphthalenes*, two *mononitronaphthalenes*, etc. This fact is readily explained with the aid of the formula or symbol, already used, numbered or lettered for the usual purpose, and which shows that the eight hydrogen atoms are not all similarly situated:



If, for example, the 1 or α- hydrogen atom is displaced by chlorine, hydroxyl, etc., the substitution product would not be identical with the corresponding compound produced by the displacement of the hydrogen atom 2 or β. In the first case the substituent would be united with a carbon atom, which is itself directly combined with one of the carbon atoms common to both nuclei, whereas, in the other case, this would not be so. Further, it will be seen that no more than *two* such isomerides could be obtained, because the

positions 1, 4, 5, 8 (the four α-positions) are identical, and so also are the positions 2, 3, 6, 7 (the four β-positions). Clearly, then, the fact that the *mono*-substitution products of naphthalene exist in *two* isomeric forms is in accordance with the given formula ; these isomeric *mono*-substitution products are usually distinguished with the aid of the letters α and β.

When *two* hydrogen atoms in naphthalene are displaced by two identical atoms or groups, *ten* isomeric di-derivatives may be obtained. The positions of the substituents, indicated by the numerals, would be,

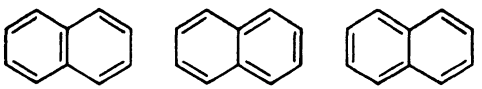
1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 2:3, 2:6, 2:7,

and all other positions, although differently numbered, would be identical with one of these ; 2:5, for example, is the same as 1:6, 3:8, and 4:7; and 4:8 is identical with 1:5. The constitutions of such *di*-derivatives, and those of the more numerous *di*-derivatives with *unlike* substituents, are thus easily shown. When the substituents are identical the two (or more) numerals precede the name, as in 1:2-*dichloronaphthalene*, but when they are different the substituents are numbered separately as in 1-*hydroxy*-4-*amino-naphthalene*, 1-*amino*-4-*hydroxynaphthalene*, and so on.

When the two atoms or groups are present in one and the same nucleus, their relative positions are similar to those of groups in the *o*-, *m*-, or *p*-position in benzene. The positions 1:2, 2:3, and 3:4 correspond with the *ortho*-, 1:3 and 2:4 with the *meta*-, and 1:4 with the *para*-position, and similarly in the case of the other nucleus. The positions 1:8 (or 4:5) and 2:6 (or 3:7) are termed the *peri*- and *amphi*-positions respectively ; groups in the *peri*-position behave in much the same way as those in the *o*-position in the benzene and naphthalene nuclei, when the occurrence of a reaction is determined by spatial distribution (pp. 556, 567).

Although the main structure of the naphthalene molecule is thus clearly established, it is impossible to indicate the nature and positions of the carbon to carbon bonds in the conventional manner. In the formula already shown, all these bonds have been inserted arbitrarily in *one* only of the two possible ways required to maintain the quadrivalency of carbon ; if both were used two structurally isomeric naphthalenes, (I) and (II), should exist and give rise to isomeric mono- and other substitution products, but no such compounds have ever been obtained. It is therefore assumed that

the naphthalene, like the benzene, molecule shows resonance and exists in the mesomeric state. The *contributors* to this state would be the structural isomerides (I) and (II) (compare *o*-xylene, p. 391) and the identical structures (II) and (III) (compare benzene, p. 392), and all the carbon to carbon bonds of the mesomeric molecule would be of an intermediate character, like those of benzene.



I II III

In order to avoid repetition it may be pointed out that *all* aromatic substances, including those such as pyridine, quinoline and *iso*-quinoline, in which a nitrogen atom takes the place of a CH group, may exist in similar mesomeric states.

Derivatives of Naphthalene

The *homologues of naphthalene*—that is to say, the *alkyl substitution products* of the hydrocarbon—are of comparatively little importance; they may be prepared from the parent substance by methods similar to those employed in the case of the corresponding benzene derivatives, as, for example, by treating naphthalene with alkyl halides in the presence of aluminium chloride (Friedel and Crafts reaction),

$$C_{10}H_8+C_2H_5I = C_{10}H_7\cdot C_2H_5+HI,$$

or with an acyl halide, followed by a Clemmensen reduction; also by treating the bromonaphthalenes with an alkyl halide and sodium (Wurtz-Fittig reaction),

$$C_{10}H_7Br+CH_3Br+2Na = C_{10}H_7\cdot CH_3+2NaBr.$$

α-Methylnaphthalene, $C_{10}H_7\cdot CH_3$, is a liquid boiling at 241°, but *β-methylnaphthalene* is a solid, melting at 37°, and boiling at 242°; both occur in coal-tar.

The *halogen mono-substitution products* of naphthalene are also of little importance. They may be obtained by treating the hydrocarbon, at its boiling-point, with the halogen (chlorine or bromine), but only the α-derivatives are formed in this way. Both the α- and the β-compounds may be obtained by treating the corresponding

naphthols (p 549), or, much better, the naphthalenesulphonic acids (p. 549), with pentachloride or pentabromide of phosphorus,

$$C_{10}H_7 \cdot SO_3H + PCl_5 = C_{10}H_7 \cdot SO_2Cl + POCl_3 + HCl,$$
$$C_{10}H_7 \cdot SO_2Cl + PCl_5 = C_{10}H_7Cl + POCl_3 + SOCl_2;$$

also by converting the naphthylamines (p. 547) into the corresponding diazonium compounds and decomposing the latter with a halogen cuprous salt (Sandmeyer reaction) or with copper powder,

$$C_{10}H_7 \cdot NH_2 \longrightarrow C_{10}H_7 \cdot N_2Cl \longrightarrow C_{10}H_7Cl.$$

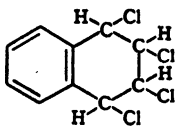
All these methods correspond with those described in the case of the halogen derivatives of benzene, and are carried out in a similar manner.

α-Chloronaphthalene, $C_{10}H_7Cl$, is a liquid, boiling at 263°, but the *β-derivative* is crystalline, melts at 61°, and boils at 265°.

α-Bromonaphthalene, $C_{10}H_7Br$, is also a liquid and boils at 279°, but the *β-derivative* is crystalline, and melts at 59°.

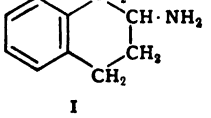
The chemical properties of these, and of other halogen derivatives of naphthalene, are similar to those of halogen derivatives of benzene; the halogen atoms are very firmly combined, and cannot be displaced by hydroxyl groups with the aid of aqueous alkalis, etc., but the bromonaphthalenes give Grignard reagents in a normal manner.

Naphthalene tetrachloride, $C_{10}H_8Cl_4$, is an important halogen *additive product*, which is produced when chlorine is passed into coarsely powdered naphthalene, at ordinary temperatures. It melts at 182°, and is converted into *dichloronaphthalenes*, $C_{10}H_6Cl_2$ (substitution products of naphthalene), when it is heated with alcoholic potash; it is readily oxidised by nitric acid, yielding phthalic and oxalic acids, a fact which shows that all the chlorine atoms are united with one and the same nucleus; the constitution of the compound, therefore, is expressed by the formula,

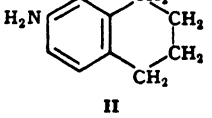


Many other additive compounds have been obtained by the reduction of certain substitution products of naphthalene with sodium and boiling amyl alcohol, but usually very much more easily by catalytic hydrogenation using nickel. In such reactions

four hydrogen atoms are usually taken up first by *one* nucleus and then *six* more are added to the other nucleus. When a naphthalene derivative is thus converted into a tetrahydro-additive compound, the atoms or groups directly united with the reduced nucleus acquire the properties which they have in aliphatic compounds, whereas those united to the unreduced nucleus retain the properties which they have in nuclear substitution products of benzene. The amino-group in ac.-*tetrahydro-β-naphthylamine*, (I), for example, has the same character as that in aliphatic amines, whereas in the case of the isomeric ar.-*tetrahydro-β-naphthylamine*, (II), the amino-group has the same properties as that in aniline, because it is combined with the unreduced nucleus.



I



II

Such tetrahydro-derivatives of naphthalene are distinguished by the prefixes *ac.* (alicyclic) or *ar.* (aromatic), according as the substituent is contained in the reduced or in the unreduced nucleus. α-Naphthylamine and α-naphthol are reduced to *ar.*-tetrahydro-compounds by sodium and boiling amyl alcohol, but β-naphthylamine and β-naphthol give the *ac.*-tetrahydro-compounds as principal products, and smaller quantities of the *ar.*-tetrahydro-derivatives. *ar.*-Tetrahydronaphthols are phenolic in character, but the *ac.*-isomerides have the properties of aliphatic alcohols.

Tetrahydronaphthalene (*tetralene*), $C_{10}H_{12}$, and **decahydronaphthalene** (*decalane*), $C_{10}H_{18}$, are prepared on the large scale by the reduction of naphthalene with hydrogen in the presence of nickel; they are liquids, boiling at 207° and *about* 187° respectively, and are used as commercial solvents (*tetralin*, *decalin*).

Nitro-derivatives. Naphthalene, like benzene, is quite readily *nitrated* by a mixture of nitric and sulphuric acids, giving mono- and di-nitro-derivatives. The chemical properties of the nitronaphthalenes are in nearly all respects similar to those of the nitrobenzenes.

α-Nitronaphthalene, $C_{10}H_7 \cdot NO_2$, may be prepared by nitrating naphthalene in acetic acid solution.

Naphthalene (5 g.) is dissolved in acetic acid (10 c.c.), nitric acid (sp. gr. 1·4 ; 5 g.) is added, and the solution is heated on a water-

bath during about half an hour; the product, which crystallises from the cold solution, is separated, washed with a little water and recrystallised from alcohol. On the large scale it is prepared by treating naphthalene with a diluted mixture of nitric and sulphuric acids.

It crystallises in pale yellow prisms, melts at 61°, and boils at 304°; on oxidation with nitric acid, it yields nitrophthalic acid (p. 541).

β-Nitronaphthalene is not formed by nitrating naphthalene, but it may be prepared by dissolving *1-amino-2-nitronaphthalene* (obtained by treating α-naphthylamine with *dilute* nitric acid) in an alcoholic solution of hydrogen chloride, adding finely divided sodium nitrite, and then heating the solution of the diazonium compound (p. 455),

$$C_{10}H_6(NO_2)\cdot N_2Cl + C_2H_5\cdot OH = C_{10}H_7\cdot NO_2 + N_2 + HCl + C_2H_4O.$$

It crystallises in yellow needles, melting at 79°.

The **amino-derivatives** of naphthalene, or *naphthylamines*,[1] are very similar in properties to the corresponding benzene derivatives, except that even the monoamino-compounds are crystalline at ordinary temperatures. They are neutral to litmus, and yet are basic and form salts with acids; these salts, however, are hydrolysed to some extent by cold water, in which, as a rule, they are only sparingly soluble. The amino-compounds may be converted into diazonium compounds, aminoazo-compounds, etc., by reactions similar to those employed in the case of the aminobenzenes, and many of the substances obtained in this way, as well as the amino-compounds themselves, are extensively employed in the manufacture of dyes.

α-Naphthylamine, $C_{10}H_7\cdot NH_2$, may be obtained by heating *α-naphthol* with ammonia at 250° under pressure,

$$C_{10}H_7\cdot OH + NH_3 = C_{10}H_7\cdot NH_2 + H_2O;$$

it is prepared commercially by reducing *α-nitronaphthalene* with iron-filings and hydrochloric acid,

$$C_{10}H_7\cdot NO_2 + 6H = C_{10}H_7\cdot NH_2 + 2H_2O.$$

Nitronaphthalene (1 part; 10 g.) is mixed with iron borings (2 parts) in a flask, and concentrated hydrochloric acid (6·5–7 parts) is added in small quantities at a time; the flask is well shaken during the operation and the mixture is kept at about 80°. As soon

[1] The radical $C_{10}H_7$ is called naphthyl.

as a test portion is completely soluble in hot water (except for metal or hydroxide), an excess of alkali is added, the base is distilled in (superheated) steam, and separated on a suction-filter.

α-Naphthylamine is crystalline, melts at 50°, and boils at 301°; it has a disagreeable smell, turns red on exposure to the air, and its salts give a blue precipitate with ferric chloride and other oxidising agents. On oxidation with a boiling solution of chromic acid, it is converted into *α-naphthaquinone* (p. 550) and phthalic acid. The *hydrochloride* is readily soluble in cold water, but is precipitated in crystals, even from dilute solutions, on the addition of concentrated hydrochloric acid.

β-Naphthylamine is not prepared from β-nitronaphthalene (which is only obtained with difficulty), but by heating *β-naphthol* with concentrated ammonia at 200°, or with ammonium sulphite and ammonia at about 160°, under pressure. It crystallises in plates, melts at 113°, and boils at 294°; it differs markedly from α-naphthylamine in being odourless, and its salts give no colouration with ferric chloride. On oxidation with potassium permanganate, it yields phthalic acid.

The two **naphthols,** or monohydroxynaphthalenes, correspond with the monohydric phenols, and are of considerable importance, as they are extensively employed in the colour industry. They both occur in coal-tar, but only in small proportions, and are therefore prepared by fusing the corresponding sulphonic acids with caustic soda (p. 549),

$$C_{10}H_7 \cdot SO_3Na + NaOH = C_{10}H_7 \cdot OH + Na_2SO_3.$$

α-Naphthol is also manufactured from α-naphthylamine, the salts of which, *unlike* those of aniline, are decomposed by water at about 200°,

$$(C_{10}H_7 \cdot NH_2)_2, H_2SO_4 + 2H_2O = 2C_{10}H_7 \cdot OH + (NH_4)_2SO_4.$$

The naphthols, on the whole, are very similar to the phenols, and, like the latter, they dissolve in caustic alkalis, yielding metallic derivatives, which are decomposed by carbonic acid; the hydrogen of the hydroxyl group in the naphthols may also be displaced by an acyl or an alkyl group, just as in phenols, and on treatment with pentachloride or pentabromide of phosphorus, a halogen atom is substituted for the hydroxyl group. The naphthols further resemble the phenols in giving colour reactions with ferric chloride.

In some respects, however, the naphthols differ from the phenols, inasmuch as the hydroxyl groups in the former more readily undergo change ; when, for example, a naphthol is heated with ammonia at 250°, it is converted into the corresponding amino-compound, whereas the conversion of phenol into aniline requires a temperature of 300–350°, other conditions remaining the same. Again, when a naphthol is heated with an alcohol and hydrogen chloride, it is converted into its alkyl derivative, whereas alkyl derivatives of phenols cannot, as a rule, be obtained in this way.

α-Naphthol, $C_{10}H_7 \cdot OH$, is formed when β-benzylidenepropionic acid is heated at about 300° (p. 542), an important synthesis, which proves that the hydroxyl group is in the α-position ; it is prepared from *α-naphthylamine* (above), or from *naphthalene-α-sulphonic acid* (below). It is crystalline, melts at 96°, and boils at 279° ; it has a faint smell, recalling that of phenol, and it dissolves freely in many organic solvents, but is only sparingly soluble in hot water. Its aqueous solution gives with ferric chloride a violet, flocculent precipitate of *α-di-naphthol*, $HO \cdot C_{10}H_6 \cdot C_{10}H_6 \cdot OH$, an oxidation product of the naphthol. It dissolves readily in caustic alkalis but not in solutions of alkali carbonates.

α-Naphthol, like phenol, is very readily attacked by nitric acid and gives a *dinitro*-derivative, $C_{10}H_5(NO_2)_2 \cdot OH$, which crystallises in yellow needles, melting at 138° ; its sodium derivative, $C_{10}H_5(NO_2)_2 \cdot ONa, H_2O$, employed in dyeing silk, is known commercially as *Naphthol yellow*.

β-Naphthol, prepared by fusing *naphthalene-β-sulphonic acid* with caustic soda, melts at 123°, and boils at 286° ; it is readily soluble in hot water, and, like the α-derivative, has a faint, phenol-like smell and forms readily soluble metallic derivatives with caustic alkalis. Its aqueous solution gives, with ferric chloride, a green colouration and a flocculent precipitate of *β-di-naphthol*, $HO \cdot C_{10}H_6 \cdot C_{10}H_6 \cdot OH$.

Sulphonic Acids. Perhaps the most important derivatives of naphthalene, from a commercial point of view, are the various mono- and di-sulphonic acids, which are obtained from the hydrocarbon itself, from the naphthylamines, and from the naphthols, and used in large quantities in the manufacture of dyes. It is unnecessary to describe individually the very numerous compounds of this class, but a few important facts may be given.

Naphthalene is readily sulphonated, yielding α- and *β-mono-*

sulphonic acids, $C_{10}H_7 \cdot SO_3H$, both of which are formed when the hydrocarbon is heated with sulphuric acid, but the lower the temperature, the larger the proportion of the α-acid. Thus, at 80° the product consists of about 96% of the α- and 4% of the β-acid, but at 160°, 15% of the α- and 85% of the β-compound are obtained (compare phenolsulphonic acid, p. 487).

Naphthalene-β-sulphonic acid may be prepared in the laboratory by the following method: Naphthalene (125 g.) is heated to and kept at 160° in a wide beaker (loosely covered with a sheet of asbestos) while 93% sulphuric acid (200 g.) is added in the course of about 15 minutes to the *well-stirred* liquid; about 5 minutes later, the product, having cooled a little, is very cautiously poured into water (150 c.c.), the solution is left until it has acquired room temperature, and the acid is separated on a suction-pump. The crude preparation is dissolved in ½ its weight of boiling water, and the solution is filtered from any unchanged naphthalene or from small quantities of *di-naphthylsulphone*, $(C_{10}H_7)_2SO_2$, which are usually present: to the filtrate concentrated hydrochloric acid (a volume equal to ⅓ of that of the water used) is added and the solution is cooled slowly. The β-sulphonic acid separates in lustrous scales ($3H_2O$).

Disulphonic acids may be obtained by strongly heating naphthalene with anhydrosulphuric acid.

Theoretically, fourteen isomeric *naphthylaminemonosulphonic acids*, $C_{10}H_6(NH_2) \cdot SO_3H$, may be obtained—namely, seven derived from α-naphthylamine, and seven from the β-base; of these compounds, thirteen seem to be known. The most important, perhaps, is 1:4-*naphthylaminemonosulphonic acid*, or *naphthionic acid*, which is practically the sole product of the action of sulphuric acid on α-naphthylamine; it is crystalline, very sparingly soluble in cold water, and is used in the manufacture of Congo red and other dyes (p. 678).

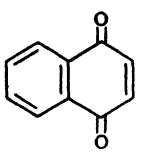
The *naphtholmonosulphonic acids*, of which, theoretically, there are also 14 isomerides, are likewise extensively used in the colour industry.

α-Naphthaquinone, $C_{10}H_6O_2$, corresponds with (*p*-benzo)-quinone, and, like the latter, is formed when various mono- and di-substitution products of the hydrocarbon (but only those in which the substituent or substituents occupy the 1- or 1:4-position) are oxidised with sodium dichromate and sulphuric acid; *α-naphthylamine*, 1-*amino*-4-*naphthol*, and 1:4-*diaminonaphthalene*, for ex-

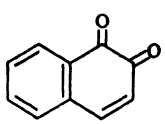
ample, may be employed. As a rule, however, naphthalene itself is oxidised with a boiling solution of chromic acid in acetic acid (a method not applicable for the preparation of quinone from benzene), as the product is then more easily obtained in a state of purity.

α-Naphthaquinone crystallises from alcohol in deep-yellow plates, melting at 125° ; it resembles quinone in colour, in having a curious pungent smell, and in being very volatile, subliming readily even at 100°, and distilling rapidly in steam. Unlike quinone, it is not easily reduced by sulphurous acid, but some reducing agents convert it into 1:4-*dihydroxynaphthalene*, $C_{10}H_6(OH)_2$, just as quinone is transformed into quinol. This close similarity in properties clearly points to a similarity in constitution, so that α-naphthaquinone may be represented by the formula given below.

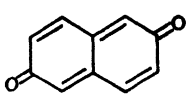
β-Naphthaquinone, $C_{10}H_6O_2$, isomeric with the α-compound, is formed when 1-amino-2-naphthol is oxidised with potassium dichromate and dilute sulphuric acid, or with ferric chloride ; it crystallises in red needles, decomposes at about 115°, and on reduction with sulphurous acid is converted into 1:2-*dihydroxynaphthalene*. It differs from α-naphthaquinone and from quinone in colour, in having no smell, and in being non-volatile, properties which, though apparently insignificant, are of some importance, as they distinguish *ortho*-quinones from *para*-quinones ; the latter are generally deep-yellow, volatile compounds, having a pungent odour, whereas the former are red, non-volatile, and odourless. β-Naphthaquinone is an *ortho*-quinone corresponding with *o*-benzoquinone, and its constitution may be represented by the formula shown below :



α-Naphthaquinone



β-Naphthaquinone



Amphi-naphthaquinone

Both α- and β-naphthaquinone are oxidised by nitric acid, giving *o*-phthalic acid, a proof that in both compounds the two oxygen atoms are united with one nucleus only ; that the one is a *para*-, the other an *ortho*-quinone, is established by their methods of formation and their conversion into compounds of known structures.

Amphi- or 2:6-**naphthaquinone,** $C_{10}H_6O_2$, may be represented by the formula just given in which the oxygen atoms are combined with different nuclei. It may be prepared by the oxidation of 2:6-dihydroxynaphthalene, in benzene solution, with lead dioxide. It is reddish-yellow, non-volatile, and odourless, and resembles, therefore, the *ortho-* rather than the *para*-quinones.

The above description of some of the more important naphthalene derivatives will be sufficient to show the close relationship between these compounds and the corresponding derivatives of benzene ; they are prepared, as a rule, by the same methods as their analogues of the benzene series, and resemble the latter closely in chemical properties ; consequently the general reactions and generic properties of benzene derivatives are met with again in the case of analogous naphthalene compounds.

The following scheme shows how some of the more important naphthalene derivatives are produced ; it should be noted that β-naphthol and β-naphthylamine are both obtained starting from the β-sulphonic acid, but that α-naphthylamine is prepared from the α-nitro-compound, and α-naphthol either from α-naphthylamine or from the α-sulphonic acid :

α-Compounds

$C_{10}H_7 \cdot NO_2 \longrightarrow C_{10}H_7 \cdot NH_2 \longrightarrow C_{10}H_7 \cdot OH \longleftarrow C_{10}H_7 \cdot SO_3H$ (at 80°)

$C_{10}H_8$ → $C_{10}H_7 \cdot NO_2$; $C_{10}H_8$ → $C_{10}H_7 \cdot SO_3H$ (at 80°)

$C_{10}H_8$ → $C_{10}H_7 \cdot SO_3H$ (at 160°)

$C_{10}H_7 \cdot NH_2 \longleftarrow C_{10}H_7 \cdot OH \longleftarrow C_{10}H_7 \cdot SO_3H$ (at 160°)

β-Compounds

In general, mono-substitutions at low temperatures usually give α-derivatives of naphthalene, whereas more vigorous conditions sometimes favour β-substitution ; the Friedel-Crafts reaction often gives mixtures of α- and β-compounds.

In the case of di-substitution, the course of the reaction is given roughly by the following rules : An *op*-directing group in the 1-position directs to the 4- and then to the 2-position as in benzene, whereas when it is in the 2-position, a 1- or sometimes a 6-derivative is formed. A *m*-directing group usually causes α-substitution in the other nucleus.

The Orientation of Naphthalene Derivatives

For the orientation of the mono-substitution products of naphthalene, it was necessary, as in the case of the di-derivatives of benzene (p. 394), to determine the structures of one or more compounds, which might then serve as standards. Now nitronaphthalene, the first product of the nitration of the hydrocarbon, oxidised by chromic acid, gave a nitrophthalic acid, which was proved to have the structure, [2COOH:NO_2 = 1:2:3] ; the nitro-group in the nitronaphthalene must therefore be in the α-position. This nitronaphthalene on reduction gave a naphthylamine, which when diazotised, etc., was transformed into a naphthol ; this compound, therefore, must also be an α-derivative, a conclusion which was fully confirmed by Fittig's synthesis of the same naphthol by simple reactions, from a compound of known constitution. These three derivatives, having thus been orientated, served as standards ; any compounds obtained from, or converted into, any one of these standards by simple substitution, must belong to the α-series ; a naphthalene derivative, $C_{10}H_7X$, isomeric with an α-compound, must consequently belong to the β-series.

The orientation of a di-derivative may sometimes be ascertained in a simple manner, but may be a task of considerable difficulty. In the first place the derivative is submitted to vigorous oxidation. Certain groups, such as HO— and NH_2—, render the substituted nucleus more easily oxidisable, and if both are united to the same benzene nucleus that particular one is disintegrated, leaving phthalic acid. Other substituents, such as halogens or NO_2— groups, render the nucleus less readily attacked, and if both are united to the same one, a di-substituted phthalic acid is obtained. In the latter case the derivative of phthalic acid can be orientated by the usual methods, and the structure of the naphthalene derivative is thus ascertained. In the former case (and also in the latter if necessary) each of the two groups is displaced in turn by hydrogen, and it is thus found whether the compound is an $\alpha\alpha$-, $\beta\beta$-, or $\alpha\beta$-derivative ; if it is proved to be either $\alpha\alpha$- or $\beta\beta$-, its orientation is completed, but this is not so if it is an $\alpha\beta$-di-derivative. When the results of oxidation show that the substituents are combined with *different* nuclei, it is easy to find whether they are in α- or in β-positions by displacing each in turn by hydrogen, but even if both are α- or both are β- the orientation is still incomplete. In such cases various other methods of investigation, including syntheses

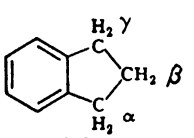
from substituted β-benzylidenepropionic acids, must be employed, before the structures of the compounds can be established.

The above account will serve to indicate the principles on which the orientation of naphthalene derivatives is based. At the present time so many di-derivatives, including all the ten theoretically possible dichloronaphthalenes, have been orientated, that it may only be necessary to convert the new compound into one of these standards.

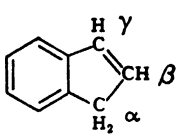
Aromatic-aliphatic Cyclic Compounds

In the molecule of naphthalene both the closed chains which are *condensed* together have an aromatic or benzenoid character. Other hydrocarbons are known in which a closed chain having aliphatic properties is condensed with a benzene nucleus. Tetrahydronaphthalene (tetralene), for example, obtained by the reduction of naphthalene, is a compound of such a type; one of the closed chains in its molecule is aromatic and shows the reactions of benzene, whereas the other contains $>CH_2$ groups, which behave like those in the molecule of a paraffin and give substitution products only with difficulty.

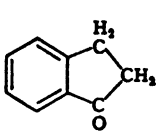
The hydrocarbon, *indane*, is a lower homologue of tetrahydronaphthalene, and its molecule consists of a closed aliphatic chain of five carbon atoms *condensed* with a benzene nucleus; the structural formula of this hydrocarbon and those of some of its derivatives are given below and the letters α, β, γ, serve to show the positions of substituents:



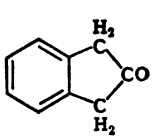
Indane



Indene



α-Indanone



β-Indanone

The α- and γ-positions in indane are, of course, identical, and γ-indanone is therefore the same as the α-compound. In the case of indene, although apparently the α-, β-, and γ-positions

are all different, only two series of substitution derivatives (*β-* and *α- or γ-*) exist, because a hydrogen atom migrates readily from the α-CH_2 group to the γ-position and *vice versa*, with a corresponding movement of the double binding.

Indane, *hydrindene*, C_9H_{10}, was first obtained by reducing coal-tar *indene* (below) with sodium and alcohol ; it has been synthesised by a method which establishes its constitution : *o*-Xylylene dibromide, prepared by brominating *o*-xylene at its boiling-point, is warmed with diethyl sodiomalonate and sodium ethoxide,

$$C_6H_4<\begin{matrix}CH_2Br\\CH_2Br\end{matrix}+CNaH(COOEt)_2+NaOEt=$$
$$C_6H_4<\begin{matrix}CH_2\\CH_2\end{matrix}>C(COOEt)_2+2NaBr+C_2H_5\cdot OH.^1$$

The *diethyl indanedicarboxylate*, so formed, is hydrolysed, the dicarboxylic acid is converted into the monocarboxylic acid in the usual manner, and the barium salt of the *indane-β-carboxylic acid* is destructively distilled ; indene is thus formed with the liberation of hydrogen. The indene is then reduced with sodium and alcohol or hydrogen and nickel. Indane boils at 177° and gives substitution derivatives of various types by the displacement of hydrogen atoms of the benzene nucleus.

Indene, C_9H_8, is contained in that fraction of coal-tar which is collected from 175 to 185°, and may be isolated from this product by precipitation with picric acid ; the *picrate* is recrystallised and then submitted to distillation in steam, whereon indene passes over. Indene boils at 182°, and readily undergoes atmospheric oxidation ; as it is an *olefine* it combines directly with bromine, giving *dibromo-indane* or *indene dibromide*, and it also combines with hydrogen (above) ; when heated alone, or with hydrochloric acid, or even when it is kept at ordinary temperatures, it undergoes polymerisation and gives a resinous substance.

α-Indanone, *α-hydrindone*, C_9H_8O, is obtained, with the evolution of hydrogen chloride, by warming *β-phenylpropionyl chloride*, $C_6H_5\cdot CH_2\cdot CH_2\cdot COCl$, with aluminium chloride, a reaction which recalls that by which acetophenone is produced from benzene and acetyl chloride. It melts at 42°, boils at 244°, and forms an *oxime* (m.p. 146°) ; when this oxime is reduced with sodium amalgam and water, it is converted into **α-indylamine** (*α-hydrindamine*),

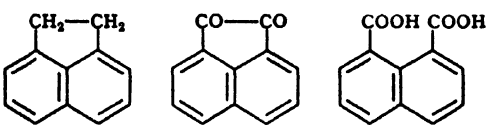
[1] This reaction really occurs in several stages which are summarised in the one equation.

$C_9H_9 \cdot NH_2$, a *dl*-base (b.p. 220°), which may be resolved into its optically active components. When hydrindamine hydrochloride is heated, it decomposes into indene and ammonium chloride.

β-Indanone, *β-hydrindone*, C_9H_8O, is produced when the calcium salt of *phenylene*-o-*diacetic acid*[1] is heated, a reaction which may be compared with that by which ketones are formed from *two* molecules of a monocarboxylic acid ; it melts at 61°, boils at 220–225°, and, like α-hydrindone, shows the ordinary reactions of a ketone.

Two **di-** and one **tri**-keto-derivatives of indane are also known ; the hydrate of triketoindane (*indantrione*), known as *ninhydrin*, is used in testing for amino-acids and proteins (pp. 618, 645).

Acenaphthene, $C_{12}H_{10}$ (I), is related to naphthalene in much the same way as hydrindene is related to benzene. It occurs in coal-tar, and is a component of ' heavy oil ' (p. 372), from which, however, it is isolated only with difficulty. It crystallises in needles, melts at 96°, and boils at 279° ; on oxidation with chromic acid in glacial acetic acid solution, it is converted into *acenaphthaquinone* (II), a yellow crystalline substance melting at 261°, which is easily oxidised further, giving *naphthalic acid* or *naphthalene*-1:8-*dicarboxylic acid* (III).



I II III

Naphthalic acid does not melt, but at about 180° it is converted into *naphthalic anhydride* (m.p. 274°) ; this fact shows that two carboxyl groups in the *peri*- or 1:8-position behave in this reaction like those in the *o*-position in the benzene or naphthalene nucleus (p. 567).

[1] This acid is obtained by treating *o*-xylylene dibromide (p. 555) with potassium cyanide, and hydrolysing the *o*-xylylene dicyanide which is thus formed.

CHAPTER 36

ANTHRACENE AND PHENANTHRENE

Anthracene, $C_{14}H_{10}$ (Gr. *anthrax*, coal), is a hydrocarbon of commercial importance, as it is the starting-point in the manufacture of alizarin, which is employed in producing Turkey-red and various other dyes ; it is obtained commercially from coal-tar. The crude mixture of hydrocarbons and other substances known as ' 50% anthracene ' (p. 374) is treated with some solvent, such as pyridine, which extracts phenanthrene, etc., and is then distilled in superheated steam, or recrystallised from pyridine, but the isolation of anthracene is very troublesome.

Anthracene crystallises from benzene in lustrous plates, which show a blue fluorescence ; it melts at 216°, boils at 340°, and dissolves freely in boiling benzene, but is only sparingly soluble in alcohol and ether. Saturated alcoholic solutions of anthracene and of picric acid, when mixed, give a precipitate of *anthracene picrate*, $C_{14}H_{10}, C_6H_2(NO_2)_3 \cdot OH$, which crystallises in ruby-red needles, melting at 138° ; this compound is resolved into its components when it is treated with a large quantity of alcohol (distinction from phenanthrene picrate, p. 565).

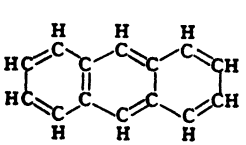
Constitution. The molecular formula of anthracene ($C_{14}H_{10}$) suggests that this hydrocarbon is related to benzene (C_6H_6), naphthalene ($C_{10}H_8$), and other *closed chain* compounds, rather than to hydrocarbons of the aliphatic series. The behaviour of anthracene towards chlorine and bromine is also, on the whole, similar to that of benzene and naphthalene—that is to say, anthracene yields additive or substitution products according to the conditions ; moreover, towards concentrated sulphuric acid it behaves like other aromatic compounds, and is converted into sulphonic acids. When treated with nitric acid, however, instead of yielding a nitro-derivative, as might have been expected, it is oxidised to *anthraquinone*, $C_{14}H_8O_2$, two atoms of hydrogen being displaced by two atoms of oxygen ; this change takes place with dilute nitric acid, but under particular conditions, the concentrated acid may give *(γ)-nitroanthracene*, $C_{14}H_9 \cdot NO_2$.

Now, the conversion of anthracene into anthraquinone is not

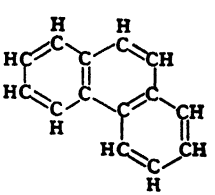
only closely analogous to that of naphthalene, $C_{10}H_8$, into α-naphthaquinone, $C_{10}H_6O_2$ (p. 551), but is also an oxidation process of a kind (namely, the substitution of oxygen atoms for an *equal* number of hydrogen atoms) which is unknown in the case of the aliphatic hydrocarbons ; anthracene, therefore, is a closed chain compound. Another highly important fact, bearing on the constitution of anthracene, is that, although the hydrocarbon and most of its derivatives are resolved into simpler substances only with very great difficulty, when this does occur, one of the products is some benzene derivative, usually phthalic acid.

Now, if the molecule of anthracene contained only one benzene nucleus, or even if, like naphthalene, it contained two condensed benzene nuclei, there would still be certain carbon and hydrogen atoms which would have to be regarded as forming *unsaturated* side chains ; but experience has shown that even saturated side chains in benzene are oxidised with comparative facility, giving carboxylic acids. Consequently, it is impossible to assume the presence of *any* side chain in anthracene, which is oxidised to the neutral substance, anthraquinone, without the loss of carbon. Arguments of this kind, therefore, lead to the conclusion that the molecule of anthracene is composed *only* of combined or condensed nuclei ; as, moreover, the hydrocarbon may be indirectly converted into phthalic acid, it must be concluded that two of these nuclei are condensed together in the *o*-position, as in naphthalene.

If, now, an attempt is made to deduce a constitutional formula for anthracene on this basis, and it is further assumed that all the closed chains are composed of *six* carbon atoms, as in naphthalene, the following suggest themselves as alternative formulae,



I



II

although, of course, neither could be accepted as final without further evidence.

Many facts, however, have led to the conclusion that the con-

stitution of anthracene must be expressed by the formula (I) and that (II) represents phenanthrene (p. 565); this formula, (I), accounts satisfactorily for all that is known about anthracene, including a number of important syntheses of the hydrocarbon, the isomerism of its derivatives and its relation to anthraquinone.

Anthracene may be obtained synthetically in various ways from compounds of known structure. It is produced when benzyl chloride is heated with aluminium chloride,

$$3C_6H_5\cdot CH_2Cl = C_6H_4<\begin{matrix}CH\\CH\end{matrix}>C_6H_4+C_6H_5\cdot CH_3+3HCl;$$

the *dihydroanthracene* (p. 560), which is formed as an intermediate product,

$$C_6H_4<\begin{matrix}H\\CH_2Cl\end{matrix}+\begin{matrix}ClCH_2\\H\end{matrix}>C_6H_4 = C_6H_4<\begin{matrix}CH_2\\CH_2\end{matrix}>C_6H_4+2HCl,$$

is converted into anthracene by the loss of hydrogen, which reduces part of the benzyl chloride to toluene (as shown in the first equation). Anthracene is also formed, together with dihydroanthracene and phenanthrene, when o-*bromobenzyl bromide* (prepared by brominating *boiling* o-*bromotoluene*) is treated with sodium,

$$2C_6H_4<\begin{matrix}CH_2Br\\Br\end{matrix}+4Na = C_6H_4<\begin{matrix}CH_2\\CH_2\end{matrix}>C_6H_4+4NaBr;$$

here, again, *dihydroanthracene* is the primary product, from which anthracene is formed by the loss of hydrogen.

Another interesting synthesis may be mentioned—namely, the formation of anthracene when a mixture of *tetrabromoethane* and benzene is treated with aluminium chloride,

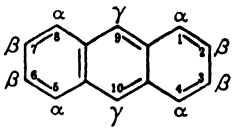
$$C_6H_4<\begin{matrix}H\\H\end{matrix}+\begin{matrix}BrCHBr\\BrCHBr\end{matrix}+\begin{matrix}H\\H\end{matrix}>C_6H_4 = C_6H_4<\begin{matrix}CH\\CH\end{matrix}>C_6H_4+4HBr.$$

All these methods of formation are accounted for in a simple manner with the aid of the formula (I).

Isomerism of Anthracene Derivatives. Further evidence in support of this formula is afforded by the study of the isomerism of the substitution products of anthracene, although, in many cases, only a few of the isomerides theoretically possible have as yet been prepared.

By the substitution of an atom or radical for one atom of hydrogen in the molecule of anthracene, it is possible to obtain *three* (but not

more than three) isomerides. This fact is readily accounted for with the aid of the formula shown below,[1] which is conventionally numbered or lettered for the usual purpose :



It will then be seen that there are three positions (α, β, γ), all of which are differently situated relatively to the rest of the molecule. These mono-substitution products are distinguished by the letters α, β, γ (or by the numerals), according to the position of the substituent ; the γ- is sometimes called the *meso*-position. When two atoms of hydrogen are displaced by identical atoms or groups, *fifteen* isomeric di-substitution products may be obtained ; these are distinguished with the aid of the numerals.

9:10-*Dihydroanthracene*, (I), $C_{14}H_{12}$, a substance of little importance, is formed when anthracene is reduced with boiling concentrated hydriodic acid, or with sodium amalgam and water. It melts at 108°, and when heated with sulphuric acid it is converted into anthracene.

Anthracene 9:10-*dichloride*, (II), $C_{14}H_{10}Cl_2$, like dihydroanthracene, is an additive product of the hydrocarbon ; it is obtained when chlorine is passed into a *cold* solution of anthracene in carbon disulphide, whereas at 100° substitution takes place, with the formation of 9-*monochloroanthracene* and 9:10-*dichloroanthracene* ; these substitution products crystallise in yellow needles, melting at 103° and 209° respectively, and they are both converted into anthraquinone on oxidation, a fact which shows the positions of the chlorine atoms.

I $C_6H_4<\begin{matrix}CH_2\\CH_2\end{matrix}>C_6H_4$ II $C_6H_4<\begin{matrix}CHCl\\CHCl\end{matrix}>C_6H_4$

The formation of the dihydride and dichloride, the ready oxidation to anthraquinone, and the Diels-Alder reaction (Part III), all indicate the high reactivity of the CH groups in the *meso*- or γ-positions in anthracene.

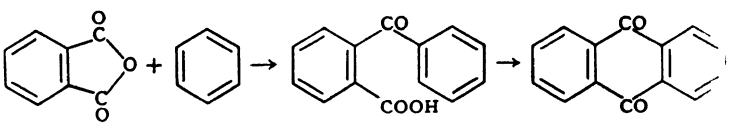
Anthraquinone, $C_{14}H_8O_2$, is formed, as already mentioned, when anthracene is oxidised with chromic or nitric acid.

[1] Compare footnote, p. 540.

Anthracene (1 part) is dissolved in boiling glacial acetic acid (about 12 parts), and a solution of chromic acid (2 parts) in glacial acetic acid is slowly added to the boiling solution. At the end of about 1½ hours, the solution is diluted with water, allowed to cool, and the anthraquinone is separated on a suction-filter ; the product is purified by recrystallisation from acetic acid or by sublimation.

Anthraquinone is manufactured by oxidising finely divided anthracene, suspended in water, with sodium dichromate and 50% sulphuric acid. The product is collected on a filter, washed, dried, and sublimed.

Anthraquinone may be produced synthetically, and is now prepared commercially, by treating a solution of phthalic anhydride in benzene with aluminium chloride ; *o-benzoylbenzoic acid*, (I), is first produced, but by the further action of the aluminium chloride (or of sulphuric acid), this intermediate product is converted into anthraquinone, (II), with the loss of a molecule of water,



I II

This synthesis proves that the molecule of anthraquinone contains two $C_6H_4<$ groups, united by two $CO<$ groups.

That the two $CO<$ groups occupy the *o*-position in the one benzene nucleus is known, because they do so in phthalic acid ; that they occupy the *o*-position in the second benzene nucleus has been proved as follows : When *bromophthalic anhydride* is treated with benzene and aluminium chloride, it gives *bromobenzoylbenzoic acid* which, with sulphuric acid, yields *bromoanthraquinone*,

$$\underset{A}{C_6H_3Br}\!<\!\begin{matrix}CO\\COOH\end{matrix}\!\!-\!\!\underset{B}{C_6H_5} = \underset{A}{C_6H_3Br}\!<\!\begin{matrix}CO\\CO\end{matrix}\!>\!\underset{B}{C_6H_4} + H_2O\ ;$$

in the molecule of this quinone the two $CO<$ groups are known to be united to the nucleus A in the *o*-position.

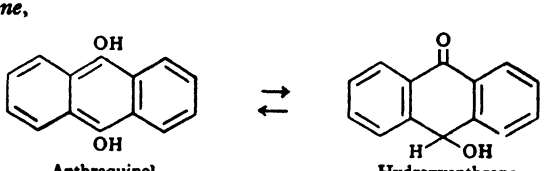
Now, when bromoanthraquinone is heated with potash at 160°, it is converted into *hydroxyanthraquinone*, which, with nitric acid, yields phthalic acid by the oxidation of the group A ; therefore the two $CO<$ groups are attached to B, as well as to A, in the *o*-position, and anthraquinone has the constitution represented

above. This conclusion confirms the structural formula of anthracene already given.

Anthraquinone crystallises from acetic acid in pale-yellow needles, melts at 286°, and sublimes at higher temperatures ; it is very stable, and is only with difficulty attacked by oxidising agents, sulphuric acid, or nitric acid. When it is distilled with zinc-dust, it is converted into anthracene. It resembles the aromatic ketones much more closely than it does the *p*-quinones ; it has no smell, is by no means readily volatile, and is not reduced by sulphurous acid ; unlike benzoquinone it is not an oxidising agent.

Test for Anthraquinone. When about 0·1 g. of finely divided anthraquinone is heated with dilute caustic soda and a little zinc-dust, an intense red colouration is produced, but when the solution is shaken in contact with the air, it is decolourised. In this reaction *anthraquinol* is formed, and dissolves in the alkali, forming a deep-red solution ; on exposure to the air, however, it is oxidised to anthraquinone, which separates as a flocculent precipitate.

Anthraquinol is formed from anthraquinone in the same way as quinol is produced from quinone and is a desmotrope of *hydroxyanthrone*,



Anthraquinol Hydroxyanthrone

Anthraquinone-β-monosulphonic acid, $C_{14}H_7O_2 \cdot SO_3H$, is formed, but only very slowly, when anthraquinone is heated with sulphuric acid at 250° ; with a large excess of anhydrosulphuric acid at 160–170°, a mixture of isomeric *disulphonic acids*, $C_{14}H_6O_2(SO_3H)_2$, is also formed. The **β-mono-**sulphonic acid is of considerable importance, as its sodium salt is employed commercially for the preparation of alizarin.

Alizarin, $C_{14}H_6O_2(OH)_2$, or 1:2-*dihydroxyanthraquinone*, occurs in madder (the root of *Rubia tinctorum*), a substance which has been used from the earliest times for dyeing Turkey-red, and which owes its tinctorial properties to two substances, alizarin and purpurin, both of which are present in the root in the form of glycosides.

Ruberythric acid, the glycoside of alizarin, is decomposed when it is boiled with acids, or when the madder extract is allowed to

undergo fermentation, with the formation of alizarin and one molecule each of glucose and xylose,

$$\underset{\text{Ruberythric acid}}{C_{26}H_{28}O_{13}}+2H_2O = \underset{\text{Alizarin}}{C_{14}H_8O_4}+C_6H_{12}O_6+C_5H_{10}O_5.$$

A dye of such great importance as alizarin naturally attracted the attention of chemists, and many attempts were made to prepare it synthetically. This was first accomplished in 1868 by Graebe and Liebermann, who found that alizarin could be produced by fusing *dibromoanthraquinone* [1] with potash,

$$C_6H_4\!<\!\overset{CO}{CO}\!>\!C_6H_2Br_2+2KOH = C_6H_4\!<\!\overset{CO}{CO}\!>\!C_6H_2(OH)_2+2KBr,$$

but the process was not a commercial success.

At the present day, however, madder is no longer used, and the alizarin of commerce is made from anthraquinone in the following manner, or by other synthetical methods :

Anthraquinone is sulphonated and the anthraquinone-β-monosulphonic acid is isolated in the form of its sparingly soluble sodium salt ; this is then heated with caustic soda and a little potassium chlorate, and is thus converted into the purple sodium derivative of alizarin,

$$C_6H_4\!<\!\overset{CO}{CO}\!>\!C_6H_3\cdot SO_3Na+3NaOH+O =$$
$$C_6H_4\!<\!\overset{CO}{CO}\!>\!C_6H_2(ONa)_2+2H_2O+Na_2SO_3;$$

from this sodium salt, alizarin is liberated with the aid of a mineral acid.

When anthraquinone-β-monosulphonic acid is fused with caustic soda, the —SO_3Na group is displaced by —ONa in the usual manner, but the *hydroxyanthraquinone* (sodium derivative) thus produced is further acted on by the alkali, giving the sodium derivative of the *dihydroxy*-compound (alizarin) and (nascent) hydrogen,

$$C_6H_4\!<\!\overset{CO}{CO}\!>\!C_6H_3(ONa)+NaOH = C_6H_4\!<\!\overset{CO}{CO}\!>\!C_6H_2(ONa)_2+2H.$$

The oxidising agent ($KClO_3$) is added in order to prevent the nascent hydrogen from reducing the still unchanged hydroxyanthraquinone.

[1] Obtained by heating anthraquinone with bromine and a trace of iodine in a sealed tube at 160°. It seems uncertain whether this product is a 1:2- or a 2:3-dibromo-compound, but the hydroxyl groups in alizarin certainly occupy the 1:2-position.

Alizarin may be prepared in the laboratory by fusing sodium anthraquinone-β-monosulphonate (10 parts), with caustic soda (30 parts) and potassium chlorate (1½ parts), in a silver basin on a sand-bath during some hours. The purple product is dissolved in water, the solution is filtered, if necessary, and the alizarin is precipitated with hydrochloric acid. The yellowish crystalline precipitate is collected on a filter, washed with water, dried, and recrystallised from toluene or sublimed.

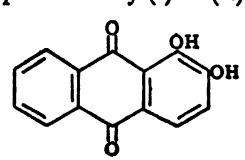
Alizarin crystallises and sublimes in dark-red prisms, which melt at 290°, and are almost insoluble in water, but moderately soluble in alcohol. As it is a dihydroxy-derivative of anthraquinone, it has the properties of a dihydric phenol; with aqueous solutions of alkalis it forms metallic derivatives, $C_{14}H_6O_2(OM)_2$, which are soluble in water, yielding intensely purple solutions. With acetic anhydride it gives a *diacetate*, $C_{14}H_6O_2(OAc)_2$, melting at 180°, and when distilled with zinc-dust, it is reduced to anthracene.

The value of alizarin as a dye is due to the fact that it yields coloured, insoluble compounds, called *lakes* (p. 659), with certain metallic hydroxides. When, for example, the purple solution of alizarin in ammonium hydroxide is added to an excess of an aqueous solution of potash alum, a red lake, the basis of a complex dye, 'Turkey red,' is formed; the ferric compound, obtained in a similar manner from iron alum, is violet-black, and lakes of other colours may be prepared from other hydroxides (p. 658).

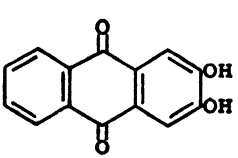
Constitution of Alizarin. Alizarin may be obtained by heating a mixture of phthalic anhydride and catechol with sulphuric acid at 150°,

$$C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle O + C_6H_4\langle\begin{matrix}OH\\OH\end{matrix} = C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle C_6H_2\langle\begin{matrix}OH\\OH\end{matrix} + H_2O.$$

This reaction is clearly analogous to that by which anthraquinone is prepared from benzene, and as catechol is *o*-dihydroxybenzene, it follows that the two hydroxyl groups in the product must also be in the *o*-position to one another; the structure of alizarin, therefore, must be represented by (I) or (II):



I



II

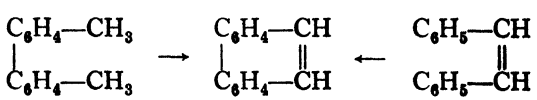
Now, alizarin yields two isomeric *mono*-nitro-derivatives, in both of which the nitro-group and the two hydroxyl groups are combined with one and the same nucleus; its constitution, therefore, must be represented by (I), because a substance having the constitution (II) could only yield *one* such nitro-derivative.

Besides alizarin, other *dihydroxy-* and also *trihydroxy-anthraquinones*, such as *purpurin* (1:2:4) and *anthrapurpurin* (1:2:7), have been obtained, but only those are of value as dyes which contain two hydroxyl groups in the same positions as in alizarin.

Phenanthrene, $C_{14}H_{10}$, an isomeride of anthracene, is a hydrocarbon of theoretical interest, but it has little commercial value. It occurs in considerable quantities in '50% anthracene,' from which it may be extracted with pyridine, as already described (p. 557). The resulting crude phenanthrene is converted into the picrate, which is first recrystallised from alcohol, to free it from anthracene picrate, and then decomposed by ammonia; the hydrocarbon is finally purified by recrystallisation.

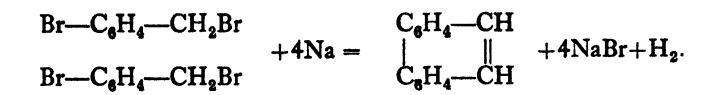
Phenanthrene forms lustrous needles, melts at 101°, and distils at about 332°; it is readily soluble in many organic liquids. When oxidised with chromic acid, it is first converted into *phenanthraquinone*, $C_{14}H_8O_2$ (isomeric with anthraquinone), and then into *diphenic acid*, $C_{14}H_{10}O_4$. This acid is decomposed when it is heated with soda-lime, yielding carbon dioxide and *diphenyl*; it is, therefore, *diphenyldicarboxylic acid*, and its formation from phenanthrene shows that the latter contains *two* benzene nuclei.

Further evidence as to its constitution is obtained by studying the methods of formation of phenanthrene. It is formed, for example, when o-*ditolyl* (prepared by treating o-*bromotoluene* with sodium) or *stilbene* [1] is passed through a red-hot tube, with the loss of hydrogen in both cases:

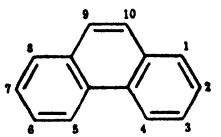


[1] *Stilbene*, or *αβ-diphenylethylene*, $C_6H_5 \cdot CH{:}CH \cdot C_6H_5$, may be prepared by treating benzaldehyde with benzyl magnesium chloride, as the secondary alcohol, $C_6H_5 \cdot CH(OH) \cdot CH_2 \cdot C_6H_5$, which is first produced, loses a molecule of water. It crystallises in prisms, melts at 124°, and, like ethylene, combines with bromine, forming *stilbene dibromide*, $C_6H_5 \cdot CHBr \cdot CHBr \cdot C_6H_5$ (m.p. 237°).

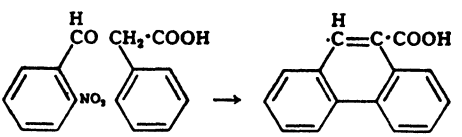
Phenanthrene is also produced, together with anthracene, by the action of sodium on o-*bromobenzyl bromide*,



The facts already given and many others prove that the structure of phenanthrene may be represented as follows : [1]



Many derivatives of phenanthrene may be synthesised by an important general method (Pschorr) : *o*-Nitrobenzaldehyde is condensed with phenylacetic acid and the product is reduced to the corresponding amino-compound ; the latter is then diazotised and the diazonium salt is treated with alcohol and copper powder, which transform it into *phenanthrene-9-carboxylic acid* with the evolution of nitrogen and the formation of a third closed chain.



Substituted phenylacetic acids, with at least one unoccupied *o*-position, and substituted *o*-nitrobenzaldehydes, may be used instead of the parent substances shown above, so that many phenanthrene derivatives of *known structures* may be thus prepared.

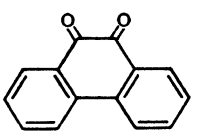
The 9:10 bond in phenanthrene has an olefinic character, as is shown by the addition of bromine, which gives 9:10-*phenanthrene dibromide*, and of hydrogen (in the presence of a catalyst) which gives 9:10-*dihydrophenanthrene* ; the oxidation (p. 567) of the hydrocarbon also occurs in the 9:10-positions.

[1] It should be noted that this formula, those just shown in the syntheses of phenanthrene, and that (II) given on p. 558, all express the same structure (compare p. 544). The numerals serve the usual purpose and are used in the case of all substitution products.

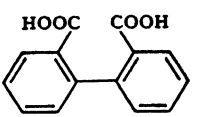
Phenanthrene may be nitrated and sulphonated but the products are usually complex mixtures; with bromine and a catalyst it gives 9-*bromophenanthrene*, from which a Grignard reagent may be prepared.

Some important alkaloids, such as morphine and codeine, and many other natural products (the steroids, Part III), are derivatives of hydrophenanthrenes.

Phenanthraquinone, (I), like anthraquinone, is formed by oxidising the hydrocarbon with chromic acid; it crystallises from alcohol in orange needles, and melts at 207°. In chemical properties it shows less resemblance to *p*-benzoquinone or to α-naphthaquinone, than to *o*-benzoquinone (p. 508), β-naphthaquinone (p. 551), and other *ortho*-diketones (*ortho*-quinones); it has no smell, and does not volatilise except when strongly heated, but it is readily reduced by sulphurous acid to 9:10-*dihydroxyphenanthrene*, $C_{14}H_8(OH)_2$, and it combines with sodium bisulphite, forming a soluble *bisulphite* compound, $C_{14}H_8O_2$, $NaHSO_3, 2H_2O$; it also yields a *dioxime*, $C_{14}H_8(:N\cdot OH)_2$ with hydroxylamine.



I



II

Diphenic acid, (II), obtained by the oxidation of phenanthrene or phenanthraquinone, crystallises in needles, and melts at 229°. When heated with acetic anhydride it is converted into *diphenic anhydride* (m.p. 217°).

This fact is noteworthy, because it shows that anhydride formation may occur, as in the case of naphthalene-1:8-dicarboxylic acid, even when the two carboxyl groups are united with *different* nuclei.

CHAPTER 37

PYRIDINE, QUINOLINE, *ISO*QUINOLINE, AND OTHER HETEROCYCLIC COMPOUNDS

Pyridine, *quinoline*, and iso*quinoline* are three closely related aromatic bases, which, together with their numerous derivatives, are of great theoretical interest; many of these derivatives occur in nature, and belong to the well-known and important class of compounds termed the *vegetable alkaloids*. Pyridine derivatives are obtained by the oxidation of coniine (p. 598) and nicotine (p. 599). *Quinoline* was first produced by fusing quinine and cinchonine (p. 607) with potash; it is also formed from strychnine (p. 609) under these conditions. Iso*quinoline* was first obtained from coal-tar; derivatives of this base are formed when the alkaloids *papaverine*, *narcotine* (p. 610), etc., are fused with potash.

Coal-tar, though consisting principally of hydrocarbons and phenols, contains small proportions of *pyridine* and its homologues; also *quinoline*, iso*quinoline*, and numerous other basic substances, including aniline. The pyridine bases are dissolved, in the form of their sulphates, in the purification of the 'light oil,' by treatment with dilute sulphuric acid (p. 373), and when the dark acid liquor is afterwards treated with an excess of caustic soda, they collect at the surface in the form of a dark-brown oil. By repeated fractional distillation, a partial separation of the various components of this oil may be effected, and crude pyridine may be obtained; by the crystallisation of their salts, or by other methods, the pyridine and some of its homologues may be prepared in a pure state.

A less important source of these bases is *bone-tar* or *bone-oil*, a dark-brown, unpleasant smelling liquid formed during the destructive distillation of bones, in the preparation of bone-black (animal charcoal); this oil contains considerable proportions of *pyridine* and *quinoline*, and their homologues, as well as other compounds such as *pyrrole* (p. 587). Bone-oil, purified by distillation, was formerly used in medicine under the name of *Dippel's oil*.

Pyridine and its Derivatives

Pyridine, C_5H_5N, is formed during the destructive distillation of various nitrogenous organic substances; hence its presence in

coal-tar and in bone-oil. It was discovered in bone-oil by Anderson in 1846.

Pure pyridine may be prepared by heating *nicotinic acid* (p. 575), or other pyridinecarboxylic acids, with soda-lime, just as pure benzene may be obtained from benzoic and phthalic acids.

For commercial purposes it is usually separated from coal-tar as already described; the crude product consists mainly of pyridine and its mono- and di-methyl derivatives, and is principally used as a solvent and in denaturing alcohol, in the preparation of methylated spirit.

Pyridine is formed when a mixture of acetylene and hydrogen cyanide is passed through a red-hot tube,

$$2C_2H_2+HCN = C_5H_5N,$$

but this synthesis gives little information as to the structure of the base. Pyridine is also obtained from piperidine (p. 571) and many of its derivatives have been produced from aliphatic compounds (p. 574).

Pyridine is a mobile liquid of sp. gr. 1·003 at 0°; it boils at 115°, is miscible with water, and possesses a pungent and very characteristic odour. It is a particularly stable substance, and is not attacked by boiling nitric acid, or by aqueous solutions of chromic acid or potassium permanganate; with halogens, and sulphuric acid, it gives *substitution* products, such as *β-monobromopyridine*, C_5H_4BrN, and *pyridine-β-sulphonic acid*, $C_5H_4(SO_3H)N$, but only with great difficulty.

Pyridine is readily reduced by *anhydrous* alcohol and sodium giving *piperidine* or *hexahydropyridine* (p. 572),

$$C_5H_5N+6H = C_5H_{11}N;$$

in the presence of water, however, the nitrogen atom is eliminated as ammonia, and *glutardialdehyde*, $CHO\cdot CH_2\cdot CH_2\cdot CH_2\cdot CHO$, is formed. When pyridine is heated with hydriodic acid at 300°, it gives pentane and ammonia.

Pyridine is a base and forms stable crystalline salts, such as the *hydrochloride*, C_5H_5N,HCl, and the *sulphate*, $(C_5H_5N)_2,H_2SO_4$. The *platinichloride*, $(C_5H_5N)_2,H_2PtCl_6$,[1] forms orange-yellow crystals melting at 240°, and is sparingly soluble in cold water;

[1] These formulae may also be written $[C_5H_5NH]Cl$, $[C_5H_5NH]_2SO_4$ and $[C_5H_5NH]_2PtCl_6$ respectively, as in the case of salts of amines and aromatic amino-compounds.

the *ferrocyanide* is also sparingly soluble and may serve for the purification of the crude base.

Pyridine is used in the production of methylated spirit, as a laboratory solvent, and as a catalyst; also to neutralise the acid formed in the benzoylation, etc., of organic bases.

Pyridine combines directly with methyl iodide (1 mol.) with the development of heat, giving an additive product, *pyridine methiodide*, C_5H_5N, CH_3I, or *methylpyridinium iodide*, $[C_5H_5NMe]I$, which crystallises from alcohol, melts at 118°, and has the properties of a quaternary ammonium salt.[1]

When methylpyridinium iodide is heated alone at 300° it undergoes isomeric change, and is converted into α- (and γ-) methylpyridine hydriodide; other alkyl halogen additive products show a similar behaviour, and the change is analogous to that which occurs in the case of the alkylanilines (p. 450).

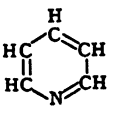
Constitution. The fact that pyridine is a base suggests some relation to the *amines*. It is, however, not a primary amine, because it does not give the carbylamine reaction; nor is it a secondary amine, because it does not react with nitrous acid; the necessary conclusion that pyridine is a *tertiary* base is further borne out by its behaviour towards methyl iodide. But since pyridine has the molecular formula, C_5H_5N, it is most improbable that it is an *open chain* tertiary amine, because such a compound would be highly unsaturated, and readily oxidised and resolved into simpler substances. The grounds for concluding that pyridine is not an unsaturated aliphatic amine are, in fact, much the same as those which led to the conclusion that the constitution of benzene is totally different from that of dipropargyl.

If now the properties of pyridine are compared with those of aromatic compounds, a general analogy is at once apparent; in spite of its great stability, pyridine shows, under certain conditions, the behaviour of an unsaturated substance, and, like benzene, naphthalene, and other closed chain compounds, yields *additive* products, such as *piperidine*.

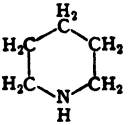
Considerations such as these led Körner, in 1869, to suggest that pyridine, like benzene, contains a closed chain or nucleus, as represented by the given formula (I, p. 571), and this view has long since been confirmed in a great many ways, notably in the following

[1] Nevertheless such salts of quaternary cyclic bases are usually named as *-inium* instead of *-onium* salts.

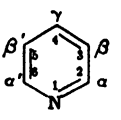
manner: *Piperidine*, or hexahydropyridine, which is formed by the reduction of pyridine, and which is reconverted into the latter on oxidation with sulphuric acid, has been prepared synthetically by a simple method (p. 573) which shows it to have the constitution (II); pyridine, therefore, may be represented by (I), the relation between the two compounds being the same as that between benzene and hexahydrobenzene,



Pyridine, I



Piperidine, II

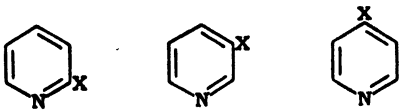


III

In accordance with this view, pyridine is structurally similar to benzene, from which, theoretically, it might be derived by the substitution of a tervalent nitrogen atom for one of the CH groups of the hydrocarbon; further, its molecule, like that of benzene, may show resonance, in which case its mesomeric form would not contain any double bond, and the linkages between the nitrogen atom and the two CH groups would be identical. These assumptions are fully confirmed by a study of the isomerism of pyridine derivatives, and the relationship between pyridine and quinoline (p. 577) affords further important evidence of the structures of the two compounds.

Isomerism of Pyridine Derivatives. The *mono*-substitution products of pyridine, as, for example, the *methylpyridines*, exist in *three* isomeric forms, which may be represented as derived from (III) (in its mesomeric state); the ring is numbered or lettered as above for the usual purpose.

Since a *mono*-substitution product may be formed by the displacement of any one of the five hydrogen atoms, the following *three*, but not more than three, isomerides may be obtained (footnote, p. 540):



The positions α and α' have been proved to be identical, and also the positions β and β', but the position γ is different from any of

the others; the letters are generally used instead of numerals to distinguish the *mono*-substitution products.

The *di*-substitution products, $C_5H_3X_2N$, exist in *six* isomeric forms, the positions of the substituents in the several isomerides being as follows, 2:3, 2:4, 2:5, 2:6, 3:4, 3:5.

All other positions are identical with one of these; 5:6, for example, is the same as 2:3, and 4:5 is identical with 3:4.

As regards the isomerism of its derivatives, pyridine may be conveniently compared with a mono-substitution product of benzene, as the effect of substituting a nitrogen atom for one of the CH groups in benzene, in this connection, is equivalent to that of displacing one of the hydrogen atoms of the hydrocarbon.

Compounds, such as pyridine, in which the linked atoms of the closed chain are not all the same, are classed as *heterocyclic*; those in which all such atoms are identical are *homocyclic*, and where these atoms are those of carbon, the compound is classed as *carbocyclic*. There are many different types of homocyclic and heterocyclic compounds; one or more atoms of nitrogen, oxygen, sulphur, etc., may be links of the latter systems.

Piperidine or *hexahydropyridine*, $C_5H_{11}N$, is formed, as already stated, when pyridine is reduced with sodium and alcohol; it may be prepared from pepper, which contains the alkaloid, *piperine* (p. 601), as the latter is decomposed by boiling alkalis yielding piperidine and piperic acid.

Piperidine boils at 106°, is miscible with water and has a very penetrating distinctive odour. It is a strong base, turns red litmus blue, and combines with acids forming stable, crystalline salts. When heated with concentrated sulphuric acid at 300°, or with nitrobenzene at 260°, it undergoes oxidation, with the loss of six atoms of hydrogen, and is converted into pyridine.

Piperidine is a *secondary aliphatic* amine and, with nitrous acid, it yields *nitrosopiperidine*, $C_5H_{10}N \cdot NO$, an oil, boiling at 218°; like secondary amines, moreover, it reacts with methyl iodide, giving *N-methylpiperidine hydriodide*,[1] $C_5H_{10}N \cdot CH_3,HI$ or $[C_5H_{10}NH \cdot CH_3]I$, and with acid chlorides, giving *N*-acyl derivatives, $C_5H_{10}N \cdot CO \cdot R$.

The important synthesis, already referred to, which establishes the constitution of piperidine, and also that of pyridine, was accom-

[1] The letter *N* before the name of the substituent signifies that the latter is directly combined with the nitrogen atom.

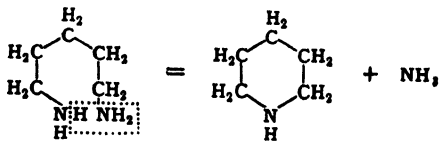
plished by Ladenburg as follows: *Trimethylene dibromide*[1] is heated with potassium cyanide in alcoholic solution, and is thus converted into *trimethylene dicyanide*,

$$Br\cdot CH_2\cdot CH_2\cdot CH_2\cdot Br+2KCN = CN\cdot CH_2\cdot CH_2\cdot CH_2\cdot CN+2KBr,$$

which, reduced with sodium and alcohol, yields *pentamethylenediamine*,

$$CN\cdot CH_2\cdot CH_2\cdot CH_2\cdot CN+8H = NH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot NH_2;$$

during this process some of the pentamethylenediamine is decomposed into piperidine and ammonia, and the same change occurs, but much more completely, when the hydrochloride of the diamine is distilled,



Piperidine is used as an accelerator in the vulcanisation of rubber and as a catalyst in many reactions.

Piperidine may be reconverted into an open chain compound in various ways: when, for example, *N*-benzoylpiperidine is treated with phosphorus pentachloride, it is converted into a dichloro-compound, $CH_2Cl\cdot[CH_2]_4\cdot N{:}CCl\cdot C_6H_5$, which decomposes when it is distilled, giving 1:5-*dichloropentane*, $CH_2Cl\cdot[CH_2]_3\cdot CH_2Cl$, and benzonitrile.

Derivatives of Pyridine. Many *alkyl* derivatives of pyridine occur in coal-tar and bone-oil, and, therefore, are present in the basic mixture obtained from light-oil in the manner already mentioned; they can be isolated only by repeated fractional distillation followed by crystallisation of their salts. The three (α, β, γ) isomeric *methylpyridines* or *picolines*, $C_5H_4(CH_3)N$, the six isomeric *dimethylpyridines* or *lutidines*, $C_5H_3(CH_3)_2N$, and the six *trimethylpyridines* or *collidines*, $C_5H_2(CH_3)_3N$, resemble the parent base in most respects; unlike the latter, however, they undergo oxidation more

[1] *Trimethylene dibromide*, $C_3H_6Br_2$, a heavy oil, b.p. 165°, is prepared by treating allyl bromide with concentrated hydrobromic acid at 0°,

$$CH_2Br\cdot CH{:}CH_2+HBr = CH_2Br\cdot CH_2\cdot CH_2Br.$$

Since trimethylene dibromide can be prepared from its elements, a *complete synthesis* of piperidine may be thus accomplished.

Trimethylene dibromide may also be obtained by treating trimethylene glycol with hydrobromic acid.

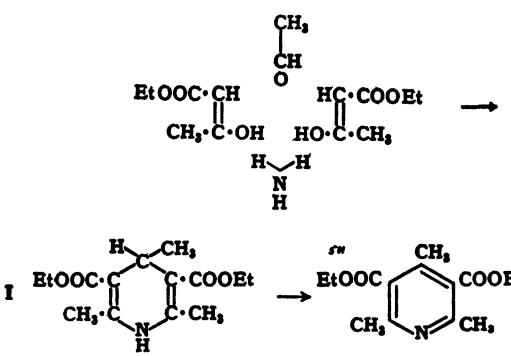
or less readily on treatment with a solution of potassium permanganate, and are converted into *pyridinecarboxylic acids*, just as the homologues of benzene yield benzenecarboxylic acids, by the oxidation of the alkyl groups or side chains to carboxyl groups,

$$C_5H_4(CH_3)N+3O = C_5H_4(COOH)N+H_2O,$$
$$C_5H_3(CH_3)_2N+6O = C_5H_3(COOH)_2N+2H_2O.$$

This behaviour has been of great use for the determination of the positions of the alkyl groups in many homologues of pyridine, that is to say, for their *orientation*; the carboxylic acids into which they are converted are easily isolated and identified by their melting-points and other properties, and their constitutions have been determined in a simple manner (p. 576).

Although pyridine itself is not easily synthesised, many of its derivatives have been obtained by the *condensation* of aldehydes with esters of β-ketonic acids in the presence of ammonia (Hantzsch).

Acetaldehyde, ethyl acetoacetate, and ammonia, for example, give *diethyl dihydrocollidinedicarboxylate* (I), which on oxidation is converted into *diethyl collidinedicarboxylate* (II). When the acid, obtained by hydrolysing this ester is heated with soda-lime, it is converted into 2:4:6-*trimethylpyridine* (*collidine*).



Since other aldehydes may be used instead of acetaldehyde, and various diketones in the place of ethyl acetoacetate, it is possible to synthesise many derivatives of pyridine by such reactions.

a- and γ-methylpyridine (but not the β-compound), like *o*- and *p*-nitrotoluene, condense with aldehydes; thus *a*-picoline and benzaldehyde, in the presence of zinc chloride, give *benzylidene-a-picoline*, $C_5H_4N\cdot CH{:}CH\cdot C_6H_5$. Similarly *a*- and γ-halogen

pyridines, like *o*- and *p*-chloronitrobenzene, react readily with ammonia, amines, etc., whereas the β-compound has the stability of unsubstituted aromatic halides; α- and γ-aminopyridines may be thus prepared, but the β-derivative is obtained by the Hofmann reaction from nicotinamide. α-Aminopyridine may also be prepared by the action of sodamide on pyridine.

The *aminopyridines* are much more readily substituted in the nucleus than is pyridine; β-aminopyridines, but not the α- and γ-bases, can be diazotised in the normal manner and the resulting diazonium salts undergo the usual reactions.

Hydroxypyridines behave like phenols in giving a colour with ferric chloride, and in having weakly acidic (also basic) properties, etc.; the α- and γ- (but not the β-) isomerides show tautomerism,



The *pyridinecarboxylic acids*, as a class, are perhaps the most important derivatives of pyridine, for the reason already given and because they are obtained as oxidation products of some of the alkaloids.

The three (α, β, γ) *monocarboxylic* acids may be prepared by oxidising the corresponding *picolines* or *methylpyridines* with potassium permanganate. The α-carboxylic acid is usually known as **picolinic acid** (m.p. 136°), because it was first prepared from α-picoline, whereas the β-compound is called **nicotinic acid** (m.p. 232°), because it was first obtained by the oxidation of nicotine (p. 599). The third isomeride—namely, the γ-carboxylic acid—is called *iso*nicotinic acid, and is the oxidation product of γ-picoline: when it is heated it sublimes without melting.

These monocarboxylic acids are all crystalline and soluble in water; they have both basic and acidic properties, and form salts with mineral acids as well as with bases, a behaviour which is similar to that of glycine.

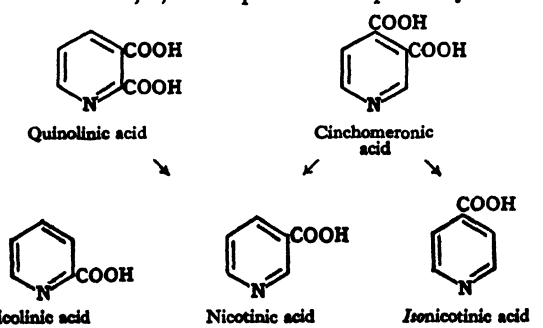
The α-carboxylic acid, and many other pyridinecarboxylic acids which contain a carboxyl group in the α-position (but only such), give a red or yellowish-red colouration with ferrous sulphate. A carboxyl group in the α-position, moreover, is usually very readily displaced by hydrogen when the acid is heated; picolinic acid, for example, is much more readily converted into pyridine than is nicotinic or *iso*nicotinic acid.

Quinolinic acid, $C_5H_3(COOH)_2N$ (*pyridine*-2:3-*dicarboxylic acid*), is produced by the oxidation of quinoline (p. 577) with potassium permanganate. It crystallises in prisms, is only sparingly soluble in water, and gives, with ferrous sulphate, an orange colouration, since one of the carboxyl groups is in the α-position. At 190° it decomposes into carbon dioxide and nicotinic acid, and when heated with lime, quinolinic acid, like *all* pyridinecarboxylic acids, is converted into pyridine.

Unlike phthalic acid, quinolinic acid is not converted into its anhydride when it is heated alone; nevertheless, when heated with acetic anhydride, it gives a crystalline *anhydride*, melting at 134°. This fact indicates that the carboxyl groups are in the *o*-position, as in phthalic acid; the formation of the acid from quinoline (p. 578) confirms this indication, and fully establishes the structure of the acid.

Cinchomeronic acid, $C_5H_3(COOH)_2N$ (*pyridine*-3:4-*dicarboxylic acid*), is produced by the oxidation of quinine (p. 607) with nitric acid, or of *iso*quinoline (p. 582) with potassium permanganate; it melts at about 260°, and when cautiously heated it is decomposed into nicotinic acid, *iso*nicotinic acid, and carbon dioxide.

Since the constitutions of quinolinic and cinchomeronic acids are proved by their methods of formation from quinoline and *iso*quinoline respectively, the fact that nicotinic acid is obtained from *both* these acids, which are 2:3 and 3:4 derivatives respectively, proves that nicotinic acid is pyridine-3-carboxylic acid; *iso*nicotinic acid which is also formed from the 3:4-acid, must therefore be pyridine-4-carboxylic acid; and the third isomeride, picolinic acid, pyridine-2-carboxylic acid. It should be noted that the α, β, and γ correspond with the 2, 3, and 4 positions respectively.



Quinoline and Isoquinoline

Quinoline, C_9H_7N (2:3-*benzopyridine*),[1] was first obtained by Gerhardt in 1842 by heating quinine with alkalis, hence its name. It occurs, together with iso*quinoline*, in that fraction of coal-tar and bone-oil bases (p. 568) which is collected between 236 and 243°, but it is difficult to obtain the pure substance from this mixture. On the other hand, quinoline is easily prepared synthetically by *Skraup's* reaction—namely, by heating a mixture of aniline and glycerol with sulphuric acid, together with arsenic acid or nitrobenzene, both of which act as oxidising agents.

Concentrated sulphuric acid (72 g.) is gradually added to a mixture of aniline (25 g.), arsenic acid (38 g.), and anhydrous glycerol (77 g.), and the mixture is then *very cautiously* heated in a large flask (with air condenser) on a sand-bath.[2] When the first reaction has subsided, the liquid is boiled during about 2½ hours. It is then diluted with water, and treated with an excess of caustic soda to liberate the quinoline and the unchanged aniline from their sulphates; the bases are then obtained from the mixture by distillation in steam. As these two bases cannot easily be completely separated by fractional distillation, the whole of the aqueous distillate is acidified with sulphuric acid, and sodium nitrite is added until nitrous acid is permanently present (p. 457); the solution is then heated in order to convert the diazonium salt into phenol, rendered alkaline with caustic soda, whereby the phenol is converted into a salt, and again submitted to distillation in steam. The quinoline is finally separated with the aid of a tap-funnel, dried over solid potash, and purified by fractional distillation.

Quinoline is a highly refractive oil, of sp. gr. 1·095 at 20°, and boils at 238°. It has a pleasant, characteristic smell, and is sparingly soluble in water. It forms crystalline salts, which, as a rule, are readily soluble in water, as, for example, the *hydrochloride*, C_9H_7N,HCl, and the *sulphate*, $(C_9H_7N)_2,H_2SO_4$. The *dichromate*, $(C_9H_7N)_2,H_2Cr_2O_7$, prepared by adding potassium dichromate to quinoline hydrochloride in aqueous solution, crystallises from water, in which it is only sparingly soluble, in glistening yellow needles,

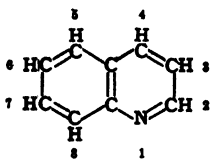
[1] The prefix benzo- or benz- is often used to indicate that a molecule contains a 'condensed' benzene ring (p. 541): thus naphthalene might be called benzobenzene and anthracene, 2:3-benzonaphthalene.

[2] The reaction is liable to be *very* vigorous, especially when nitrobenzene is used and, as soon as bubbles form, the burner is temporarily withdrawn.

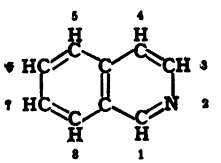
melting at 167°. The *platinichloride*, $(C_9H_7N)_2,H_2PtCl_6,2H_2O$, is only very sparingly soluble in water.[1]

Constitution. Quinoline is alkaline to litmus, but it does not give the reactions of a primary or those of a secondary base ; on the other hand, it combines with methyl iodide to form the additive product, *methylquinolinium iodide*[2] (*quinoline methiodide*), C_9H_7N,CH_3I or $[C_9H_7N\cdot CH_3]I$, m.p. 133°, and in this and other respects shows the behaviour of a *tertiary base.*

Now the relation between pyridine, C_5H_5N, and quinoline, C_9H_7N, is much the same as that between benzene, C_6H_6, and naphthalene, $C_{10}H_8$, both as regards molecular composition (the difference being C_4H_2 in both cases) and chemical behaviour ; possibly, therefore, quinoline is derived from pyridine, just as naphthalene is derived from benzene and, if so, its constitution would be expressed by one of the following formulae :



I



II

Further, quinoline differs from pyridine, just as naphthalene differs from benzene, in being relatively easily oxidised, and when heated with an alkaline solution of potassium permanganate it yields *quinolinic acid*, $C_5H_3(COOH)_2N$, a derivative of pyridine. This fact proves that the molecule of quinoline contains a pyridine nucleus ; but it also contains a benzene nucleus, as is shown by its formation from aniline by Skraup's method. Its constitution, therefore, must be expressed by *one* of the above formulae, as these facts admit of no other interpretation. But formula (II) is inadmissible, because it does not account for the formation of quinoline from aniline. For these and many other reasons, quinoline is represented by (I) (and *iso*quinoline, p. 582, by II).

The molecules of quinoline and of *iso*quinoline probably show the usual benzenoid resonance and in the mesomeric state all the carbon to carbon and nitrogen to carbon bonds would have the character

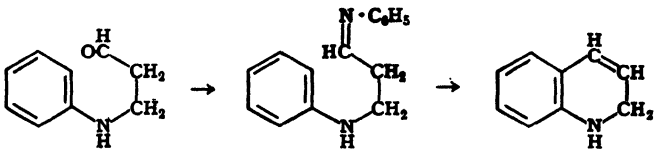
[1] Compare, footnote, p. 569. [2] Footnote, p. 570.

previously explained; the arrangement of single and double bonds in (I) and (II) is therefore chosen arbitrarily.

This formula, (I), shows clearly that quinoline is related both to benzene and to pyridine in structure and, therefore, in chemical behaviour; with its aid many syntheses of quinoline and its derivatives have been suggested and accomplished. It also accounts for the observed isomerism of quinoline derivatives, and shows, for example, that *seven* mono-substitution products, $X \cdot C_9H_6N$, should exist, because all the hydrogen atoms are differently situated; in the case of the *methylquinolines* all the seven isomerides are known.

The relationship between these and other isomerides, and the structures of quinoline derivatives in general, are easily expressed if the rings are numbered conventionally as above; positions 2, 3 and 4 in the pyridine ring of (I) are very often distinguished as α, β and γ respectively.

The formation of quinoline from aniline and glycerol by Skraup's reaction involves, no doubt, a series of changes. Probably acraldehyde, formed from the glycerol by the sulphuric acid, adds one molecule of aniline, (III), and condenses with a second; the product, (IV), then loses a molecule of aniline giving dihydroquinoline, (V), which is finally oxidised to quinoline.



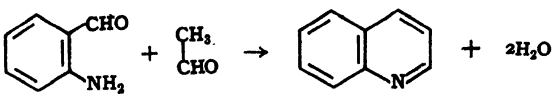
III IV V

That the condensation with the benzene nucleus takes place in the *o*-position to the amino-group is proved by the oxidation of quinoline to a pyridine derivative (quinolinic acid).

Many derivatives of quinoline may be obtained by Skraup's reaction, from substitution products of aniline, in which one at least of the *o*-positions to the NH_2— group is not occupied; when, for example, any one of the three toluidines is employed, a *methylquinoline* is formed, and it is known that the product is a *Bz*-methylquinoline, that is to say, that the methyl group is combined with carbon of the benzene nucleus. Further, the constitutions of the compounds obtained from *o*- and *p*-toluidine respectively are

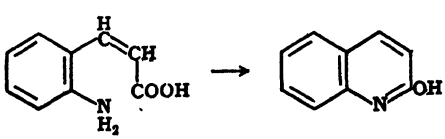
completely established, whereas in the case of *m*-toluidine, which gives *two* products, it is known that one of these is 5- and the other is 7-methylquinoline, although not which is which. Other Bz-derivatives of quinoline may be obtained in a similar manner, and Skraup's reaction may also be used for the preparation of analogues of quinoline from the naphthylamines and other aromatic amino-compounds.

Quinoline may also be obtained synthetically by other reactions which throw light on, or establish, its structure. It is formed when the vapour of allylaniline, $C_6H_5 \cdot NH \cdot CH_2 \cdot CH{:}CH_2$, is passed over strongly heated lead oxide and also when *o*-aminobenzaldehyde is condensed with acetaldehyde in the presence of dilute alkali,



Many quinoline derivatives can be prepared by the latter reaction, with the aid of a substituted *o*-aminobenzaldehyde and another aldehyde, ketone, or β-ketonic ester in the place of acetaldehyde (Friedländer).

2-*Hydroxyquinoline* (*carbostyril*) is produced by the reduction of *o*-nitrocinnamic acid (p. 528), which is first converted into *o*-amino-cinnamic acid, and then loses the elements of water,



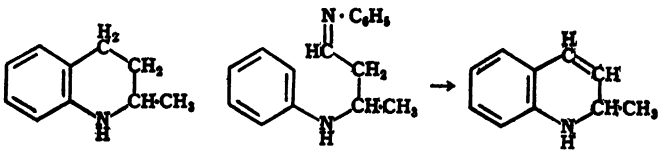
When hydroxyquinoline is treated with phosphorus pentachloride it gives *α-chloroquinoline*, which is reduced by hydriodic acid and converted into quinoline.

Since the carbonyl group of a carboxylic acid does not condense with an amino-group to form —N=C(OH)— it may be assumed that the *o*-aminocinnamic acid is first converted into its *lactam*, —NH—CO—, which then by tautomeric change gives the *lactim*, —N=C(OH)—.

Many derivatives of quinoline are obtained by the condensation of aniline or its substitution products with aldehydes in the presence of hydrochloric acid and zinc chloride (Döbner and Miller); aniline

and acetaldehyde, for example, give 2-*methylquinoline* (*quinaldine*), a base (b.p. 247°), which on reduction with sodium and alcohol is transformed into dl-*tetrahydroquinaldine* (b.p. 247°, I).

The *mechanism*, that is to say, the nature and sequence of the various reactions, in the formation of quinaldine is not known. Possibly crotonaldehyde, formed from acetaldehyde, reacts with aniline as does acraldehyde in the Skraup reaction, giving (II), which then condenses to (III) with the loss of aniline; from (III), quinaldine could then be produced by oxidation by an anil, such as $Ph \cdot N{:}CH \cdot CH_3$, which would be reduced to a secondary amino-compound.

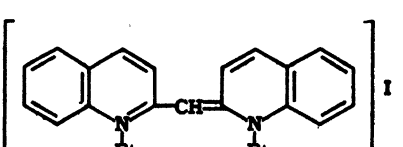


I II III

The properties of quinoline derivatives are in general similar to those of corresponding substances of the pyridine series.

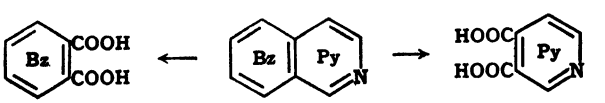
The methyl groups of α-methylquinoline (quinaldine) and γ-methylquinoline (lepidine) show the same reactivity as those of α- and γ-pyridines (p. 574). This reactivity is increased when the tertiary base is converted into a quaternary salt, and makes possible the preparation of various very important substances which are used for rendering photographic plates or films more sensitive to the green, yellow, or red rays of the spectrum, whereby their efficiency, particularly in long-distance photography is greatly enhanced.

A mixture of 2-iodoquinoline ethiodide and quinaldine ethiodide, for example, treated with alcoholic potash, gives 1:1′-*diethyl* pseudo*cyanine iodide*, (I). Similar substances are known in which the non-nuclear —CH= group of the *pseudo*cyanines is changed to —CH=CH—CH= (*carbocyanines*) whereas the *cyanines* have a —CH= group joining the nuclei in the 4:4′-, instead of the 2:2′-positions; krypto*cyanines* have a —CH=CH—CH= group, also in the 4:4′-positions.



***Iso*quinoline,** C_9H_7N (3:4-*benzopyridine*), occurs in coal-tar quinoline, and may be isolated by converting the mixed bases of the fraction collected at 236–243° into the hydrogen sulphates, C_9H_7N, H_2SO_4, and recrystallising the product from alcohol (88%) until the crystals melt at 205°. The sulphate of *iso*quinoline, thus obtained, is decomposed with alkali and the base is dried and distilled. *Iso*quinoline melts at 25°, and boils at 242°; it is a tertiary base, very like quinoline in chemical properties, and gives a crystalline *methylisoquinolinium iodide*, C_9H_7N, MeI (m.p. 159°).

The close relationship between quinoline and *iso*quinoline indicates that the molecule of the latter, like that of quinoline, is composed of a benzene and a pyridine nucleus condensed together. This view is established by the fact that when *iso*quinoline is oxidised with permanganate, it yields phthalic acid together with *cinchomeronic acid*, $C_5H_3(COOH)_2N$, which is known to be a pyridinedicarboxylic acid. The constitution of *iso*quinoline is therefore expressed by the formula given below, with the aid of which these results are easily explained; oxidation takes place in two directions, in the one case the pyridine (Py), in the other the benzene (Bz), nucleus being disintegrated:

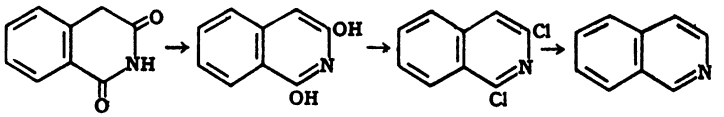


Phthalic acid — *Iso*quinoline — Cinchomeronic acid

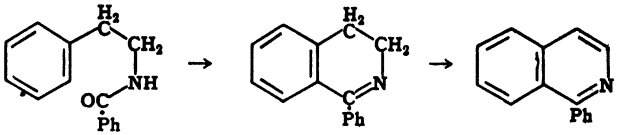
This view of the constitution of *iso*quinoline is also established by the following synthesis of the base: *o*-Nitrotoluene is converted into o-*cyanotoluene* (o-*tolunitrile*) by methods corresponding with those employed in preparing phenyl cyanide from nitrobenzene (p. 458), and this cyano-derivative is then chlorinated at its boiling-point. The product (o-*cyanobenzyl chloride*), $CN \cdot C_6H_4 \cdot CH_2Cl$, is treated with potassium cyanide, and the o-*cyanobenzyl cyanide*, $CN \cdot C_6H_4 \cdot CH_2 \cdot CN$, is transformed into o-*homophthalic acid*, $HOOC \cdot C_6H_4 \cdot CH_2 \cdot COOH$ (a *homo*logue of phthalic acid), by hydrolysis.

Homophthalimide, prepared by heating the ammonium salt of the acid (p. 521), may be directly converted into *iso*quinoline by passing its vapour over strongly heated zinc-dust. This change may also be brought about by treating the homophthalimide with

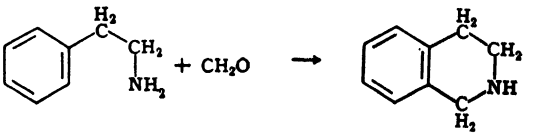
phosphorus oxychloride and then reducing the product (*dichloro-*isoquinoline) with hydriodic acid : [1]



*Iso*quinoline derivatives may be synthesised by heating acyl β-phenylethylamines with phosphorus pentoxide in toluene or xylene solution, and oxidising the resulting dihydro-compounds,



also by condensing β-phenylethylamine or one of its derivatives with aldehydes and oxidising the tetrahydro*iso*quinolines thus formed,



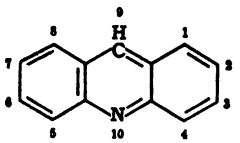
β-Phenylethylamine and its derivatives may be obtained by reducing the oximes of phenylacetaldehydes.

1-*Methyl*iso*quinoline*, but not 3-*methyl*iso*quinoline*, shows reactivity of the same kind as the α- and γ-derivatives of pyridine and quinoline.

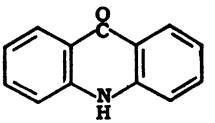
Acridine, $C_{13}H_9N$, occurs in crude coal-tar anthracene and is a crystalline, feebly basic compound, which melts at 111°, and sublimes even at 100° ; solutions of acridine or of its salts show a blue fluorescence. It behaves like a tertiary base, and combines directly with methyl iodide, giving *methylacridinium iodide* ; on oxidation with permanganate, it is converted into *acridinic acid* (quinoline-2:3-dicarboxylic acid), just as quinoline is converted into pyridine-2:3-dicarboxylic acid.

[1] In these and many similar formulae some of the C and H symbols of the *rings* are omitted, but symbols for hetero-atoms are always shown with their attached hydrogen atoms (if any) : a corner of a hexagon or pentagon from which only single lines are drawn indicates a CH_2 group, $>=O$ signifies $>C=O$, and so on.

Acridine is related to anthracene in the same way as quinoline is related to naphthalene and pyridine to benzene. There are unfortunately two systems in common use of numbering the acridine structure : that used here and in the sequel is as shown :



Acridine



Acridone

Acridine can be synthesised by heating diphenylamine with formic acid and zinc chloride, as the *N*-formyl derivative of the base undergoes an inner condensation, with the loss of the elements of water ; this is a general reaction, since by using other acids, many alkyl or aryl substituted acridines can be obtained.

Certain acridine derivatives are very important in medicine and surgery (p. 671).

9:10-*Dihydroacridine* can be obtained by the reduction of acridine and also by heating *oo'*-diaminodiphenylmethane with acids ; it is readily oxidised, giving acridine.

Acridone, $C_{13}H_9ON$, can be obtained by the oxidation of acridine and can also be synthesised in various ways, as, for example, by heating *phenylanthranilic acid* (N-*phenyl*-o-*aminobenzoic acid*), $C_6H_5 \cdot NH \cdot C_6H_4 \cdot COOH$, with sulphuric acid at 100° ; it melts at 354°, and towards methyl iodide behaves like a secondary base, giving N-*methylacridone*. With phosphorus pentachloride it reacts in the tautomeric form and gives 9-*chloroacridine*. When strongly heated with zinc-dust, it is reduced to acridine.

Cyclic bases. It will be seen from the above description of piperidine, pyridine, quinoline, etc., that aromatic bases in which the basic group, >NH, or >N, is *part of a closed chain*, show much the same chemical behaviour as *open chain*, secondary or tertiary bases respectively, so far as these particular groups are concerned.

The *secondary* bases, such as piperidine, which contain the >NH group, yield *nitrosoamines*, and with an alkyl halide, they are converted into *N*-alkyl substitution products, just as diethylamine, for example, gives triethylamine.

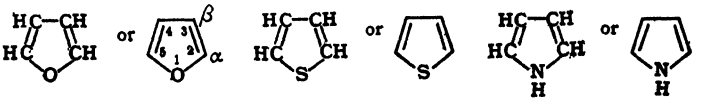
These alkyl derivatives of the secondary closed chain compounds

are therefore tertiary bases, and with alkyl halides, form *additive* products which are quaternary ammonium salts. The hydrogen atom of the >NH group in secondary closed chain bases is also displaceable by the acetyl and other acyl radicals.

The *tertiary* bases, such as pyridine and quinoline, in which the nitrogen atom is not directly united with hydrogen, do not yield nitroso- or acetyl derivatives, but they unite with *one* molecule of an alkyl halide giving *additive* quaternary compounds.

Furan, Thiophene, and Pyrrole

Furan, thiophene, and pyrrole are three *heterocyclic* compounds (p. 572), the structures of which may be respectively represented by the following formulae :



Furan Thiophene Pyrrole [1]

Each is the parent substance of many derivatives, which in some ways behave like aliphatic, and in others like aromatic, compounds, and thus form connecting links between the two types.

Furan, C_4H_4O, occurs in wood-tar and may be obtained by heating the barium salt of *furancarboxylic acid* with soda-lime (Limpricht); it boils at 32° and is practically insoluble in water. With hydrogen in the presence of Raney nickel it gives *tetrahydrofuran*, which is decomposed by hydrochloric acid into *4-chloro*-n-*butanol.*

Furfuraldehyde, $C_4H_3O \cdot CHO$ (*furfural*), is obtained quantitatively when pentoses, such as arabinose and xylose, are distilled with hydrochloric acid; it may be supposed that the pentose first loses two molecules of water,

$$H \cdot CH(OH) \cdot CH(OH) \cdot CH(OH) \cdot CH(OH) \cdot CHO \longrightarrow CH=CH \cdot CH=C(OH) \cdot CHO$$

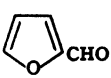
[1] The names ' furan ' and ' pyrrole ' are misleading, since the termination *an-* suggests *ane*, which denotes a saturated hydrocarbon, and *ole* suggests a phenolic ether, such as anisole.

and, by a further loss of water, is then converted into the aldehyde (I, below).

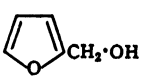
Furfuraldehyde is usually prepared by heating bran with dilute sulphuric acid and then distilling the product in steam.

It boils at 162°, and yields a phenylhydrazone (m.p. 97°), which is practically insoluble in water; by weighing the phenylhydrazone, which can thus be obtained when a vegetable product is distilled with acid, the quantity of the pentoses contained in the sample may be determined.

Furfuraldehyde shows most of the normal aldehyde reactions and can be oxidised and reduced in the usual manner. When shaken with caustic potash, it yields a mixture of furfuralcohol (II) and furancarboxylic acid, just as benzaldehyde gives benzyl alcohol and benzoic acid (p. 496). It may also be transformed into *furoin*, $C_4H_3O \cdot CO \cdot CH(OH) \cdot C_4H_3O$, and *furil*, $C_4H_3O \cdot CO \cdot CO \cdot C_4H_3O$, successively, in the same way as benzaldehyde is converted into benzoin and benzil (p. 501).



I

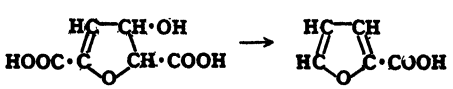


II

Furfuraldehyde may be very readily detected by the deep-red colour which it gives when aniline is added to its alcoholic solution. It is used with phenol in the preparation of synthetic resins.

Furancarboxylic acid, $C_4H_3O \cdot COOH$ (*furoic acid*, *pyromucic acid*), is prepared by oxidising furfuraldehyde with alkaline permanganate, but was first obtained by heating mucic acid.

Mucic acid, $COOH \cdot [CH(OH)]_4 \cdot COOH$, first loses the elements of water (2 mol.), giving *dehydromucic acid* (III), which is then decomposed into pyromucic acid (IV), carbon dioxide, and water,



III IV

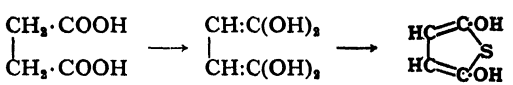
Furancarboxylic acid (m.p. 132°) is very like benzoic acid in properties and can, for example, be brominated, nitrated and sulphonated in the usual way.

Thiophene, C_4H_4S, was discovered by V. Meyer as a result of the observation that whereas coal-tar benzene shows the indophenin reaction (p. 376), pure benzene (from benzoic acid) does not.

At that time it was thought that the blue colouring matter, called indophenin, was formed by the condensation of one molecule of isatin with one molecule of benzene. V. Meyer showed that indophenin has the empirical formula, $C_{12}H_7ONS$, and is produced from isatin and thiophene (p. 594).

Thiophene may be extracted from coal-tar benzene (which contains about 0·6% of this sulphur compound) by shaking the crude hydrocarbon with concentrated sulphuric acid ; the thiophene dissolves in the form of *thiophenesulphonic acid*, $C_4H_3(SO_3H)S$, which may be isolated by one of the usual methods, and converted into its lead salt ; when the latter is heated with ammonium chloride, thiophene passes over.

Thiophene may also be obtained by heating sodium succinate with phosphorus trisulphide ; it may be assumed that in this reaction the succinic acid is first converted into the di-enolic isomeride, and then into *dihydroxythiophene*, which is finally reduced by hydrogen sulphide, formed during the reaction.



Under similar conditions, laevulic acid is converted into *methylthiophene*, C_4H_3MeS, a compound which occurs in crude coal-tar toluene.

Thiophene, b.p. 84°, and its derivatives show a remarkably close resemblance to benzene and its derivatives ; corresponding compounds have almost the same boiling-points, and are very similar in chemical properties.

Pyrrole, C_4H_5N, was discovered in bone-oil by Runge in 1834, and was more fully investigated by Anderson. It is formed by passing a mixture of acetylene and ammonia through a red-hot tube,

$$2C_2H_2+NH_3 = C_4H_5N+H_2,$$

by heating succinimide with zinc-dust, and by heating the ammonium salt of mucic acid with glycerol at about 200°. (Compare formation

of pyromucic acid and furan.) It boils at 131°, has an odour recalling that of chloroform, and turns brown on exposure to the air.

Pyrrole and its derivatives impart a crimson colour to a pine-chip moistened with hydrochloric acid and held in the vapour of the substance ; in contact with strong acids, pyrrole is rapidly converted into an orange-red substance (pyrrole red), hence the name, pyrrole, from Gr. *pyrros*, red.

Pyrrole is a very feeble base, and also, like diphenylamine, shows acidic properties ; when heated with potassium it gives a crystalline *potassium* derivative, C_4H_4NK, which, however, is hydrolysed by water.

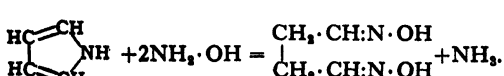
Pyrrole is of great physiological interest, because the molecules of some very important animal and vegetable substances, such as haemin and chlorophyll consist mainly of pyrrole nuclei (Part III).

Tetraiodopyrrole, C_4I_4NH, is obtained when pyrrole is treated with iodine and an alkali ; it forms brown, odourless crystals, which decompose at about 140°, and is sometimes used as an antiseptic in the place of iodoform.

Potassium pyrrole reacts with alkyl halides, giving *N*-alkyl derivatives, but when these compounds are strongly heated they undergo isomeric change ; the alkyl group *migrates* to the adjacent carbon atom and *C*-alkyl substitution products of pyrrole are formed (compare pyridine methiodide, p. 570). With methyl magnesium iodide pyrrole gives *N*-pyrryl magnesium iodide, which reacts with methyl iodide yielding mainly β-methylpyrrole ; with other alkyl halides, however, α-derivatives are formed.

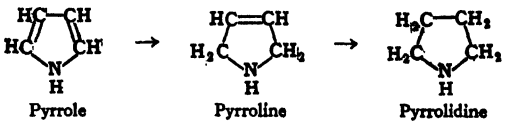
Very interesting reactions also occur when pyrrole is heated with sodium ethoxide and a di- or tri-halogen derivative of methane ; with methylene di-iodide, for example, pyridine is formed, whereas chloroform and bromoform give *β-chloro-* and *β-bromo-pyridine* respectively, by the inclusion of a CH or CX group in the pyrrole ring.

Another interesting change takes place when pyrrole is treated with hydroxylamine ; the closed chain undergoes *fission* and the dioxime of succindialdehyde is formed,



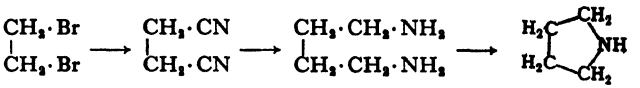
Reduction Products of Pyrrole. When pyrrole is reduced with zinc and acetic acid, it yields *pyrroline* (b.p. 91°), which on further

reduction with sodium and alcohol is transformed into *pyrrolidine* (b.p. 89°):

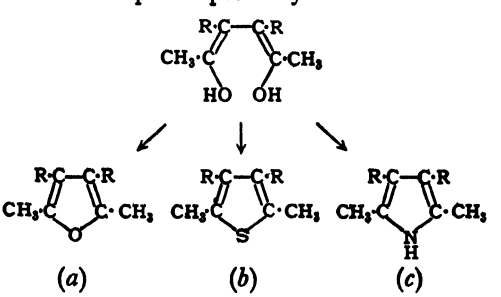


The reduction of pyrrole is accompanied by a great increase in the basic nature of the heterocyclic compound; pyrroline gives stable salts with acids, and pyrrolidine is strongly basic, like diethylamine or piperidine, which it closely resembles in other respects.

Pyrrolidine has been synthesised by reactions very similar to those employed in the synthesis of piperidine (p. 573), which may be summarised as follows:



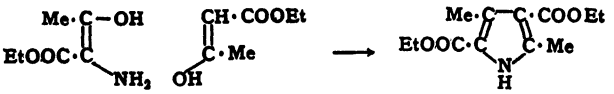
Many derivatives of furan, thiophene, and pyrrole may be prepared synthetically from 1:4- or γ-diketones such as *acetonylacetone*, $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CO \cdot CH_3$,[1] which contain the group —CO·CHR·CHR·CO—. When such diketo-compounds are treated with (*a*) sulphuric or hydrochloric acid, (*b*) phosphorus trisulphide, or (*c*) ammonia, they are transformed into derivatives of (*a*) furan, (*b*) thiophene, and (*c*) pyrrole respectively. In these changes the diketo-compound probably reacts in the di-enolic form:



In the place of 1:4-diketones, 1:4-dialdehydes and γ-ketonic esters (which can react in di-enolic forms) may also be used.

[1] Acetonylacetone is obtained when ethyl sodioacetoacetate is treated with chloroacetone, $CH_2Cl \cdot CO \cdot CH_3$, and the product is then submitted to ketonic hydrolysis.

Derivatives of pyrrole may be synthesised by condensing an α-aminoketone (or aminoketonic ester) with a β-ketonic ester (or β-diketone);



The amino-derivative is usually prepared by reducing an *iso*nitroso-compound and both reactions may sometimes be performed in one operation by reduction in the presence of the ketonic ester (or β-diketone) with zinc and acetic acid (Knorr.)

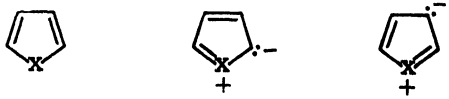
General properties of Furan, Thiophene and Pyrrole Derivatives. Furan derivatives are generally much more easily substituted than the corresponding benzene compounds and the entering group takes up the α-position, unless this is blocked; mercurichloride derivatives are readily produced. Alkyl furans can be halogenated, nitrated and sulphonated, and undergo the Friedel-Crafts reaction with acyl halides in the usual way. Halogenofurans are unreactive. Hydroxy-compounds do not react as phenols, and the di-enolic form of succinic anhydride, which would be dihydroxyfuran, is unknown. α-Aminofurans are very unstable and cannot be diazotised; the β-compounds can be diazotised but the resulting diazonium salts, although coupling with, for example, β-naphthol, do not show many of the usual reactions.

Derivatives of thiophene are also usually more reactive than those of benzene, but less so than those of furan; they are readily nitrated, sulphonated and mercurated, and undergo the Friedel-Crafts reaction with acyl halides. As with furan, substituents enter mainly the α-position. α-Thiophenealdehyde shows the reactions of benzaldehyde, but the aminothiophenes cannot be diazotised.

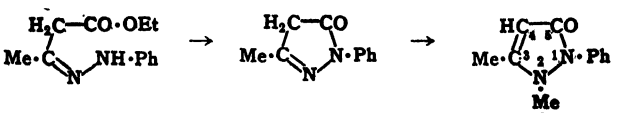
Pyrrole derivatives show the very facile substitutions characteristic of phenols, again in the α-position; they react with a mixture of hydrogen cyanide and hydrogen chloride, in the presence of aluminium chloride, as do phenols, giving aldehydes, and will couple with diazo-compounds yielding azo-derivatives, from which amines may be obtained by reduction. Even with iodine, tetraiodo-substitution derivatives are often formed. Sulphonation and nitration may occur normally, or resins may be formed, according to the nature of the substituents already present in the pyrrole ring.

It is seen, therefore, that in general the three heterocyclic compounds behave like aromatic rather than aliphatic substances, although they are not so stable as benzene; these properties are

probably due to resonance, and the contributory forms of the mesomeric structures might be as shown (X = O, S or NH):



Antipyrine, $C_{11}H_{12}ON_2$, *phenazone* or 1-*phenyl*-2:3-*dimethyl*-5-*pyrazolone*, is a rather important heterocyclic compound which is manufactured by heating ethyl acetoacetate with phenylhydrazine and then methylating the product with methyl chloride under pressure; the phenylhydrazone (I), which is first formed, loses a molecule of alcohol, giving a 1-*phenyl*-3-*methylpyrazolone* (II) which, when methylated, is converted into 1-*phenyl*-2:3-*dimethyl*-5-*pyrazolone* (III). As the structure of this compound (III) has been determined by other syntheses, it must be concluded that the 2:3-double binding in (II) migrates before methylation.

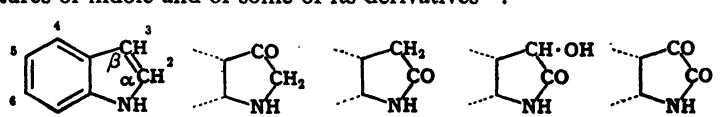


I II III

Antipyrine is crystalline (m.p. 114°), and readily soluble in water; it is a strong mono-acidic base, and is a potent antipyretic. Its *salicylate* is also used as an antipyretic, under the name of *salipyrine*.

Indole and its Derivatives

The molecule of indole is composed of a benzene nucleus which is *condensed* in the *o*-position with a pyrrole nucleus and may be called benzo- or pheno-pyrrole. Indole is related to indigo-blue, and some of its simpler derivatives were prepared by Baeyer in his researches on that very important dye. The following formulae, based principally on the results of Baeyer's work, show the structures of indole and of some of its derivatives [1]:



Indole Indoxyl Oxindole Dioxindole Isatin

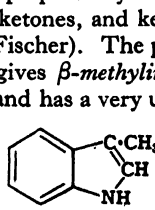
[1] The dotted lines indicate the benzene nucleus.

Most of these compounds show tautomerism, and give derivatives of either their enolic, —C(OH)=CH—, or lactim, —C(OH)=N—, forms (p. 580).

Indole, C_8H_7N, the parent substance of this group, is related to indene as well as to pyrrole and the other compounds shown above; some of its derivatives, such as *tryptophane* (p. 626), are of great interest, as they are found among the decomposition products of certain proteins; indole occurs in coal-tar, from which it is extracted commercially.

Indole can be obtained by heating oxindole or indigo-white (p. 681) with zinc-dust. It melts at 52°, is volatile in steam, and has an odour similar to that of α-naphthylamine; its vapours and its solutions impart a cherry-red colour to a pine-chip moistened with alcohol and hydrochloric acid, and, like indene, it forms a crystalline picrate. It is only a feeble base, and is converted into resinous substances by acids. Its properties in general are similar to those of pyrrole, but it usually undergoes substitution in the β-, instead of the α-position.

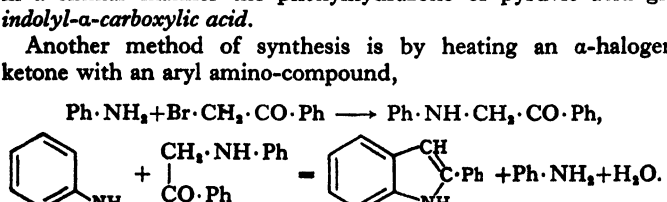
Many indole derivatives have been prepared by heating the phenylhydrazones of aliphatic aldehydes, ketones, and ketonic acids with hydrochloric acid or zinc chloride (Fischer). The phenylhydrazone of propionaldehyde, for example, gives *β-methylindole* (*skatole*), a compound which occurs in faeces, and has a very unpleasant smell,

$$C_6H_5\cdot NH\cdot N{:}CH\cdot CH_2\cdot CH_3 =$$  $$+NH_3;$$

in a similar manner the phenylhydrazone of pyruvic acid gives *indolyl-α-carboxylic acid.*

Another method of synthesis is by heating an α-halogeno-ketone with an aryl amino-compound,

$$Ph\cdot NH_2 + Br\cdot CH_2\cdot CO\cdot Ph \longrightarrow Ph\cdot NH\cdot CH_2\cdot CO\cdot Ph,$$



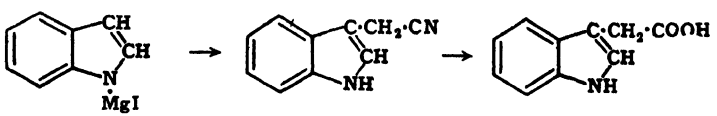
2:3-*Dihydroindole*, *indoline*, C_8H_9N, may be prepared by the reduction of indole with hydrogen in the presence of nickel; it boils at 230° and is a strong secondary base. With nitrous acid it gives a nitrosoamine and with phenyldiazonium chloride, a diazo-amino-compound, both of which undergo isomeric changes with

acids similar to those of the corresponding benzene derivatives (R = NO or N_2Ph),



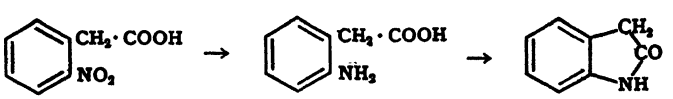
Indolyl-3-acetic acid, heteroauxin (m.p. 164°), is a very interesting substance. It has been isolated from urine and is one of those compounds, plant hormones or vitamins, known as auxins, which regulates the growth of plants.

It may be prepared from indolyl magnesium iodide and chloroacetonitrile, followed by hydrolysis,



Indoxyl, C_8H_7ON, is produced by fusing phenylglycine or phenylglycine-*o*-carboxylic acid with caustic alkalis in the absence of air (p. 682). It forms yellow crystals, melts at 85°, and in alkaline solution undergoes atmospheric oxidation, giving indigo-blue (indigotin). The α-methylene group is reactive and condenses with aldehydes, giving *indogenides*; similarly, with isatin it gives *indirubin*, an isomeride of indigo.

Oxindole, C_8H_7ON, can be obtained by reducing isatin or dioxindole, and also by the reduction of *o*-nitrophenylacetic acid,



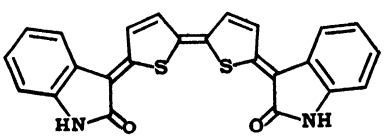
this last reaction shows that oxindole may be regarded as the lactam of *o*-aminophenylacetic acid, into a salt of which it is converted by hot alkali. Oxindole crystallises in needles, melting at 127°, and, in a moist condition, is oxidised to dioxindole on exposure to the air. The β-methylene group is reactive and condenses with nitrous acid, benzaldehyde, etc., in the usual way.

Dioxindole, $C_8H_7O_2N$, is obtained by reducing isatin with zinc-dust and hydrochloric acid; it melts at 180°, and when treated with sodium amalgam and water, it is converted into oxindole. In aqueous solution it undergoes atmospheric oxidation to isatin.

Isatin, $C_8H_5O_2N$, is produced by oxidising indigo-blue with nitric acid; it crystallises in orange-red prisms, melting at 203°, and is practically insoluble in cold water, but it dissolves readily in caustic alkalis, giving *yellow* solutions of salts derived from the *lactim*. When isatin is treated wtih phosphorus pentachloride in benzene solution, it is converted into *isatin chloride*, also a derivative of the lactim, which gives indigotin on reduction with zinc-dust and acetic acid.

The β-carbonyl group in isatin shows the normal ketonic reactions with hydroxylamine, hydrazines, hydrocyanic acid, etc., and condenses easily with reactive methylene groups such as those in acetone and indoxyl (p. 593).

The indophenin reaction (p. 376) is due to a similar condensation with the reactive hydrogen atoms of thiophene.

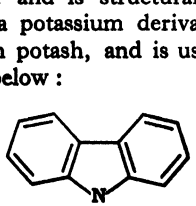


Indophenin

With aqueous alkali isatin gives a salt of *isatinic acid*. It can be acetylated and benzoylated in the usual manner and chlorinated, nitrated and sulphonated in the 5-position (p. 591). Its sodium salt with methyl iodide gives an *N*-methyl derivative, but the silver salt gives an *O*-ether.

Isatin can be synthesised by treating *o*-nitrobenzoyl chloride with silver cyanide, hydrolysing the cyanide to the acid, and then reducing the latter; the *o-aminobenzoylformic acid* (*o-aminophenylglyoxylic acid, isatinic acid*), $C_6H_4(NH_2)\cdot CO\cdot COOH$, thus formed passes spontaneously into its lactam, isatin.

Carbazole (*dibenzopyrrole*), $C_{12}H_9N$, occurs in crude anthracene obtained from coal-tar and is structurally related to indole. It melts at 246°, forms a potassium derivative, $C_{12}H_8NK$, when it is strongly heated with potash, and is used in making dyes. Its constitution is shown below:



CHAPTER 38

VEGETABLE ALKALOIDS

FROM very early times many crude products of the vegetable kingdom have been used in medicine, and subsequently the physiologically active compounds contained therein were isolated and studied. As a rule they were found to be nitrogenous substances, having a basic or alkaline character, and were therefore classed as the *vegetable alkaloids*. This term is still used, but can hardly be defined; it is applied to compounds which differ widely in properties and in constitution, but broadly, a vegetable alkaloid is a nitrogenous, basic compound which often has a pronounced physiological action. The term alkaloid, may also be applied to similar active substances prepared synthetically, and not known to occur in nature. The following general statements refer more particularly to the important medicinal products of the vegetable kingdom.

Most alkaloids are composed of carbon, hydrogen, oxygen, and nitrogen, have a relatively high molecular weight, and are crystalline and non-volatile, but a few, notably *coniine* and *nicotine*, are composed of carbon, hydrogen, and nitrogen only, and are volatile liquids; with the exception of these liquid compounds, which are readily soluble, the alkaloids are usually sparingly soluble in water, but they dissolve in alcohol, chloroform, ether, and other organic solvents; with acids, they form salts, most of which are soluble in water and crystallise well. Most alkaloids are optically active, usually laevorotatory (coniine is dextrorotatory), and have been largely used for the resolution of *dl*-acids. Many alkaloids have a very bitter taste, and are highly poisonous; many, moreover, are extensively used in medicine, and their value in this respect can hardly be overrated.

The extraction of alkaloids from plants, and their subsequent purification, are frequently matters of considerable difficulty, partly because, in many cases, two or more similar alkaloids occur together, partly because soluble, neutral and acidic substances, such as glycosides, tannic acid, malic acid, etc., are often also present in the crude product in large proportions. Generally speaking, the alkaloids may be extracted from the macerated vegetable matter

with dilute acids, which convert the alkaloids into soluble salts. The filtered solution may then be treated with sodium carbonate or ammonia to liberate the alkaloids, which, when they are sparingly soluble, are precipitated, and may be separated by filtration ; if not, the alkaline solution is extracted with ether, chloroform, etc.[1] An alternative procedure is to macerate the vegetable product with alkali, extract the alkaloid with a solvent, and then shake the solution with a dilute acid ; the neutral substances remain in the organic solvent, while the alkaloid dissolves in the aqueous layer in the form of a salt. The alkaloid or its salt is then further purified by recrystallisation, or in some other manner. Several examples of the extraction of alkaloids are given later in some detail (pp. 607, 609, 610).

Most alkaloids give insoluble precipitates with a solution of tannic, picric, phosphomolybdic, or phosphotungstic acid, and with a solution of mercuric iodide in potassium iodide, etc. ; these reagents, therefore, are often used for their detection and isolation. In cases of alkaloid poisoning, it is usual, after the stomach-pump has been used, to wash out the stomach with dilute tannic acid, or to administer strong tea (which contains tannin), in order to render the alkaloids insoluble, and relatively harmless.

Generally speaking, the alkaloids are tertiary aromatic bases, but the constitutions of some of them have not yet been fully established, owing partly to their complexity, partly to the difficulty of resolving them into simpler molecules, which might throw some light on their structures. The more important general methods, which have been used to determine the constitution of an alkaloid, may be summarised as follows :

(1) Hydrolysis : For the decomposition of esters (p. 603) and amides (p. 601).

(2) Fusion with alkali, destructive distillation with zinc-dust, etc. : Under such treatment many alkaloids afford simpler compounds of known structure, such as pyridine, quinoline, *iso*quinoline, etc.

(3) Decomposition with hydriodic acid : Many alkaloids contain one or two, sometimes three or more, methoxy-groups, (—O·CH_3),

[1] A mixture of benzene (3 vol.) and amyl alcohol (1 vol.) is often used by pharmacists, under the name of ' benzolated amylic alcohol,' as a solvent for the extraction of alkaloids.

united with a benzenoid nucleus, and when they are heated with concentrated hydriodic acid, they give methyl iodide and a hydroxy-compound (p. 484),

$$n(\text{—O·CH}_3)+n\text{HI} = n(\text{—OH})+n\text{CH}_3\text{I};$$

by estimating the methyl iodide, obtained from a given quantity of a compound of known molecular weight, it is possible to ascertain the number of methoxy-groups in the molecule; other alkyloxy-groups may be determined in a similar manner. This method was first devised by Zeisel, and is of general application; it is conveniently carried out as follows:

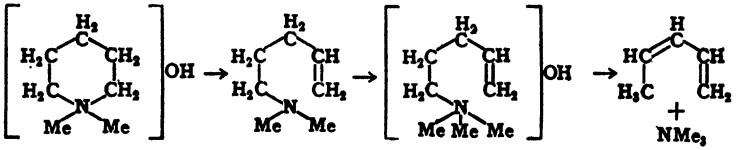
A weighed quantity (0·2–0·4 g.) of the alkaloid is placed in a long-necked distillation flask, together with an excess (15–25 c.c.) of *distilled* hydriodic acid (b.p. 126°), free from hydrogen sulphide.[1] The outlet tube of the flask is connected with two small wash-bottles (in series), which contain a concentrated aqueous-alcoholic solution of silver nitrate, and a slow stream of carbon dioxide (free from hydrogen chloride) is passed into the hydriodic acid and through the whole apparatus. The distillation flask is heated in an oil- or glycerol-bath, so that the hydriodic acid is raised nearly to its boiling-point. The methyl iodide, which is formed, reacts with the silver nitrate, and the precipitated silver iodide is afterwards estimated.

(4) *Exhaustive methylation* followed by the decomposition of the product: This combined process is used for the elimination of a nitrogen atom from a base, and the first step is to convert the base into a quaternary hydroxide by treatment with methyl iodide and silver (hydr)oxide alternately. Piperidine, for example, is thus transformed into *N*-methylpiperidine hydriodide, *N*-methylpiperidine, *dimethylpiperidinium iodide* and *dimethylpiperidinium hydroxide* (I) successively.

When strongly heated, the hydroxide loses the elements of water and gives *pentylenedimethylamine* (II). (Compare tetraethylammonium hydroxide, p. 219.) This base is now methylated and the quaternary hydroxide (III) is finally decomposed into 1-*methylbutadiene* (*piperylene*, IV) and trimethylamine. The primary product

[1] Hydriodic acid, prepared from iodine and hydrogen sulphide, often contains the latter; in that case the precipitated silver iodide is contaminated with silver sulphide, and should be boiled with dilute nitric acid before it is collected.

of this last reaction is probably $CH_2{:}CH \cdot CH_2 \cdot CH{:}CH_2$, which undergoes isomeric change into 1-methylbutadiene :



I II III IV

(5) Graded oxidation : With the aid of various oxidising agents, the molecule of the alkaloid may be disintegrated, giving simpler compounds, the structures of which are known or may be determined (pp. 600, 608).

By the combination of methods such as these, the structures of many of the less complex alkaloids have been settled and the compounds themselves have then been synthesised. Even before the complete constitutional formula has been determined, it may have been possible to prove that a given alkaloid is derived from some known compound. A classification of the alkaloids based on such knowledge of their structures thus becomes possible, and is adopted in the following account of the more important members of this group.

Alkaloids derived from Pyridine

Coniine, $C_8H_{17}N$, one of the relatively simple alkaloids, is contained, with other bases, in the spotted hemlock (*Conium maculatum*), more particularly in the seeds, from which it may be obtained by distillation with an aqueous solution of caustic soda. It is an oil, boiling at 166°, and readily soluble in water ; it has a most penetrating odour, and turns brown on exposure to the air. Coniine is a strong secondary base ; its *hydrochloride*, $C_8H_{17}N, HCl$, and most of its other salts are readily soluble in water. Both the base and its salts are exceedingly poisonous,[1] and cause death in a short time by paralysing the muscles of respiration. Coniine is dextrorotatory.

Coniine hydrochloride distilled over heated zinc-dust, gives *conyrine*,[2]

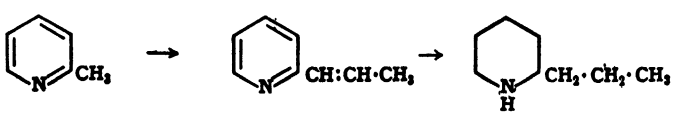
$$C_8H_{17}N \longrightarrow C_8H_{11}N + 3H_2,$$

[1] Persons condemned to death in ancient Greece were often poisoned with hemlock ; it was in this way that the life of Socrates was ended.

[2] As a rule, strongly heated zinc-dust acts as a reducing agent (p. 412).

which on oxidation yields pyridine-α-carboxylic acid (picolinic acid). Conyrine, therefore, is either α-propyl- or α-*iso*propyl-pyridine. Hydriodic acid converts coniine into *normal* octane and ammonia; the side chain in conyrine, therefore, is a *normal* propyl and not an *iso*propyl group. From these and other facts it would appear that coniine is d-*α-propylpiperidine* (III).

This structure was fully confirmed by Ladenburg's synthesis of the compound; as this was the first case in which a naturally occurring alkaloid was obtained artificially, the synthesis is of great historical interest: Piperidine (which can be obtained from its elements, p. 573) is converted into pyridine [1] (p. 572), and from the latter the methiodide is prepared. This salt is heated at 300°, whereby it is transformed into α-picoline (methylpyridine) hydriodide (p. 570). The α-picoline (I), heated with acetaldehyde (or paraldehyde) at 250°, is transformed into *α-propenylpyridine* (II), which is then reduced to *α-propylpiperidine* (*dl*-coniine, III) with sodium and alcohol. The *dl*-coniine is next converted into its *d*-tartrate, and the salt is fractionally crystallised from water; the more sparingly soluble salt of the *d*-base, which is deposited (leaving the salt of the *l*-base in the mother-liquor), is separated and decomposed with alkali. The *d*-coniine thus obtained is identical with that from hemlock.



I II Coniine, III

Nicotine, $C_{10}H_{14}N_2$, is present in the leaves of the tobacco-plant (*Nicotiana tabacum*), combined with malic or citric acid, and may be obtained from these leaves by the methods already indicated (p. 595).

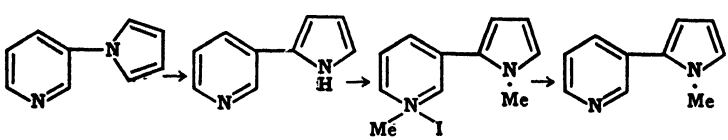
It is an oil, boils at 247° at 730 mm., has a very pungent odour, and rapidly turns brown on exposure to the air; it is readily soluble in water and organic solvents, and is laevorotatory. Nicotine is exceedingly poisonous, and two or three drops taken into the stomach are sufficient to cause death in a few

[1] Although coniine is a derivative of piperidine, it is necessary here to convert the piperidine into pyridine in order to substitute a methyl group for an α-hydrogen atom of the nucleus (p. 570).

minutes. It shows no very characteristic reactions, but its presence may be detected by its extremely pungent odour (which recalls that of a foul tobacco-pipe). The crude base is an important insecticide.

Nicotine is a di-acidic base, and forms crystalline salts, such as the *hydrochloride*, $C_{10}H_{14}N_2, 2HCl$. It combines directly with two molecules of methyl iodide, yielding *nicotine dimethiodide*, $C_{10}H_{14}N_2, 2CH_3I$, a fact which shows that it is a di-tertiary base (p. 585). When oxidised with chromic acid it yields nicotinic acid (pyridine-β-carboxylic acid); it is, therefore, a β-pyridine derivative.

The results of various investigations having indicated that the β-substituent is a univalent radical derived from *N*-methylpyrrolidine (p. 589), the synthesis of nicotine was accomplished by Pictet as follows [1]: Nicotinic acid (pyridine-β-carboxylic acid) was transformed successively into its ester and its amide, and the latter was converted into β-aminopyridine by Hofmann's reaction. The salt formed from β-aminopyridine and mucic acid (p. 313), when heated, gave N-*β-pyridylpyrrole* (I), which, like other *N*-substitution products of pyrrole (p. 588), underwent isomeric change into *β-pyridyl-α-pyrrole* (II) when it was passed through a heated tube. This *C*-pyrrole derivative, with potash and methyl iodide, gave the product (III), which, heated with lime, was converted into *nicotyrine* (IV), a base which is obtained by the oxidation of nicotine with silver oxide :

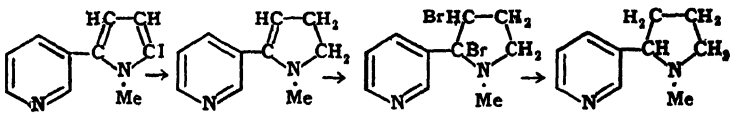


I II III IV

Now nicotyrine could not be directly reduced to nicotine, because those reagents which effected the reduction of the pyrrole ring also added hydrogen to the pyridine nucleus. This difficulty was overcome by treating the nicotyrine with iodine and caustic soda, and reducing the iodo-substitution product (V) with zinc and hydrochloric acid The *dihydronicotyrine* (VI), thus formed, was converted into its dibromide (VII), which, on reduction with tin

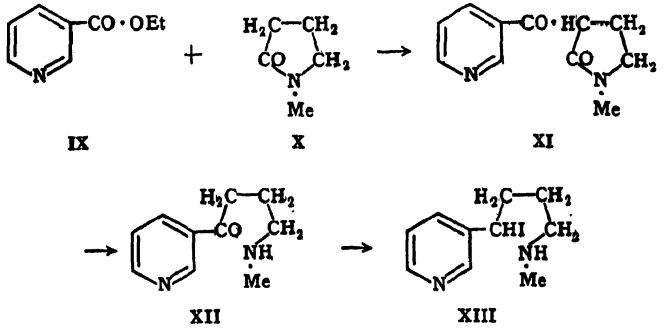
[1] The syntheses of nicotine and those of some of the simpler alkaloids described in this chapter will indicate the manner in which it is possible to build up relatively complex molecules, when their structures have been determined by analytical processes, such as those already mentioned; their committal to memory is unnecessary except for Honours Degree students.

and hydrochloric acid, yielded *dl*-nicotine (VIII); the resolution of this base with tartaric acid furnished *l*-nicotine, identical with the naturally occurring compound :



V VI VII Nicotine, VIII

Later, a somewhat simpler synthesis was devised by Späth and Bretschneider : The ethyl ester of nicotinic acid (IX) condenses with *N*-methyl-α-pyrrolidone (X), in the presence of sodium ethoxide, yielding a substance (XI) which changes into (XII), with the loss of carbon dioxide, when it is heated with hydrochloric acid. This ketone (XII) is then reduced (zinc-dust and alkali) to the corresponding alcohol, which is converted into the iodide (XIII) with hydriodic acid. Aqueous alkali transforms the iodide into *dl*-nicotine (VIII), which may be resolved as before :



IX X XI XII XIII

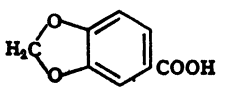
Piperine, $C_{17}H_{19}O_3N$, occurs to the extent of about 8–9% in pepper, especially in black pepper (*Piper nigrum*), from which it is easily obtained by warming the ground peppercorns with milk of lime, evaporating the mixture to dryness, and extracting the residue with ether.

It melts at 129°, and is almost insoluble in water; it is only a very weak base, is optically inactive, and is not of any physiological importance. On hydrolysis it gives piperidine and piperic acid,

$$C_{17}H_{19}O_3N + H_2O = C_5H_{11}N + C_{12}H_{10}O_4,$$

and it may be obtained again by treating piperidine with the chloride of piperic acid.

Piperic acid unites directly with four atoms of bromine, yielding a compound, $C_{12}H_{10}O_4Br_4$, and therefore its molecule probably contains two ethylenic linkages. On oxidation it gives piperonylic acid, which is known to have the structure (I), because it is decomposed by boiling hydrochloric acid into protocatechuic acid (II) and carbonaceous substances. Piperic acid therefore must contain only one (unsaturated) side chain (which gives rise to the carboxyl group of piperonylic acid), and is probably represented by (III),



I

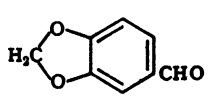


II

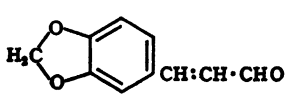


III

This conclusion was confirmed and the complete synthesis of piperine was accomplished in the following manner: Protocatechuic aldehyde, obtained from catechol by the Tiemann-Reimer reaction, is treated with methylene di-iodide and alkali and is thus transformed into *piperonal* (IV), a compound obtained by oxidising piperic acid with permanganate. Piperonal is condensed with acetaldehyde to yield (V), which with sodium acetate and

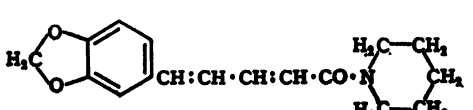


IV



V

acetic anhydride (Perkin reaction), gives piperic acid (III). The chloride of piperic acid reacts with piperidine to form piperine, and thus the structure of the alkaloid is proved to be as shown:



Piperine

Atropine, $C_{17}H_{23}O_3N$ (daturine), is prepared from the deadly nightshade (*Atropa Belladonna*) which, like henbane (*Hyoscyamus niger*), and thorn apple (*Datura Stramonium*), contains various isomeric and closely related alkaloids, of which atropine and *hyoscyamine* are the more important; the latter is optically active, but readily racemises on treatment with bases, giving atropine. Atropine, therefore, is *dl*-hyoscyamine.

Atropine crystallises in prisms, and melts at 118°; it is readily soluble in alcohol and ether, but almost insoluble in water. It is a strong base, and forms well-characterised salts, of which the *sulphate*, $(C_{17}H_{23}O_3N)_2,H_2SO_4$, is readily soluble, and, therefore, most commonly used in medicine; both the base and its salts are extremely poisonous, about 0·15–0·2 g. causing death. Atropine sulphate is largely used in ophthalmic surgery, owing to its remarkable property of dilating the pupil, when its solution is applied to the eye.

Test for Atropine. When a trace of atropine is moistened with fuming nitric acid, and evaporated to dryness on a water-bath, it yields a yellow residue, which, on the addition of alcoholic potash, gives an intense violet colouration, gradually changing to red.

When atropine is boiled with baryta-water it is readily hydrolysed, yielding dl-*tropic acid* and *tropine*,

$$C_{17}H_{23}O_3N+H_2O = C_6H_5\cdot CH<\begin{matrix}CH_2\cdot OH\\COOH\end{matrix}+C_8H_{15}ON,$$

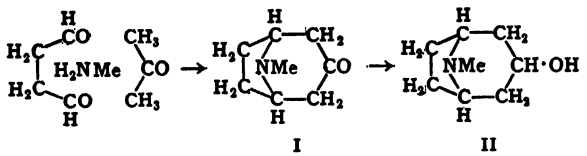
and conversely, tropic acid and tropine react in the presence of hydrochloric acid to form atropine.

Tropine is proved to be an alcohol as it is oxidised by chromic acid to a ketone, *tropinone*, $C_8H_{13}ON$; it loses the elements of water when it is heated with acids, giving *tropidine*, $C_8H_{13}N$, an unsaturated base. Tropidine, by the processes of exhaustive methylation and decomposition of the resulting quaternary hydroxide (compare, p. 597) is converted into a di-olefinic tertiary base, $C_7H_9\cdot NMe_2$, which, by a repetition of the same processes, is finally decomposed into cyclo*heptatriene* (IV), trimethylamine and water. The molecule of tropine, therefore, contains a closed chain of *seven* carbon atoms, a conclusion which is confirmed by the fact that (normal) pimelic acid can also be obtained from tropine by a series of reactions including exhaustive methylation, etc. Tropine, degraded by other methods, gives *α-ethylpyridine*.

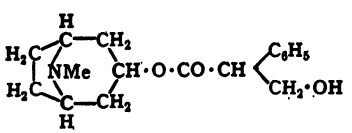
These facts indicated that the molecule of tropine contained, not

only a saturated closed chain of seven carbon atoms, but also a saturated closed chain consisting of five atoms of carbon and one atom of nitrogen. After a great deal of further investigation its probable structure (II) was determined, and finally established by a long and difficult synthesis by Willstätter.

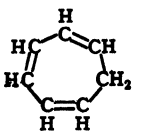
A very simple synthesis was accomplished later by Robinson, who obtained tropinone (I) by the interaction of succindialdehyde (p. 588), methylamine, and acetone or its dicarboxylic acid[1]; the tropinone can be reduced to tropine (II), and finally this alcohol can be converted into its tropic ester, which is atropine (III).



I II



Atropine, III



IV

Tropic acid has been synthesised as follows: Acetophenone is converted into the dichloride with phosphorus pentachloride, and the product is treated with alcoholic potassium cyanide,

$$\begin{matrix}\mathrm{Ph}\\ \mathrm{Me}\end{matrix}\!>\!\mathrm{CCl_2}+\mathrm{KCN}+\mathrm{EtOH}=\begin{matrix}\mathrm{Ph}\\ \mathrm{Me}\end{matrix}\!>\!\mathrm{C}\!<\!\begin{matrix}\mathrm{OEt}\\ \mathrm{CN}\end{matrix}+\mathrm{KCl}+\mathrm{HCl};$$

the nitrile, heated with hydrochloric acid, undergoes hydrolysis and also loses the elements of alcohol, yielding atropic acid, $\mathrm{PhC(:CH_2)\cdot COOH}$. By the successive action of hydrogen chloride and aqueous alkali the elements of water are added to this unsaturated acid and *dl*-tropic acid is formed.

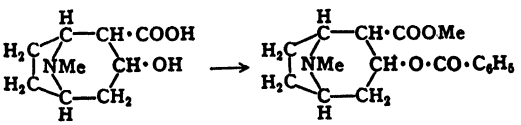
Cocaine, $\mathrm{C_{17}H_{21}O_4N}$, and several other alkaloids of less importance, are contained in coca-leaves (*Erythroxylon Coca*), in combination with cinnamic and other acids.

It crystallises in prisms, melts at 98°, is laevorotatory, and sparingly soluble in water; it forms well-characterised salts, of which

[1] Calcium acetonedicarboxylate gives a better yield than acetone; the *calcium tropinonedicarboxylate* thus obtained is converted into the acid and the latter is decomposed by heat.

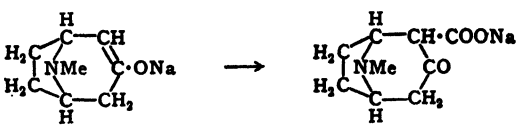
the *hydrochloride*, $C_{17}H_{21}O_4N, HCl$, is generally employed in medicine. Cocaine is a very valuable local anaesthetic, and is used in minor surgical operations, as its external application takes away all sensation of pain; it is poisonous, however, and one grain injected subcutaneously has been attended with fatal results.

When heated with acids or alkalis, cocaine is readily hydrolysed, with the formation of benzoic acid, methyl alcohol, and l-*ecgonine*, which is a monocarboxylic acid derived from tropine, and has the constitution (I),



I Cocaine, II

Cocaine (II) is the methyl *ester* of *benzoyl*-l-*ecgonine*, and is formed when the methyl ester of *l*-ecgonine is benzoylated. *dl*-Ecgonine has been synthesised from tropinone: This ketone gives an enolic sodium derivative (III) which, on treatment with carbon dioxide, yields the sodium salt of tropinonecarboxylic acid (IV); on reduction with sodium amalgam the acid is converted into *dl*-ecgonine, the optically inactive form of the *l*-isomeride obtained from cocaine.

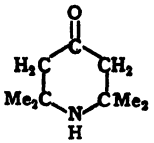


III IV

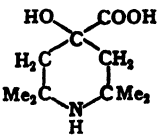
Synthetic Local Anaesthetics

Since the grouping $>N—\overset{\vee}{C}—\overset{\vee}{C}—CO—O—R$, which occurs in its molecule, might be responsible for the physiological properties of cocaine, several other substances containing this or a similar group have been prepared synthetically, and have, in fact, been found to be useful as local anaesthetics.

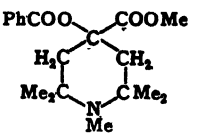
α-Eucaine is prepared by the following series of reactions: Triacetonamine (I), which is obtained by condensing acetone with ammonia, is treated with hydrogen cyanide, and the cyanohydrin thus formed is hydrolysed; the product (II), successively benzoylated and methylated, yields α-eucaine (III),



I



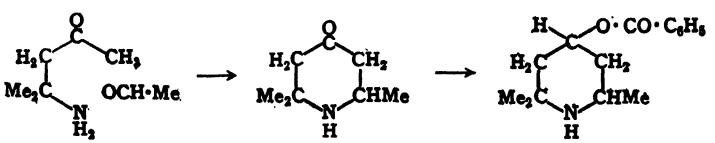
II



α-Eucaine, III

α-Eucaine is less toxic than cocaine, but as it has certain ill-effects it has now been superseded by benzamine, procaine and amylocaine.

Benzamine (or *β-eucaine*) is prepared from *diacetonamine*, $CH_3 \cdot CO \cdot CH_2 \cdot CMe_2 \cdot NH_2$, a simpler condensation product of acetone and ammonia. The hydrogen oxalate of this base, when it is heated with paraldehyde (or acetal) in alcoholic solution, yields the oxalate of a trimethylketopiperidine (IV). On reduction with sodium and boiling amyl alcohol, this keto-derivative gives the corresponding secondary alcohol, of which there are two *dl*-stereo-isomeric forms, melting at 163° and 138° respectively. The base melting at 138° gives a hydrochloride which, heated with benzoyl chloride, yields the hydrochloride of benzamine (V) :



IV V

Benzamine has anaesthetic properties equal to those of cocaine, and its salts are easily soluble in water and stable in boiling solution ; the solutions can therefore be readily sterilised.

Procaine is quite a different type of compound and may be prepared as follows : Ethylene chlorohydrin is first condensed with *p*-nitrobenzoyl chloride and the product (I) is treated with diethylamine. The compound so formed (II) is then reduced to the base procaine (III), the hydrochloride of which is also known as *novocaine* :

$$NO_2 \cdot C_6H_4 \cdot CO \cdot Cl + HO \cdot CH_2 \cdot CH_2 \cdot Cl \longrightarrow NO_2 \cdot C_6H_4 \cdot CO \cdot O \cdot CH_2 \cdot CH_2 \cdot Cl$$

I

$$NO_2 \cdot C_6H_4 \cdot CO \cdot O \cdot CH_2 \cdot CH_2 \cdot NEt_2$$

II

$$NH_2 \cdot C_6H_4 \cdot CO \cdot O \cdot CH_2 \cdot CH_2 \cdot NEt_2.$$

III

The compound (II) may also be prepared from ethylene oxide and diethylamine which give β-diethylaminoethanol; the alcohol is then treated with *p*-nitrobenzoyl chloride. Procaine is a powerful local anaesthetic, less toxic than cocaine; it is much used in dentistry and minor surgical operations.

Amylocaine is also a well-known local anaesthetic. It may be prepared by treating chloroacetone with dimethylamine, converting the product (IV) into a tertiary alcohol (V) with ethyl magnesium bromide, and then benzoylating the alcohol; *stovaine* is the hydrochloride of the base amylocaine (VI),

$$\underset{\text{IV}}{CH_3\cdot CO\cdot CH_2\cdot NMe_2} \qquad \underset{\text{V}}{CH_3\cdot CEt(OH)\cdot CH_2\cdot NMe_2}$$

$$\underset{\text{VI}}{CH_3\cdot CEt(O\cdot COPh)\cdot CH_2\cdot NMe_2}.$$

Alkaloids derived from Quinoline

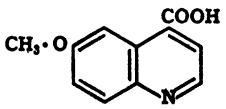
Quinine, $C_{20}H_{24}O_2N_2$, cinchonine (p. 608), and about thirty other allied alkaloids, occur in the bark of various species of *Cinchona* and related plants, usually as salts; some barks contain as much as 10% of quinine.

A paste made from the powdered bark with water and lime or caustic soda is dried and extracted with benzene; the benzene solution of the alkaloids is shaken with diluted sulphuric acid and the hot aqueous liquid is neutralised (litmus) with sodium carbonate. From the cooled solution quinine sulphate crystallises, the sulphates of cinchonine and the other alkaloids remaining in solution; the sulphate is purified by recrystallisation from boiling water and the base precipitated with ammonium hydroxide.

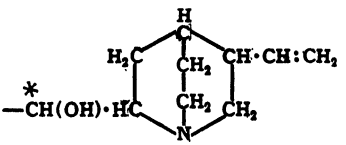
Quinine crystallises with water (3 mol., one of which is lost at about 20°), melts at about 177° when anhydrous, and is only very sparingly soluble (1 in 1906 at 15°) in water; it is a very feeble di-acidic base, but generally forms well-defined salts, such as the *sulphate*, $(C_{20}H_{24}O_2N_2)_2,H_2SO_4,8H_2O$. Many of its salts are soluble in water, and are very much used in medicine as tonics, and in cases of malaria and other intermittent fevers; as these salts have an intensely bitter taste, various simple derivatives of quinine, having little or no taste, have been prepared for use in medicine. Quinine is laevorotatory. *Dilute* solutions of quinine salts show a light-blue fluorescence.

Test for Quinine. When a solution of a quinine salt is treated with a slight excess of chlorine or bromine-water, and ammonium hydroxide is then added, a highly characteristic, emerald-green colouration is produced.

Quinine is a di-tertiary base, because it combines with methyl iodide to form *quinine dimethiodide*, $C_{20}H_{24}O_2N_2,(CH_3I)_2$; it is a derivative of quinoline, because on oxidation with chromic acid it yields *quininic acid* or *6-methoxyquinoline-4-carboxylic acid* (I):



I



II

The carbon atom which remains in the form of the carboxyl group in this acid is that marked with an asterisk in the complex (II), which completes the structure of the alkaloid.

Quinine has been synthesised from its elements, but the process is such a long and difficult one that the synthetic alkaloid is not likely to compete with the natural product.

Cinchonine, $C_{19}H_{22}ON_2$, accompanies quinine in almost all the cinchona-barks, and is present in some kinds (in the grey bark, from Huanuco in Peru) to the extent of 2%.

The mother-liquors from the crystals of quinine sulphate (p. 607) are treated with caustic soda, and the precipitate is dissolved in the smallest possible quantity of boiling alcohol; the crude cinchonine, which separates from the cold solution, is then converted into the sulphate, and the salt is crystallised from water.

Cinchonine crystallises in prisms, decomposes at about 240°, and resembles quinine in many respects, but is dextrorotatory; its salts are antipyretics, but are much less active than those of quinine.

Oxidising agents, such as nitric acid or potassium permanganate, readily attack cinchonine, and convert it into various substances, one of the more important of which is *cinchoninic acid* (*quinoline-4-carboxylic acid*).

The formation of this acid and other facts prove that cinchonine is a quinoline-derivative; its structure is very closely related to that of quinine; quinine, in fact, is a *methoxy*cinchonine.

Strychnine, $C_{21}H_{22}O_2N_2$, and brucine, two highly poisonous alkaloids, are present in the seeds of *Strychnos Nux-vomica* and of *Strychnos Ignatii* (Ignatius' beans), which contain 2–3% of the mixed bases.

A paste made from powdered nux-vomica with water and 25% of its weight of lime is dried at 100°, powdered, and extracted with boiling chloroform; the alkaloids are then extracted from the chloroform solution with diluted sulphuric acid and precipitated with an excess of ammonium hydroxide. The crude mixture of strychnine and brucine is extracted with 25% alcohol, which dissolves the brucine, and the strychnine is purified by crystallisation from alcohol.

The mixed bases from the various alcoholic mother-liquors are precipitated as oxalates, and the salts are extracted with alcohol in which strychnine oxalate is the more soluble; the residual brucine oxalate is dissolved in hot water, boiled with animal charcoal, and the base, precipitated by ammonium hydroxide, is purified by recrystallising its sulphate.

Strychnine crystallises in rhombic prisms, and decomposes at about 270°; although it is very sparingly soluble in water (1 part in 6400 at 25°), its solution has an intensely bitter taste, and is very toxic. Strychnine, in fact, is one of the more poisonous alkaloids, half a grain of the sulphate having caused death in twenty minutes.

Test for Strychnine. Strychnine is very readily detected, as it shows many characteristic reactions, of which the following is the most important: When a small quantity of powdered strychnine is treated with a little concentrated sulphuric acid in a porcelain basin, and a little powdered potassium dichromate is then dusted over the liquid, an intensely violet solution, which gradually becomes bright red, and then yellow, is produced.

Although the molecule of strychnine contains two atoms of nitrogen, it is, like brucine, only a mono-acidic base, forming salts, such as the *hydrochloride*, $C_{21}H_{22}O_2N_2,HCl$; many of the salts are soluble in water. It is a (laevorotatory) tertiary base, and combines with methyl iodide to form *strychnine methiodide*, $C_{21}H_{22}O_2N_2,CH_3I$, a quaternary salt.

When strongly heated with potash, strychnine yields *quinoline* and other products; probably, therefore, it is a derivative of this base.

Brucine, $C_{23}H_{26}O_4N_2$, crystallises in prisms, with $4H_2O$, and

melts, when anhydrous, at 178°. It is more readily soluble in water and in alcohol than is strychnine, and, although very poisonous, it is not nearly so deadly as the latter (its physiological effect is only about $\frac{1}{21}$th of that of strychnine).

Test for Brucine. When a solution of a brucine salt is treated with nitric acid, a deep brownish-red colouration is obtained, and the solution becomes yellow when it is warmed; if now stannous chloride is added, an intense violet colouration is produced. This colour reaction serves as a delicate test, either for brucine or for nitric acid.

Although its molecule contains two atoms of nitrogen, brucine, like strychnine, is a mono-acidic (laevorotatory) base. The *hydrochloride*, for example, has the composition, $C_{23}H_{26}O_4N_2,HCl$; brucine is also a tertiary base, and combines with methyl iodide to form *brucine methiodide*, $C_{23}H_{26}O_4N_2,CH_3I$.

Alkaloids contained in Opium

The juice of certain kinds of poppy-heads (*Papaver somniferum*) contains a great variety of alkaloids, of which *morphine* is the most important, but *codeine*, *narcotine*, *thebaine*, and *papaverine* may also be mentioned. All these compounds are present in combination with *meconic acid*,[1] and partly also with sulphuric acid.

When incisions are made in the poppy-heads, and the juice which exudes is left to dry, it assumes a pasty consistency, and is called *opium*. An alcoholic tincture of opium, containing 1 g. of anhydrous morphine per 100 c.c., is known as *laudanum*.

Preparation of Morphine. Opium is extracted with hot water, and the extract is boiled with milk of lime, and filtered from the precipitate, which contains the calcium salt of meconic acid, and all the alkaloids, except morphine. The filtrate is then concentrated, digested with ammonium chloride until ammonia ceases to be evolved (to decompose the soluble calcium derivative of morphine), and kept for some days; the morphine, which separates, is collected and purified by recrystallisation from boiling alcohol.

Morphine, $C_{17}H_{19}O_3N$, crystallises in prisms, with $1H_2O$, and is only sparingly soluble in water and cold alcohol, but dissolves in

[1] *Meconic acid,* $C_5HO_3(OH)(COOH)_2$, is a closed chain hydroxydicarboxylic acid (Part III). It gives, with ferric chloride, an intense dark-red colouration. In cases of suspected opium-poisoning a test for this acid is always applied, because of the delicacy of this colour reaction.

caustic alkalis and in lime-water, from which it is precipitated on the careful addition of acids; it has, in fact, the properties of a phenol. At the same time, it is a mono-acidic (laevorotatory) base, and forms well-characterised salts with acids; the *hydrochloride*, $C_{17}H_{19}O_3N$, HCl, $3H_2O$, crystallises from water in needles, and is the salt commonly employed in medicine. Morphine is a tertiary base, and gives with methyl iodide *morphine methiodide*, $C_{17}H_{19}O_3N$, CH_3I.

Morphine has a bitter taste, and is so poisonous that one grain of the hydrochloride may be a fatal dose; the human system, however, may become so accustomed to the habitual administration of opium that, after a time, very large quantities may be taken daily without fatal effects. Morphine is extensively used in medicine as a narcotic, especially in cases of intense pain.

Tests for Morphine. When a little iodic acid is dissolved in water, and a few drops of a solution of morphine hydrochloride are added, a brownish colouration is at once produced, owing to the liberation of iodine, and the solution then gives, with starch-paste, a deep-blue colouration.

A solution of morphine, or of a morphine salt, gives a deep-blue colouration with ferric chloride, but perhaps the most delicate test for the alkaloid is the following: A trace of morphine is dissolved in concentrated sulphuric acid, and the solution is kept during fifteen hours; if then treated with nitric acid, it gives a bluish-violet colour, which changes to blood-red. This reaction is clearly shown by 0·01 mg. of morphine.

The molecule of morphine contains two hydroxyl groups, one of which is phenolic, the other alcoholic; it is to the phenolic hydroxyl group that morphine owes its property of dissolving in alkalis and giving a blue colour with ferric chloride. *Heroin* is the diacetyl derivative of morphine and is also a narcotic.

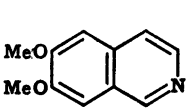
When heated with potash and methyl iodide, morphine gives *methylmorphine*, $C_{17}H_{17}ON(OCH_3)\cdot OH$, which is identical with *codeine*. Codeine is insoluble in alkalis, and, therefore, is not a phenol; it behaves, however, like an alcohol, and gives *acetylcodeine*, $C_{17}H_{17}ON(OCH_3)\cdot OAc$, with acetic anhydride.

When morphine is distilled with zinc-dust a considerable yield of phenanthrene is obtained, together with basic substances; it is concluded therefore that the molecule of morphine (and also that of codeine) contains a phenanthrene complex.

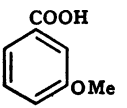
Apomorphine, $C_{17}H_{17}O_2N$, is formed, together with water, when morphine hydrochloride is heated with concentrated hydrochloric acid at 140–150°; its hydrochloride is used in medicine as an emetic.

Papaverine, $C_{20}H_{21}O_4N$, is one of the simpler alkaloids which occur in opium, and melts at 148°; it is of no physiological importance.

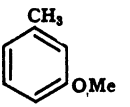
When papaverine is heated with hydriodic acid it gives four molecules of methyl iodide and therefore contains four methoxyl groups (p. 597). On fusion with alkali it yields 6:7-dimethoxy-*iso*quinoline (I), and either veratric acid (II), or 4-methyl-dimethylcatechol (1:2-dimethoxy-4-methylbenzene, III), according to the experimental conditions:



I



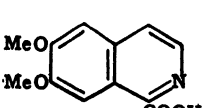
II



III

These products contain the nitrogen and all the carbon atoms of the papaverine molecule, which therefore is a derivative of *iso*quinoline; it is also proved that the carbon atom in the 4-position of (II) or (III) forms the link between the benzene and the *iso*quinoline nuclei, but the position of this connecting link in the *iso*quinoline nucleus has still to be settled.

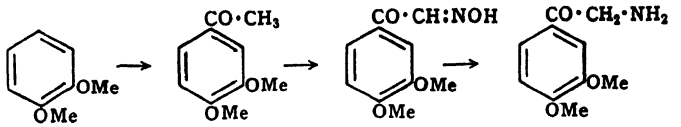
Now when papaverine is oxidised it affords a ketone, *papaveraldine*, which, on further oxidation gives, among other products, 6:7-dimethoxy*iso*quinoline-1-carboxylic acid, (IV); as the carbon atom of the carboxyl group of this acid must be that of the carboxyl group of (II), the position of the link between (I) and (II), and the structure of papaverine, (XIII), are established.



IV

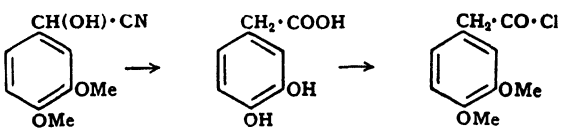
Papaverine has been synthesised as follows (Pictet): (1) Veratrole (dimethylcatechol, V) is converted into the acetyl derivative, (VI),

by the Friedel-Crafts reaction, and the product is treated with amyl nitrite and sodium ethoxide; the *iso*nitroso-derivative, (VII), is then reduced with stannous chloride and hydrochloric acid to the amino-compound, (VIII) :



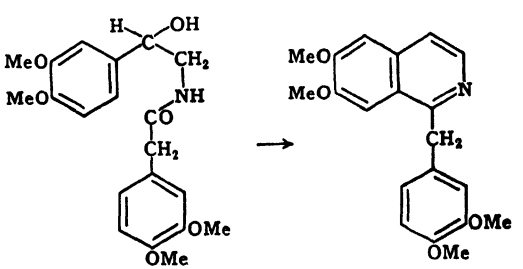
V VI VII VIII

(2) The cyanohydrin of *O*-methylvanillin, (IX), is heated with hydriodic acid, whereby it is reduced, *de*methylated and hydrolysed in one operation. The product, (X), is *di*methylated and converted into its acid chloride, (XI), which is then condensed with (VIII) in the presence of alkali to obtain the amide :



IX X XI

(3) The carbonyl group (derived from VIII) of the condensation product is reduced, and the alcohol, (XII), so formed, treated with phosphorus pentoxide in boiling xylene solution, gives papaverine, (XIII) :

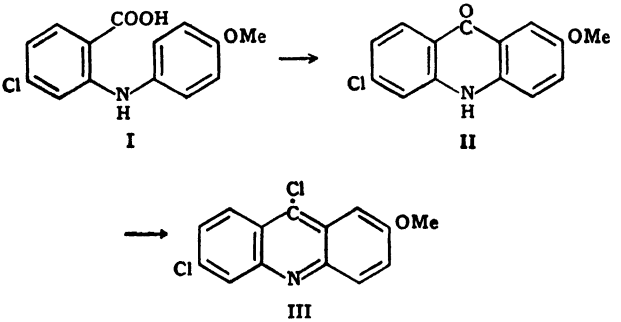


XII Papaverine, XIII

Synthetic Antimalarial Compounds

Atebrin, ***mepacrine hydrochloride,*** is an important acridine derivative used extensively as an antimalarial drug instead of quinine.

It is prepared as follows: (1) 2:4-Dichlorobenzoic acid is condensed with *p*-anisidine in the presence of copper powder and the resulting derivative of anthranilic acid, (I), is heated with sulphuric acid; the product, 2-*methoxy*-6-*chloroacridone*, (II), treated with phosphorus pentachloride, yields 2-*methoxy*-6:9-*dichloroacridine*, (III).



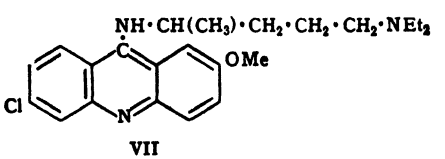
(2) β-Chlorotriethylamine, (IV), is condensed with ethyl sodioacetoacetate and the ester so produced is submitted to ketonic fission; the resulting ketone, (V), reduced in the presence of ammonia, gives α-methyl-δ-diethylaminobutylamine, (VI):

IV $Et_2N \cdot CH_2 \cdot CH_2Cl$

V $Et_2N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CO \cdot CH_3$

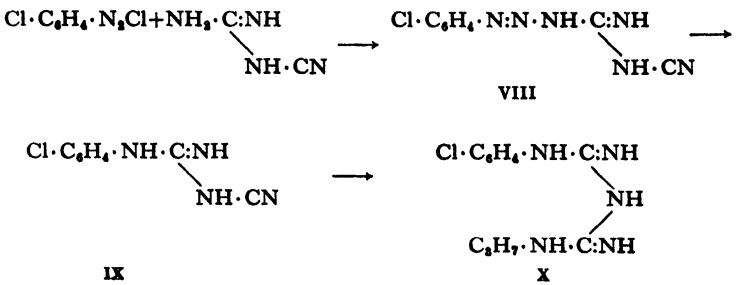
VI $Et_2N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CH_3$

(3) Finally, the condensation of (III) and (VI) yields (VII), the dihydrochloride of which is atebrin:



'**Paludrine**' (N_1-p-*chlorophenyl*-N_5-iso*propylguanylguanidine*, X) is also a very important prophylactic and curative agent in the treatment of malaria, and is more effective and less toxic than atebrin or quinine; it has also a much simpler structure than either of these substances to which it is chemically unrelated.

It is prepared by treating dicyandiamide, a polymeride of cyanamide, with *p*-chlorophenyldiazonium chloride ; the product, (VIII), with hydrochloric acid gives (IX) which is condensed with *iso*-propylamine :



CHAPTER 39

AMINO-ACIDS AND RELATED COMPOUNDS

THE **amino-acids,** of which glycine is an example, are substances of very great physiological importance. Many of them are obtained by the hydrolysis with acids, alkalis, or digestive enzymes of those highly complex components of animals and plants, which are termed the **proteins** (p. 641); it is concluded therefore that the macromolecule of a protein is produced in organisms by the condensation of a large number of molecules of relatively simple amino-acids. All such naturally-occurring amino-acids, with the exception of β-alanine (p. 623), have an amino-group in the α-position.

As a rule the product of hydrolysis of a protein is a mixture of some 14–19 different amino-acids, and the separation of its various components is a task of great difficulty. This is due partly to the complexity of the mixture, but more particularly to the fact that amino-acids are generally very readily soluble in water, but insoluble in ether and all other solvents, which do not mix with water, except the higher alcohols. Consequently they cannot be extracted from their aqueous solutions by the usual methods; further, they cannot be distilled, and, when impure, they do not crystallise readily. Owing initially to the work of E. Fischer, who devised new synthetical methods of preparation, and new processes for the separation and isolation of amino-acids from the products of protein hydrolysis, some of these difficulties have been largely overcome.

Preparation. The more important general synthetical methods are the following:

(1) The halogen substitution products of aliphatic acids are treated with alcoholic ammonia,

$$CH_3\cdot CHBr\cdot COOH+3NH_3 = CH_3\cdot CH(NH_2)\cdot COONH_4+NH_4Br.$$

(2) The esters of halogen acids are treated with potassium phthalimide, and the products are hydrolysed with hydrochloric acid at about 200° (p. 522),

$$C_6H_4\langle^{CO}_{CO}\rangle NK+CH_2Br\cdot CH_2\cdot CH_2\cdot CH(COOEt)_2 = KBr+ C_6H_4\langle^{CO}_{CO}\rangle N\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH(COOEt)_2;$$

$$C_6H_4\langle^{CO}_{CO}\rangle N\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH(COOEt)_2+4H_2O = C_6H_4(COOH)_2+NH_2\cdot[CH_2]_4\cdot COOH+2C_2H_5\cdot OH+CO_2.$$

(3) The cyanohydrin of an aldehyde or ketone is treated with the theoretical quantity of ammonia—or an aldehyde or ketone is treated with ammonium sulphate and potassium cyanide—and the nitrile of the α-amino-acid, which is thus formed, is hydrolysed with hydrochloric acid (Strecker),

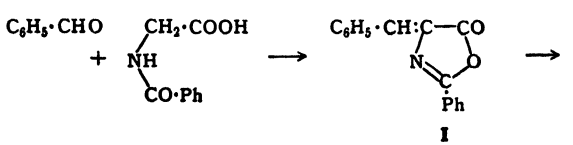
$$Me_2CH\cdot CH_2\cdot CH<^{OH}_{CN}+NH_3 = H_2O+Me_2CH\cdot CH_2\cdot CH<^{NH_2}_{CN};$$

$$Me_2CH\cdot CH_2\cdot CH(NH_2)\cdot CN+2H_2O+2HCl = HCl, Me_2CH\cdot CH_2\cdot CH(NH_2)\cdot COOH+NH_4Cl.$$

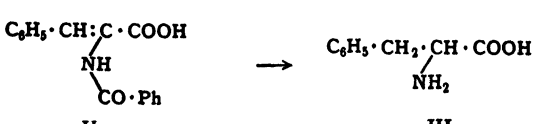
(4) An α-ketonic acid is reduced with hydrogen and a catalyst in the presence of ammonia,

$$R\cdot CO\cdot COOH+NH_3+H_2 = R\cdot CH(NH_2)\cdot COOH+H_2O.$$

(5) Amino-acids containing aromatic or heterocyclic groups may be prepared by the *azlactone* method : Hippuric acid is heated with an aldehyde, sodium acetate and acetic anhydride and the resulting *oxazolone* (azlactone, I) is hydrolysed to the benzoyl derivative of an unsaturated amino-acid, (II) ; this is (*a*) reduced catalytically and the benzoyl group removed by hydrolysis, or (*b*) boiled with acetic anhydride, hydriodic acid and red phosphorus (cf. pp. 626, 651).



I



II III

in either case the final product is the saturated α-amino-acid, (III).

Properties. The mono-amino-acids are crystalline and usually decompose when they are strongly heated, with the evolution of carbon dioxide, so that, as a rule, they have not a definite melting-point ; some of them have a sweet taste. They are neutral to

common indicators, and, in fact, may be regarded as *salts*, since the carboxyl and amino-groups of the same or of different molecules neutralise one another, just as do an acid and an amine, to give di-polar, twin (or *zwitter*) ions, $^{+}NH_3 \cdot CRR' \cdot COO^{-}$; such a view would account for the high, indefinite melting-point, solubility in water and insolubility in organic solvents of an amino-acid. When an amino-acid is treated with a strong acid, such as hydrochloric acid, it forms a *hydrochloride*, of which *glycine hydrochloride*, $Cl[NH_3 \cdot CH_2 \cdot COOH]$, is an example; an amino-acid also forms metallic salts, such as sodium glycine, $[NH_2 \cdot CH_2 \cdot COO]Na$.

The *primary* amino-acids are decomposed by nitrous acid, just as are the primary amines, giving the corresponding hydroxy-acids; by measuring the volume of nitrogen thus evolved the quantity of such an amino-acid in a given solution may be determined. Amino-acids cannot be estimated by simple titration with acids or alkalis in aqueous solution because their salts are so very much hydrolysed; after the addition of an excess of formalin, however, they can be titrated with alkali, because in the presence of the latter, *methylene-imino*-derivatives, $(CH_2{:}N—)$, which are not amphoteric, are formed (Sörensen).

Some amino-acids are decomposed by acetic anhydride in the presence of pyridine with the formation of an acetylamino-derivative of a ketone,

$$C_6H_5 \cdot CH_2 \cdot CH(NH_2) \cdot COOH + (CH_3 \cdot CO)_2O = C_6H_5 \cdot CH_2 \cdot CH(NHAc) \cdot CO \cdot CH_3 + H_2O + CO_2.$$

When heated, α-amino-acids (2 mol.) may condense with the loss of water (2 mol.), giving di-amides (p. 620), analogous to the lactides (p. 271); β-amino-acids (1 mol.) may lose ammonia (1 mol.), giving olefinic acids; γ- and δ-amino-acids (1 mol.) may lose water (1 mol.), giving *lactams*, corresponding with the lactones (p. 287).

Amino-acids give a red colouration with ferric chloride, and when warmed with an aqueous solution of *triketoindane hydrate* (*ninhydrin*, p. 556), a deep blue colouration.

Esters of the amino-acids may be produced by the usual method of esterification—namely, by passing hydrogen chloride into a solution of the acid in an excess of an alcohol. If, then, the alcohol is evaporated and the *hydrochloride* of the ester is cautiously decomposed with a cold solution of an alkali, the ester can be immediately extracted with a suitable solvent and finally obtained as an oil,

which may be purified by distillation under greatly reduced pressure. The esters of the amino-acids, therefore, are of great use; with their aid the amino-acids may be extracted from the products of hydrolysis of a protein, and, to a greater or less extent, these esters may then be separated from one another by fractional distillation.

Some amino-acids are soluble in moist *n*-butyl alcohol and may be extracted from their neutral aqueous solution with this solvent; a preliminary extraction in this way, before esterification, may often simplify the separation of complex amino-acid mixtures.

Resolution of dl-*amino-acids*. All the amino-acids which are obtained from natural products, with the exception of glycine and β-alanine, are *optically active*, whereas the corresponding synthetical compounds, of course, are *dl*-substances. Owing to the amphoteric nature of the amino-acids, they do not, as a rule, form stable salts with either optically active acids or bases, which otherwise might be used for their resolution. They may, however, be separated into their optical isomerides by the following methods: (1) The amino-acid is converted into its *benzoyl*-derivative by the Schotten-Baumann method (p. 514), or into a *formyl* derivative. The amino-group thereby loses its basic character and the *benzoylated* or *formylated* product is a sufficiently strong acid to form stable salts with bases, such as the alkaloids. The acylamino-acid, therefore, may be combined with an optically active base, and the product may then be resolved in the usual way. (2) The amino-acid is converted into its ester (above) which is a sufficiently strong base to give, with optically active acids, stable salts which may often be resolved. The *d*- and *l*-acylamino-acids, or the *d*- and *l*-esters, which are then regenerated from their salts, are finally reconverted into the *d*- and *l*-amino-acids respectively, by hydrolysis.

It is thus possible to synthesise many of the *dl*-amino-acids, and then to resolve them into optically active compounds, which are identical with those produced from the proteins.

Ptomaines or Toxines. Many of the amino-acids are attacked by various putrefactive organisms, giving basic substances, such as *putrescine*, *cadaverine*, and *neurine* (p. 627), which are classed as ptomaines, and some of which are very poisonous. These compounds are formed during the putrefaction of fish, meat, and other animal products which contain proteins, and the toxic action of such putrid matter is partly due to their presence.

Putrescine, $NH_2 \cdot [CH_2]_4 \cdot NH_2$ (*tetramethylenediamine*), is crystal-

line, and melts at 27°; it has a most unpleasant and penetrating smell. It is miscible with water, and is a strong di-acidic base.

Putrescine has been obtained synthetically by converting ethylene dibromide into the dicyanide, and then reducing the latter with sodium and alcohol,

$$CN \cdot CH_2 \cdot CH_2 \cdot CN + 8H = NH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NH_2.$$

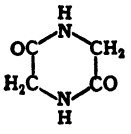
Cadaverine, or *pentamethylenediamine*, boils at 178–179°, and, like putrescine, is a di-acidic base; its synthesis has already been given (p. 573).

Polypeptides. A natural protein, as stated above, doubtless consists of a very large number of molecules of the same or of different amino-acids, which have united together with the elimination of water; the first stage in such a condensation of α-amino-acids may be represented by the general equation,

$$2\,NH_2 \cdot CRR' \cdot COOH\ ^{1} = NH_2 \cdot CRR' \cdot CO \cdot NH \cdot CRR' \cdot COOH + H_2O.$$

The product so formed from two molecules of an amino-acid is called a *di-peptide*; by condensation with another molecule of the same, or of a different amino-acid, a di-peptide may be transformed into a *tri-peptide*, and so on.

In order to throw light on the nature of the proteins, such condensations were carried out by E. Fischer, and the following methods were used for this purpose: The ethyl ester of glycine undergoes spontaneous decomposition in aqueous solution, giving a *diamide, glycine anhydride* (or *diketopiperazine*, I), which is hydrolysed by hot concentrated hydrochloric acid, to the hydrochloride of *glycyl-glycine* (II).



I

$\longrightarrow NH_2 \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot COOH$

II

When this *di-peptide*, glycyl-glycine (or its ester), is treated with chloroacetyl chloride, it yields a compound (III), and the latter, with concentrated ammonia, gives a *tri-peptide* (IV),

III $Cl \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot COOH$

IV $NH_2 \cdot CH_2 \cdot CO|NH \cdot CH_2 \cdot CO|NH \cdot CH_2 \cdot COOH$

[1] R and R′ may represent either hydrogen or an alkyl (or other) radical.

The tri-peptide may now be treated with chloroacetyl chloride and ammonia successively, and thus converted into a *tetra-peptide*; and these processes, by which a $—CO·CH_2·NH_2$ group is substituted for an atom of hydrogen of an amino-group, may be continued.

In another method, the amino-acid is treated with phosphorus pentachloride and acetyl chloride, and the acid chloride, which is thus produced, in the form of its hydrochloride, is then caused to react with an ester of an amino-acid,

$$NH_2·CRR'·COOH+PCl_5 = HCl, NH_2·CRR'·COCl+POCl_3;$$

$$HCl, NH_2·CRR'·COCl+NH_2·CRR'·COOEt = HCl, NH_2·CRR'·CO·NH·CRR'·COOEt+HCl.$$

The product is then made the starting-point of further similar condensations.

A more recent process for the synthesis of polypeptides uses *benzyloxyformyl chloride*, $C_6H_5·CH_2·O·CO·Cl$, prepared from benzyl alcohol and phosgene. This compound reacts with amino-acids, in alkaline solution, to give benzyloxyformyl (*carbobenzoxy*) derivatives, $C_6H_5·CH_2·O·CO·NH·CRR'·COOH$, which can then be converted into their acid chlorides; the latter react with the amino-group of an amino-acid and the product is then reduced to a dipeptide with hydrogen and palladium,

$$C_6H_5·CH_2·O·CO·NH·CRR'·CO·Cl+NH_2·CH_2·COOH = C_6H_5·CH_2·O·CO·NH·CRR'·CO·NH·CH_2·COOH+HCl;$$

$$C_6H_5·CH_2·O·CO·NH·CRR'·CO·NH·CH_2·COOH+H_2 = C_6H_5·CH_3+CO_2+NH_2·CRR'·CO·NH·CH_2·COOH.$$

This series of operations may then be repeated.

The most complex substance produced by E. Fischer was an *octadecapeptide*, the molecule of which contained 15 glycyl- or $—NH·CH_2·CO—$ and three *leucyl-* or $—NH·CH(C_4H_9)·CO—$ groups (p. 623); this compound has a molecular weight of 1213, and its constitution is expressed by the formula,

$$\begin{array}{l} \qquad\qquad\qquad\quad C_4H_9 \\ <[NH·CH_2·CO]_3·NH·CH·CO·[NH·CH_2·CO]_6·NH·CH_2·COOH \\ \quad CO·CH·NH·[CO·CH_2·NH]_3·CO·CH·NH_2 \\ \qquad\quad | \qquad\qquad\qquad\qquad\quad | \\ \qquad C_4H_9 \qquad\qquad\qquad\qquad C_4H_9 \end{array}$$

It is in many respects similar to the natural proteins, and gives the colour reactions of those substances; like the latter it does not

diffuse through a parchment membrane and is precipitated from its solutions by tannic acid, etc.

On the other hand, certain enzymes such as pepsin and trypsin which hydrolyse proteins, have little, if any, action on synthetic polypeptides: this does not, however, prove that proteins are not very complex open chain polypeptides. The difference is possibly due to the fact that in the large protein molecules there are practically no free carboxyl or amino-groups such as are present in a simpler polypeptide. The graded hydrolysis of proteins gives certain polypeptides, identical with some of those which have been prepared synthetically.

Classification of Amino-Acids.[1] The more important amino-acids obtained from proteins are of various types and may be classified as follows:

Mono-amino-derivatives of aliphatic mono-carboxylic acids: Glycine, *d*-Alanine, *l*-Serine, *d*-Valine, *l*-Leucine, d-*Iso*-leucine.

Di-amino-derivatives of aliphatic mono-carboxylic acids: *d*-Arginine, *d*-Lysine, *d*-Ornithine.

Mono-amino-derivatives of aliphatic di-carboxylic acids: *l*-Aspartic acid, *d*-Glutamic acid, *d*-Hydroxyglutamic acid.

Aromatic amino-acids: *l*-Phenylalanine, *l*-Tyrosine.

Heterocyclic amino-acids: *l*-Histidine, *l*-Tryptophane, *l*-Proline, *l*-Hydroxyproline.

The above-named compounds, together with the thio-amino-acids (*l*-cystine and *l*-methionine), all of which are obtained from proteins, are briefly described below; a short account of certain alkyl-amino-acids and related compounds which are obtained from animals, but which are not products of protein hydrolysis, is also given.

Amino-monocarboxylic Acids

Glycine (aminoacetic acid), the simplest amino-acid which is obtained from proteins, has already been described; it forms about 25% of the products of hydrolysis when glue or gelatin is decomposed with dilute sulphuric acid.

[1] The following description of individual amino-acids and the section on purine derivatives (p. 636), except uric acid, are of importance mainly to medical students, and their consideration may be omitted by those studying for a pass degree.

***d*-Alanine,** $CH_3 \cdot CH(NH_2) \cdot COOH$ (*α-aminopropionic acid*), is one of the principal products of the hydrolysis of fibroin (the main component of silk) and has been obtained synthetically by the methods already described. It decomposes at about 297°, and with nitrous acid, it gives *d*-lactic acid.

dl-*Alanine* and its structural isomeride, *β-aminopropionic acid* (*β-alanine*), $NH_2 \cdot CH_2 \cdot CH_2 \cdot COOH$, may be prepared by treating the corresponding bromopropionic acids with ammonia.

***l*-Serine,** $HO \cdot CH_2 \cdot CH(NH_2) \cdot COOH$ (*β-hydroxy-α-aminopropionic acid*), easily racemises, so that although it may be a component of many proteins, the *dl*-compound is obtained when silk-fibroin, casein, etc., and related substances, such as gelatin and keratin, are decomposed with acids; the *dl*-acid decomposes at about 246° and has a sweet taste.

***l*-Cystine,** $HOOC \cdot CH(NH_2) \cdot CH_2 \cdot S \cdot S \cdot CH_2 \cdot CH(NH_2) \cdot COOH$, is a derivative of alanine and is formed in considerable proportions by the hydrolysis of several proteins, such as those of wool and hair, of which it is the chief sulphur-containing component. The *dl*-acid may be obtained by the atmospheric oxidation of *α-amino-β-mercaptopropionic acid*, $HS \cdot CH_2 \cdot CH(NH_2) \cdot COOH$ (or *cysteine*) in alkaline solution. It is sparingly soluble in cold water and decomposes at about 260°.

***l*-Methionine,** $CH_3 \cdot S \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$, a methyl derivative of the next homologue of *l*-cysteine, is also an important constituent of proteins.

***d*-Valine,** $CHMe_2 \cdot CH(NH_2) \cdot COOH$ (*α-amino*isov*aleric acid*), is an important product of the hydrolysis of casein, zein (the protein of wheat and maize), and edestin (from hemp seed).

***l*-Leucine,** $CHMe_2 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$ (*α-amino*iso*caproic acid*), is very widely distributed in the animal kingdom, and is a substance of great physiological importance. It is found in the lymphatic glands, the spleen, and especially in the pancreas; in typhus and some other diseases it is present in considerable quantity in the liver. It is produced during the putrefaction or the hydrolysis of many proteins, especially haemoglobin (p. 646), milk-albumin, and casein (p. 645), from the last of which it may be prepared.

Leucine crystallises in glistening plates, melts at about 293°, and is sparingly soluble in water; when carefully heated it sublimes unchanged, but when rapidly heated it decomposes into *iso*amyl-

amine, $CHMe_2 \cdot CH_2 \cdot CH_2 \cdot NH_2$, and carbon dioxide. It undergoes atmospheric oxidation in aqueous solution in the presence of charcoal, giving *iso*valeric acid, carbon dioxide, and ammonia,

$$CHMe_2 \cdot CH_2 \cdot CH(NH_2) \cdot COOH + O_2 = C_4H_9 \cdot COOH + CO_2 + NH_3.$$

Its aqueous solution is laevorotatory, but that of its hydrochloride shows dextro-rotation; when boiled with baryta-water leucine racemises.

dl-*Leucine* has been prepared synthetically from *iso*valeraldehyde (p. 617), and in the form of its benzoyl or formyl derivative, it has been resolved into its components; the *l*-leucine obtained in this way is identical with that prepared from proteins.

*d-Iso*leucine, $CHMeEt \cdot CH(NH_2) \cdot COOH$ (*α-amino-β-methyl-valeric acid*), is produced by the hydrolysis of proteins contained in beetroot-sap, cereals, potatoes, etc., and when these materials are used for the preparation of alcohol, the d-*iso*leucine, which is first produced, is afterwards converted into active amyl alcohol by the action of accompanying enzymes. *l*-Leucine, under similar conditions, gives rise to *iso*butylcarbinol.

Di-amino-monocarboxylic Acids

***d*-Arginine**, $NH_2 \cdot C(:NH) \cdot NH \cdot [CH_2]_3 \cdot CH(NH_2) \cdot COOH$, is an important compound, derived from αδ-diamino-*n*-valeric acid, and is formed by the hydrolysis of many proteins; a polypeptide or *protamine* (*salmine*) obtained from Rhine salmon gives as much as 87% of arginine. On hydrolysis with a solution of barium hydroxide, arginine gives carbamide and ***d*-ornithine**, $NH_2 \cdot [CH_2]_3 \cdot CH(NH_2) \cdot COOH$ (*αδ-diaminovaleric acid*).

***d*-Lysine**, $NH_2 \cdot [CH_2]_4 \cdot CH(NH_2) \cdot COOH$ (*αε-diaminocaproic acid*), occurs among the hydrolytic products of casein, egg-albumin, and other proteins. In the putrefactive decomposition of proteins ornithine gives tetramethylenediamine, and lysine gives pentamethylenediamine. Unlike mono-amino-carboxylic acids, arginine and lysine have well-marked basic properties.

Mono-amino-dicarboxylic Acids

***l*-Aspartic acid**, $HOOC \cdot CH_2 \cdot CH(NH_2) \cdot COOH$ (*aminosuccinic acid*) is formed by the hydrolysis of many proteins; in common with other members of this group it has well-marked acidic properties.

***l*-Asparagine,** $NH_2 \cdot CO \cdot CH_2 \cdot CH(NH_2) \cdot COOH$, a mono-amide of *aminosuccinic acid* (aspartic acid), occurs in many plants, particularly in asparagus, and in the young shoots of beans, peas, and lupines, from which it may be obtained by extraction with water. It is readily soluble in water, sparingly soluble in alcohol and ether. When heated with acids or alkalis, it is converted into *l*-aspartic acid.

***d*-Asparagine** also occurs, together with *l*-asparagine, in the young shoots of lupines; it has a sweet taste, but that of *l*-asparagine is very unpleasant.

It is noteworthy that when an aqueous solution of equal quantities of *d*- and *l*-asparagine is evaporated, hemihedral crystals of the two active modifications are deposited side by side; a racemic compound is not formed.

***d*-Glutamic acid,** $HOOC \cdot CH(NH_2) \cdot CH_2 \cdot CH_2 \cdot COOH$ (*α-aminoglutaric acid*), occurs in the sprouting seeds of various plants, and is an important product of the hydrolysis of casein and of gliadin, the protein of wheat and rye, which gives more than 40% of the acid; it forms lustrous crystals which decompose at about 202°.

Glutamine, a monoamide of glutamic acid, is an important constituent of many proteins.

Aromatic Amino-acids

***l*-Phenylalanine,** $C_6H_5 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$ (*β-phenyl-α-aminopropionic acid*), is formed by the hydrolysis of cheese, egg-albumin, gelatin, etc.; the *dl*-acid has been synthesised from benzaldehyde as already described (p. 617), and has been resolved into its *d*- and *l*-components.

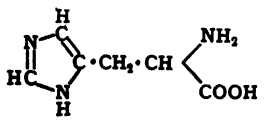
***l*-Tyrosine,** $HO \cdot C_6H_4 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$, or *β*-p-*hydroxyphenyl-α-aminopropionic acid*, is formed in the decomposition of many proteins. It is found in the liver in some diseases, in the spleen, pancreas, and in cheese (its name is derived from Gr. *tyros*, cheese). It was first prepared by fusing cheese with potash (Liebig, 1846). Tyrosine is sparingly soluble in water, and with mercuric nitrate in aqueous solution, it gives a yellow precipitate, which, when boiled with dilute nitric acid, acquires an intense red colour.

Tyrosine melts at about 316° and decomposes into carbon dioxide and p-*hydroxyphenylethylamine*, $HO \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot NH_2$. The

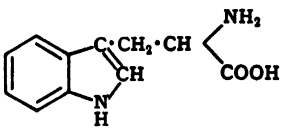
dl-acid has been synthesised from *p*-hydroxybenzaldehyde by the azlactone method.

Heterocyclic Amino-acids

***l*-Histidine**, $C_6H_9O_2N_3$ (*β-iminazolyl-α-aminopropionic acid*), was first found among the products of hydrolysis of *sturine*, a polypeptide obtained from the sturgeon, and is formed from many proteins; it decomposes at about 253° and with putrefactive bacteria gives *histamine* (β-aminoethyliminazole).



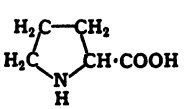
Histidine



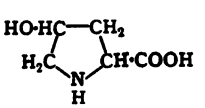
Tryptophane

***l*-Tryptophane**, $C_{11}H_{12}O_2N_2$ (*β-indolyl-α-aminopropionic acid*), is a decomposition product of egg- and blood-albumin, and in the presence of putrefactive bacteria, it is converted into *β-aminoethylindole* and carbon dioxide. *dl*-Tryptophane has been synthesised by the azlactone method (p. 617) from β-aldehydoindole, prepared from indole with chloroform and sodium ethoxide.

***l*-Proline**, $C_5H_9O_2N$ (*pyrrolidine-α-carboxylic acid*), occurs among the products of hydrolysis of gliadin, salmine, gelatin, casein, etc.; ***l*-hydroxyproline** also occurs among the products of the hydrolysis of gelatin.

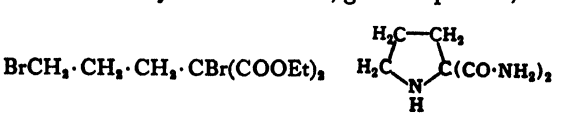


Proline



Hydroxyproline

dl-Proline has been synthesised as follows: Diethyl γ-bromopropylmalonate, from trimethylene dibromide and diethyl malonate, is brominated to give (I); this dibromide with ammonia yields (II), which, boiled with hydrochloric acid, gives *dl*-proline,



I II

Alkylamino-acids and Related Compounds

Sarcosine, $CH_3 \cdot NH \cdot CH_2 \cdot COOH$ (*methylglycine*), was first obtained (Liebig, 1847) by boiling creatine with baryta-water (p. 628); it is also formed when caffeine is similarly treated, but apparently it is not produced by the hydrolysis of proteins. It may be prepared synthetically from chloroacetic acid and methylamine,

$$CH_3 \cdot NH_2 + CH_2Cl \cdot COOH = CH_3 \cdot NH \cdot CH_2 \cdot COOH + HCl.$$

Sarcosine melts and decomposes at 210–220°, giving dimethylamine and carbon dioxide,

$$CH_3 \cdot NH \cdot CH_2 \cdot COOH = CH_3 \cdot NH \cdot CH_3 + CO_2.$$

Choline, $CH_2(OH) \cdot CH_2 \cdot N(CH_3)_3 \cdot OH$ (*β-hydroxyethyltrimethylammonium hydroxide*), is an alcohol related to betaine (below). It is one of the products of the hydrolysis of lecithin (p. 630), and is widely distributed in the animal and vegetable kingdoms. It was discovered by Strecker in bile (Gr. *cholē*), and its constitution was established by Baeyer. Choline is contained in hops, and also in the alkaloid, sinapine, which occurs in mustard-seeds; it is produced in corpses, as the result of putrefactive changes.

Choline is a strongly alkaline liquid, miscible with water; a characteristic salt is the *platinichloride*, $(C_5H_{14}ON)_2PtCl_6$, which crystallises from water in plates.

When a strong aqueous solution of choline is boiled, glycol and trimethylamine are formed,

$$CH_2(OH) \cdot CH_2 \cdot N(CH_3)_3 \cdot OH = CH_2(OH) \cdot CH_2 \cdot OH + N(CH_3)_3,$$

a decomposition which clearly shows the constitution of the substance. Choline was first synthesised by Wurtz, who obtained it by evaporating an aqueous solution of ethylene oxide with trimethylamine,

$$\begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix} > O + N(CH_3)_3 + H_2O = CH_2(OH) \cdot CH_2 \cdot N(CH_3)_3 \cdot OH.$$

Neurine, $CH_2{:}CH \cdot N(CH_3)_3 \cdot OH$ (*vinyltrimethylammonium hydroxide*), is formed when choline is heated with baryta-water, and is also a decomposition product of lecithin, from which it is doubtless produced by bacterial action in corpses. It is exceedingly poisonous, and is one of the important ptomaines.

Betaine, $HOOC \cdot CH_2 \cdot N(CH_3)_3 \cdot OH$ (*lycine*), may be regarded

as a derivative of sarcosine, or of glycine. It occurs in beetroot (*Beta vulgaris*), and is obtained in large quantities as a by-product in the manufacture of beet-sugar; it is also found in some seeds, especially in those of the cotton-plant.

Betaine is very soluble in water, and can be obtained in deliquescent crystals, which may be those of the hydroxy-acid, but at 100° they lose the elements of water and are converted into a *salt*, $^{+}N(CH_3)_3 \cdot CH_2 \cdot CO \cdot O^{-}$.

This salt, also called betaine, can be obtained from chloroacetic acid and trimethylamine,

$$Me_3N + Cl \cdot CH_2 \cdot COOH = Me_3N^{+} \cdot CH_2 \cdot COO^{-} + HCl;$$

it melts at about 293°, partly undergoing isomeric change into methyl dimethylaminoacetate, $N(CH_3)_2 \cdot CH_2 \cdot COOMe$. Corresponding derivatives of other α-, β-, and γ-amino-acids also lose a molecule of water, giving inner salts, or *betaines* of the type shown above.

Muscarine, $CH_3 \cdot CH_2 \cdot CH(OH) \cdot CH(CHO) \cdot N(CH_3)_3 \cdot OH$, is found in the fungus, Fly Agaric (*Amantia muscaria*), which is highly toxic to flies. It is a strong base, and is very poisonous to man, acting especially on the heart.

Creatine, $NH{:}C(NH_2) \cdot N(CH_3) \cdot CH_2 \cdot COOH$, is a very important substance found in the muscles, nerves, and blood, and also in considerable proportions in meat extract, from which it was isolated by Chevreul in 1843. The muscles contain about 0·4% of creatine, and it has been calculated that those of a full-grown man contain no less than 90–100 grams of this substance. The name creatine is derived from Gr. *kreas*, flesh.

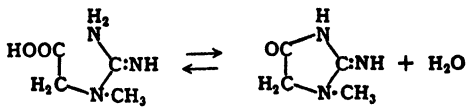
Creatine crystallises from water in hydrated prisms ($1H_2O$); it is moderately soluble in water, very sparingly soluble in alcohol. It has a neutral reaction and a bitter taste, and forms salts with 1 equivalent of an acid, but it does not possess acidic properties. When evaporated with acids it is converted into *creatinine* (p. 629), and when heated with baryta-water, it is decomposed into urea and *sarcosine*,

$$NH{:}C(NH_2) \cdot N(CH_3) \cdot CH_2 \cdot COOH + H_2O = NH_2 \cdot CO \cdot NH_2 + NH(CH_3) \cdot CH_2 \cdot COOH.$$

Creatine has been synthesised by heating cyanamide with sarcosine in alcoholic solution,

$$N{\vdots}C \cdot NH_2 + HN(CH_3) \cdot CH_2 \cdot COOH = NH{:}C(NH_2) \cdot N(CH_3) \cdot CH_2 \cdot COOH.$$

Creatinine, $C_4H_7ON_3$, can be prepared from creatine, into which it is reconverted by alkalis. It is found (about 0·13%) in urine, and is also present in the muscles, especially after great exertion ; in both these cases it may be produced from creatine.



Creatinine is much more soluble in water than is creatine ; it is a strong base, and yields salts, such as the hydrochloride, $C_4H_7ON_3,HCl$. When zinc chloride is added to its aqueous solution, a highly characteristic, sparingly soluble compound, $(C_4H_7ON_3)_2,ZnCl_2$, separates in fine needles, and this compound is used in the estimation of creatinine. Creatinine reduces Fehling's solution, and gives with phosphomolybdic acid a yellow, crystalline precipitate.

Compounds found in the Bile

The digestion of fats in the animal body depends on their decomposition in the intestines by hydrolysing enzymes ; in order to facilitate such reactions, the fats, which are of course very sparingly soluble in water, are there emulsified by various agents, of which *glycocholic acid* and *taurocholic acid* are examples, contained in the bile.

Glycocholic acid, $C_{24}H_{39}O_4\cdot NH\cdot CH_2\cdot COOH$, occurs in human bile in the form of its sodium salt, $C_{26}H_{42}O_6NNa$. It forms needles, melts at 154°, and is soluble in water and alcohol, but very sparingly so in ether ; its alcoholic solution is dextrorotatory. When boiled with alkalis, it yields (salts of) *cholic acid* and glycine,

$$C_{24}H_{39}O_4\cdot NH\cdot CH_2\cdot COOH+H_2O = C_{24}H_{40}O_5+NH_2\cdot CH_2\cdot COOH.$$

Taurocholic acid, $C_{24}H_{39}O_4\cdot NH\cdot CH_2\cdot CH_2\cdot SO_3H$, also occurs in human bile and in the bile of the ox and other animals, in the form of its sodium salt, $C_{26}H_{44}O_7NSNa$. It crystallises in needles, is readily soluble in alcohol, and is dextrorotatory. When boiled with alkalis, it gives cholic acid and taurine (as salts),

$$C_{24}H_{39}O_4\cdot NH\cdot CH_2\cdot CH_2\cdot SO_3H+H_2O = C_{24}H_{40}O_5+NH_2\cdot CH_2\cdot CH_2\cdot SO_3H.$$

Taurine, $NH_2\cdot CH_2\cdot CH_2\cdot SO_3H$, or $^+NH_3\cdot CH_2\cdot CH_2\cdot SO_3^-$ (*β-aminoethanesulphonic acid*), was discovered by Gmelin, in 1824, in

ox-gall (p. 629). It is readily soluble in water, but insoluble in alcohol, and decomposes at about 240°; it is neutral to indicators, but forms salts, such as the sodium salt, $NH_2 \cdot CH_2 \cdot CH_2 \cdot SO_3Na$, with bases.

Cholic acid, $C_{24}H_{40}O_5$, crystallises in plates (m.p. 197°), which are sparingly soluble in water, readily so in alcohol and ether; its solutions are dextrorotatory.

In addition to cholic acid, several other closely related acids occur, in combination with glycine or taurine, in the bile of man and of various animals (Part III).

Lecithin is very widely distributed throughout the animal and vegetable kingdoms and is an example of a group of substances known as *phosphatides*. It is found in small proportions in bile and in most organs of the body, and is especially prominent in the brain-substance and nerve tissues, the blood corpuscles, and the liver; it occurs in considerable proportions in yolk of egg (hence its name, from Gr. *lecithos*, yolk of egg), and is also found in plants, particularly in the seeds.

Lecithin is a waxy, amorphous, very hygroscopic substance, readily soluble in alcohol and ether; in contact with water, it swells up and forms an opalescent, colloidal solution.

It is dextrorotatory, but is readily racemised. When hydrolysed it gives choline (1 mol.), two or more (saturated or unsaturated) monocarboxylic acids (2 mol. in all), such as stearic, palmitic, or oleic acid, and glycerophosphoric acid (1 mol.),[1] or its decomposition products.

The constitution of lecithin may, therefore, be represented by the formula,

$$\begin{array}{l} CH_2 \cdot O \cdot CO \cdot R \\ | \\ CH \cdot O \cdot CO \cdot R \\ | \\ CH_2 \cdot O \cdot PO(OH) \cdot O \cdot CH_2 \cdot CH_2 \cdot NMe_3 \cdot OH, \end{array}$$

in which —CO·R represents the radical of one of the acids just mentioned, or that of some other monocarboxylic acid; the natural product, however, is a mixture of this α- with the corresponding

[1] *Glycerophosphoric acid,* $C_3H_5(OH)_2 \cdot O \cdot PO(OH)_2$ (*glyceryl monophosphate*), is a thick syrup, prepared from glycerol and metaphosphoric acid; salts of glycerophosphoric acid are used in medicine as a source of phosphorus.

β-glycerophosphoric acid compound. Many varieties of lecithin occur in animals and plants, differing from one another as regards the organic acids which they give on hydrolysis.

Cephalin, which usually occurs together with lecithin, is similar to the latter in structure but the substituted phosphoric acid derivative is condensed with β-hydroxyethylamine instead of with choline. Cephalin, like lecithin, is a mixture of closely related substances.

CHAPTER 40

URIC ACID AND OTHER PURINE DERIVATIVES

THE principal compounds described in this chapter are closely related in structure and are classed as the *purine* derivatives (p. 636). Some of them occur in the vegetable kingdom or in the animal kingdom only; others are found in both. Uric acid and other purine derivatives of animal origin are formed in the human body from the decomposition or degradation products of the highly complex proteins (p. 641).

Uric acid and Ureides

Uric acid, $C_5H_4O_3N_4$, occurs in human urine, which, when concentrated, deposits the acid as a light yellow powder; sometimes uric acid gradually accumulates in the bladder, forming considerable masses (stones), or is deposited in the tissues of the body (gout and rheumatism). It was discovered (in 1776) by Scheele in urinary calculi. It also occurs in large proportions as ammonium urate in the excrement of birds (*guano*) and reptiles, and is conveniently prepared by boiling the excrement with caustic soda, until all the ammonia has been expelled, and then pouring the hot filtered liquid into hydrochloric acid; the uric acid gradually separates as a fine crystalline powder.

Uric acid is practically insoluble in alcohol and ether, and very sparingly so in water (1 part dissolves in 88,000 parts of water at 18°, and in 1800 parts at 100°).

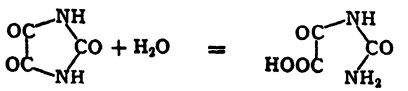
It behaves like a weak dibasic acid; with sodium carbonate solution it yields a sodium hydrogen salt, $C_5H_3O_3N_4Na, \frac{1}{2}H_2O$, but with sodium hydroxide solution it gives the normal sodium salt, $C_5H_2O_3N_4Na_2, H_2O$. The metallic hydrogen salts, like the acid, are all very sparingly soluble in water, but the lithium hydrogen salt is more soluble (1 in 368 parts at 19°) than those of the other alkali metals, and for this reason lithium carbonate is used in medicine, in cases of gout and rheumatism.

Test for Uric Acid. When uric acid (say 0·05 g.) is evaporated to dryness in a porcelain basin with a few drops of concentrated nitric acid, it gives first a yellow and then a reddish pink residue,

which dissolves in ammonia, forming a purple red solution (*murexide* reaction). When it is heated alone, uric acid decomposes, giving ammonia, carbon dioxide, urea, cyanuric acid, and other products.

The first important evidence as to its structure was obtained by a study of the oxidation products of the acid; when treated with nitric acid under suitable conditions, it yields *oxalylurea*, *mesoxalylurea*, and *urea*.

Oxalylurea (*parabanic acid*), $C_3H_2O_3N_2$, is crystalline, soluble in water and alcohol and decomposes at about 243°; it yields a silver derivative, $C_3O_3N_2Ag_2$, and thus behaves like a dibasic acid. When treated with baryta-water, it is hydrolysed in two stages, yielding first *oxaluric acid*, and then oxalic acid and urea,



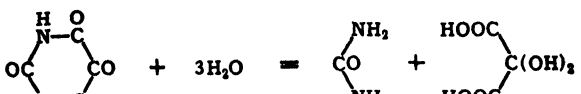
Oxalylurea Oxaluric acid

$$NH_2 \cdot CO \cdot NH \cdot CO \cdot COOH + H_2O = C_2H_2O_4 + CO(NH_2)_2.$$

The constitution of *oxalylurea* is further established by the synthesis of the compound from a mixture of oxalic acid and urea, in the presence of phosphorus oxychloride.

Mesoxalylurea (*alloxan*), $C_4H_2O_4N_2$, crystallises from water in hydrated prisms ($4H_2O$). In contact with the skin its aqueous solution produces, after some time, a purple stain; ferrous salts colour the aqueous solution indigo-blue.

When boiled with alkalis, it is converted into urea and a salt of *mesoxalic acid*,[1]



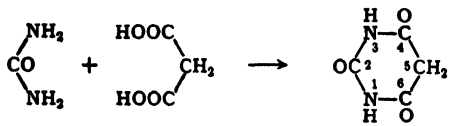
Mesoxalylurea Mesoxalic acid

Oxalylurea and mesoxalylurea are classed as *ureides*, a term which is also applied to simple open chain acyl derivatives of

[1] *Mesoxalic acid*, or *dihydroxymalonic acid*, is formed when dibromomalonic acid, $CBr_2(COOH)_2$, is boiled with baryta-water; it melts at 119°, and is one of the few compounds in the molecule of which there is a group, $>C(OH)_2$, stable at 100°. This group is probably present also in the molecule of alloxan.

urea, such as *acetylurea*, $NH_2 \cdot CO \cdot NH \cdot CO \cdot CH_3$, and *diacetylurea*, $CO(NH \cdot CO \cdot CH_3)_2$. The more important ureides, however, are cyclic compounds, derived from urea by the displacement of one of the hydrogen atoms of both the NH_2— groups by a bivalent acid radical, and in addition to the two examples given above the derivative of malonic acid is of interest.

Malonylurea (*barbituric acid*), $C_4H_4O_3N_2$, may be prepared by heating a mixture of urea and malonic acid with phosphorus oxychloride at 100°,



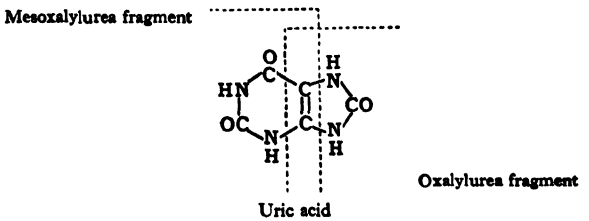
and also by boiling an alcoholic solution of urea with diethyl sodiomalonate; it crystallises from water in prisms ($2H_2O$), and from its solution in ammonia, silver nitrate precipitates a *silver* derivative, $C_4H_2O_3N_2Ag_2$.

Numerous derivatives of malonylurea are used as soporifics or anaesthetics, as, for example, 5:5-*diethylmalonylurea* (*barbitone*, *Veronal*), 5-*phenyl*-5-*ethylmalonylurea* (*phenobarbitone*), 1:5-*dimethyl*-5-cyclo*hexenylmalonylurea* (*Evipan*) and the sodium derivative of 5-*ethyl*-5-*β*-*pentylmalonylthiourea* (*soluble thiopentone*).

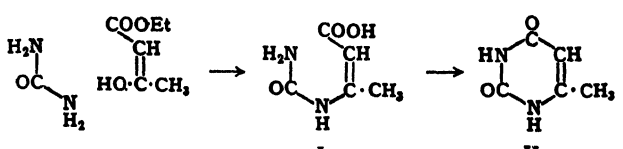
It will be seen from the formulae of the ureides of dicarboxylic acids that the molecules of these compounds, like those of succinimide and phthalimide contain imido-groups —CO·NH·CO—; as the hydrogen atom of such a group is displaceable by metals, and the ureides thus formed salts, some of them were given names such as parabanic acid, barbituric acid, etc., before their structures were known. Uric acid, and other members of the purine group which give metallic salts, are also imides and not carboxylic acids. It is not easy to decide whether the molecules of these salt-forming ureides contain the lactam group —CO·NH—, or the tautomeric lactim —C(OH):N— complex, and either formulation may be used [1]; it is known, however, that when the metallic salts react with methyl iodide, every methyl group in the product is directly combined with nitrogen. The first product of hydrolysis of a ureide of this type, such as oxalylurea, is called a *ureido-acid*, as, for example, oxaluric acid.

[1] The lactam formulae are used here but the systematic names are often those of the lactim (p. 637).

Syntheses of Uric Acid. The constitutions and relationships of the above, and of other *degradation* products of uric acid, having been established—mainly by Baeyer—the following structural formula for the acid was suggested by Medicus in 1875 :

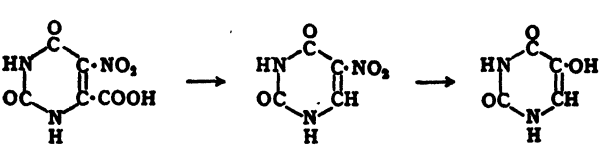


This formula, which was based on the formation of the three oxidation products, oxalylurea, mesoxalylurea, and urea, was finally established by the following synthesis of uric acid by Behrend and Roosen : Ethyl acetoacetate (in the enolic form) condenses with urea, giving *ethyl β-uramidocrotonate* ; and the corresponding acid, *β-uramidocrotonic acid*, (I), which is obtained by hydrolysis, readily loses water and forms *methyluracil*, (II).



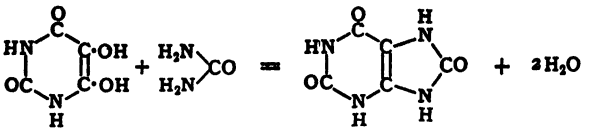
I II

When methyluracil is treated with nitric acid, not only is the methyl radical oxidised to carboxyl, but a nitro-group is also substituted for an atom of hydrogen. The *nitrouracilic acid*, (III), which is thus obtained, is decomposed in boiling alkaline solution, giving *nitrouracil*, (IV), which, when treated with tin and hydrochloric acid, is converted into a mixture of *aminouracil* and *hydroxyuracil*, (V).



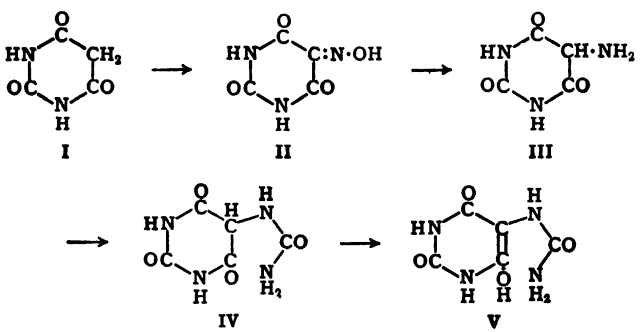
III IV V

Bromine-water oxidises hydroxyuracil to *dihydroxyuracil* (*dialuric acid*, VI), which, when heated with urea and sulphuric acid, yields uric acid, (VII).



VI VII

A later synthesis of uric acid was carried out as follows : *Malonyl-urea* (*barbituric acid*, I), is treated with nitrous acid, by which it is converted into *violuric acid*, (II). On reduction. this acid gives *uramil*, (III), which reacts with potassium cyanate in aqueous solution to form pseudo*uric acid*, (IV) :



I II III

IV V

When this acid is melted with oxalic acid, or heated with hydrochloric acid, it loses the elements of water and gives uric acid (above) ; in this last stage (accomplished by E. Fischer) the *pseudo*-uric acid probably first undergoes a tautomeric change into the enolic form, (V).

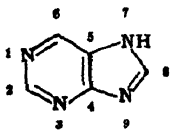
Methyluric Acids. When an alkaline solution of uric acid is shaken with an excess of methyl iodide, mono-, di-, tri-, and finally a tetra-methyluric acid, are formed ; in all these compounds, the methyl groups are directly combined with nitrogen.

Other Purine Derivatives [1]

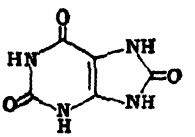
Uric acid, and many other related important natural products, may be regarded as derived from *purine* ; this compound and many

[1] Compare footnote, p. 622.

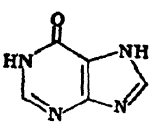
f its derivatives were synthesised by E. Fischer. The names and ɔrmulae of the more important members of the purine group are iven below, and in order to indicate the positions of the sub-tituents, the structure of the parent substance is numbered con-entionally as shown.



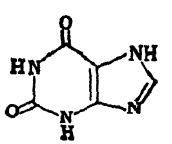
Purine



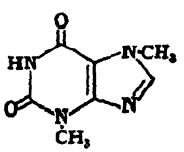
Uric acid
(2:6:8-trihydroxypurine)[1]



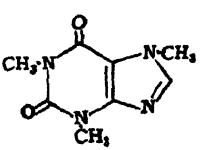
Hypoxanthine
(6-hydroxypurine)



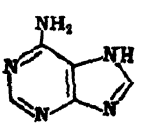
Xanthine
(2:6-dihydroxypurine)



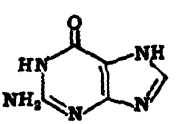
Theobromine
(3:7-dimethylxanthine)



Caffeine
(1:3:7-trimethylxanthine)



Adenine
(6-aminopurine)

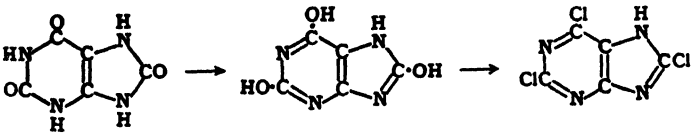


Guanine
(2-amino-6-hydroxypurine)

Purine, $C_5H_4N_4$, may be obtained from uric acid by first heating the acid at about 160° with a large excess of phosphorus oxychloride, which converts it into 2:6:8-*trichloropurine*; in this transformation the uric acid reacts as if it were a trihydroxy-compound (2:6:8-

[1] Compare footnote, p. 634.

trihydroxypurine) or tri-lactim, since three atoms of hydrogen *and* three atoms of oxygen are displaced by three atoms of chlorine :



Uric acid (Lactam structure) — Uric acid (Lactim structure) — 2:6:8-Trichloropurine

The 2:6:8-trichloropurine thus obtained, treated with hydriodic acid at 0°, is converted into 2:6-*di-iodopurine*, and this compound, with zinc-dust and water, is reduced to purine.

Purine melts at 216°, and is very readily soluble in water ; it has both basic and acidic properties.

Hypoxanthine, $C_5H_4ON_4$ (*sarkine*, or 6-*hydroxypurine*), has been found, usually accompanied by xanthine, in the blood and in urine ; also in the muscles, spleen, liver, pancreas, and marrow. It is sparingly soluble in water, but dissolves readily in both acids and alkalis ; it may be obtained from adenine, as described later.

Xanthine, $C_5H_4O_2N_4$ (2:6-*dihydroxypurine*), occurs in small proportions in the blood, the liver, the urine, and in urinary calculi ; it is also present in tea. It may be obtained by treating guanine with nitrous acid or from uric acid ; 2:6:8-trichloropurine with sodium ethoxide, gives 2:6-*diethoxy*-8-*chloropurine*, which is converted into xanthine by hydriodic acid.

Xanthine is an ill-defined powder, sparingly soluble in water, but readily soluble in alkalis ; it gives a lead derivative, which, when heated with methyl iodide, yields *theobromine*. When oxidised with potassium chlorate and hydrochloric acid, it is resolved into urea and mesoxalylurea.

Theobromine, $C_7H_8O_2N_4$ (3:7-*dimethylxanthine*), occurs in cocoa-beans, and resembles caffeine in properties ; when treated with an ammoniacal solution of silver oxide, it yields *silver theobromine*, which reacts readily with methyl iodide, giving caffeine.

Theophylline, $C_7H_8O_2N_4$ (1:3-*dimethylxanthine*), an isomeride of theobromine, occurs in tea and melts at 264°.

Caffeine, $C_8H_{10}O_2N_4$ (*theine*, 1-*methyltheobromine*, or 1:3:7-*trimethylxanthine*), occurs in coffee-beans (1–1·5%), in tea (2–5%), in kola nuts (1–2%), and in other vegetable products.

Tea (1 part) is macerated with hot water (4 parts), milk of lime (1 part) is added, and the mixture is evaporated to dryness on a water-bath; the caffeine is then extracted by means of chloroform, the extract is evaporated, and the crude base is purified by recrystallisation from water.

Caffeine crystallises in needles ($1H_2O$), melts at 235°, and at higher temperatures sublimes unchanged; it has a bitter taste, and is sparingly soluble in cold water and alcohol. It is a feeble base, and forms salts with strong acids only; even the *hydrochloride*, $C_8H_{10}O_2N_4,HCl$, is hydrolysed by water. Caffeine is a nerve stimulant and also a diuretic; its salts, generally the *citrate*, are used in medicine.

Tests for Caffeine. When caffeine (say 0·05 g.) is evaporated with concentrated nitric acid (1–2 drops) in a porcelain basin, it gives a yellow residue, which, after having been cautiously heated over a free flame until it has turned brown, gives a purple red solution with ammonia (murexide reaction, p. 633). A solution of caffeine (0·05 g.) in chlorine-water (about 5 c.c.) yields, on evaporation, a yellowish-brown residue, which dissolves in dilute ammonia, giving a purple solution.

Caffeine may be obtained from uric acid in various ways, as, for example, by the following stages:

Uric acid ⟶ trichloropurine ⟶ diethoxychloropurine ⟶ xanthine ⟶ theobromine ⟶ caffeine.

A simpler method, which has been employed commercially, is to convert uric acid into tetramethyluric acid (p. 636), which with phosphorus oxychloride at 160° gives chlorocaffeine, a methyl group being displaced by chlorine; on reduction with hydriodic acid the chloro-derivative gives caffeine.

Adenine, $C_5H_5N_5$ (*6-aminopurine*), may be prepared from the nuclei of cells, and is thus often found in the extracts of animal tissues. It crystallises from water in pearly plates ($3H_2O$). Nitrous acid converts it into *hypoxanthine*, the amino- being displaced by a hydroxyl group. It has been obtained synthetically from trichloropurine, which, when treated with ammonia, gives *6-amino-2:8-dichloropurine*; the latter, on reduction with hydriodic acid, gives adenine.

Guanine, $C_5H_5ON_5$ (*2-amino-6-hydroxypurine*), has been found in guano, the liver, the pancreas, and in animal tissues. It can be

obtained from 2:6:8-trichloropurine, which, when heated with alkalis, gives 6-hydroxy-2:8-dichloropurine; this compound is converted into 8-chloroguanine with alcoholic ammonia, and the product, reduced with hydriodic acid, gives guanine. It is an ill-defined powder, which combines with acids to form crystalline salts. When treated with nitrous acid, it yields xanthine, and on oxidation, it gives oxalylurea and guanidine.

In the animal body guanine is transformed into xanthine, and adenine into hypoxanthine, which is then converted into xanthine; the last-named compound is further oxidised to uric acid and, in most mammals, to allantoin. With the exception of uric acid, these purine bases also occur in the vegetable kingdom, especially in germinating seeds.

CHAPTER 41

PROTEINS, HORMONES AND VITAMINS

THE cells of plants and of animals are wonderful laboratories in which compounds of the greatest variety and many of very great complexity are synthesised. It is known that many simple reactions, such as hydrolysis, condensation, oxidation, reduction and so on, may be brought about by enzymes—organic catalysts—without the aid of vigorous reagents such as are used in a chemical laboratory, but how the enzymes themselves originate and exactly how they operate in living organisms have still to be determined.

Plants, exposed to sunlight, absorb carbon dioxide from the air; water and dissolved mineral matter—which must include nitrates or ammonium salts—from the soil; and from these simple materials produce carbohydrates, fats, and proteins and all they require for their sustenance and growth. In addition they produce a vast number of other very important compounds of various types, such as alkaloids, terpenes, essential oils, resins and gums, rubber, colouring matters, glycosides, purines and so on, the functions of many of which are unknown.

Animals, on the other hand, cannot synthesise the components of their bodies from the simple materials utilised by plants; they must be supplied with vegetable carbohydrates, fats, and proteins, as food, from which they in their turn elaborate the great variety of compounds essential to their life.

Two types of very abundant components of plants, namely carbohydrates and fats, have already been described, and also some (principally degradation) products, from animal sources, but the most important and the most complex components of animals, the proteins, have still to be very briefly considered.

The Proteins

Raw white of egg, when separated from the yolk, membrane, and shell, is a viscous, colourless and transparent fluid, miscible with water; on exposure to the air it rapidly loses water, and when dried artificially it quickly shrivels up, giving 12–15% of a translucent amorphous solid, which contains some mineral matter.

When its aqueous solution is half-saturated with ammonium sulphate, a part of it (egg-globulin, *ovaglobulin*) is precipitated and a part (egg-albumin, *ovalbumin*) remains in solution, but both these products are mixtures; the globulins differ from the albumins, inasmuch as they are only soluble in water in the presence of a certain very small proportion of mineral salts; otherwise there is no simple way to distinguish between them.

When white of egg is put into boiling water it undergoes a remarkable change, and is said to have *coagulated*; it is now insoluble in water and opaque, and forms a solid mass, which, however, still contains a large percentage of water; during coagulation, it is probable that chemical as well as physical changes have occurred.

On exposure to the air under ordinary (non-sterile) conditions, raw undried white of egg soon begins to putrefy—that is to say, it is decomposed by bacteria, yielding a great number of products, among which are hydrogen sulphide, ammonia, ptomaines (p. 619), and various amino-acids. Further, when white of egg is heated with dilute mineral acids or with alkalis, it undergoes a profound decomposition, affording successively various highly complex products (albumoses, propeptones, peptones), and finally a mixture of many amino-acids. Similar results are obtained with the aid of digestive enzymes, such as pepsin.

Now egg-albumin and egg-globulin may be taken as examples of a very ill-defined group of substances classed as **proteins**; this term includes such diverse materials as the fibrinogen and haemoglobin of the blood, the main components of the yolk, as well as the white of egg, of lean steak and of cheese, and those of many other foodstuffs.

Apart from water, fat and bone, proteins form not only the most important part of all animal matter (Gr. *prōteios*, primary), but they also occur in considerable proportions in all plants, especially in the seeds (peas, beans, cereals, etc.). It is, in fact, from these vegetable proteins that those contained in animals are formed; taken as food, they are hydrolysed by various enzymes in the body and the soluble products are then assimilated by the animal organism.

The investigation of the proteins—perhaps the most complex of all natural products—is a task of the greatest difficulty. Even their isolation from the colloidal mixtures in which they occur is seldom possible, as they lack those properties which are used for the separation, purification and identification of organic compounds in general. Only a very few, such as ovalbumin, have been obtained in a crystal-

line form, recognisable as individual compounds, and it is difficult, therefore, to give a general account even of their physical properties.

They are usually insoluble not only in water but also in inert organic solvents, with the exception of aqueous alcohol, in which a few may be dissolved. Some of those which are insoluble in water dissolve in aqueous solutions of certain salts, and are thus soluble in the fluids of animal and vegetable organisms. They are non-volatile, even *in vacuo*, and they cannot be converted into volatile or crystalline derivatives which might be more easily isolated. They are optically active and laevorotatory.

One of the very interesting properties shown by some proteins is that, already mentioned, of undergoing *coagulation*, a change which is readily brought about by heat; but different proteins coagulate at somewhat different temperatures, varying roughly between 55° and 75°, and some are also coagulated by alcohol, mineral acids and various other reagents. Coagulation cannot be reversed, but is preceded by the process of *denaturation*, which may be reversible; denatured proteins are insoluble at the isoelectric point, but dissolve in dilute acids or alkalis.

Proteins consist of carbon, hydrogen, oxygen, nitrogen, and usually sulphur; some contain phosphorus as well, but owing to the great difficulties of their purification, the determination of their percentage composition is a very arduous task. As found in nature, all proteins contain mineral matter, and consequently, on ignition, leave a small percentage of ash; after the removal of these mineral components, if possible, by repeated precipitation, dialysis, etc., or when their presence is allowed for, the percentage composition of the various proteins is found to vary within fairly wide limits, as shown by the following figures:

Carbon	50·0–55·0%
Hydrogen	6·9– 7·3%
Nitrogen	15·0–19·0%
Oxygen	19·0–24·0%
Sulphur	0·0– 2·4%

Crystalline ovalbumin has the composition C = 51·48, H = 6·76, N = 18·14, O = 22·66, S = 0·96%; its *empirical* formula, calculated from these values, is approximately $C_{146}H_{226}O_{50}N_{44}S$, which requires C = 51·2, H = 6·6, N = 18·0, and S = 0·9%; as, however, a slight error in the analytical results would make a great difference in the empirical formula, that just given is only a rough approximation.

The molecular weights of some of the proteins have been determined by various special methods, and from the concordant experimental results, it may now be inferred with some assurance that the minimum value for the simpler proteins is about 17,600, or fourteen times as great as that of the octadecapeptide synthesised by E. Fischer.

The molecular weights of all proteins seem to be approximately multiples of about 17,600 and fall into groups obtained by multiplying this figure by 1, 2, 4, 8, 16, 24, 48, 96, 168, 192, or 384. A molecular weight of nearly seven million ($384 \times 17{,}600 = 6{,}760{,}000$) has been found in certain cases. When some proteins are dissolved in water or aqueous salt solutions, the molecular weights vary with changes in the hydrogen ion concentration and such variations are reversible.

Little can be said about their general chemical properties; most of the proteins are neutral, but a few are acidic and dissolve in dilute alkalis; others are very feebly basic. Except for certain constituents of some (conjugated) proteins they all consist, mainly if not entirely, of complex polypeptides.

The X-ray investigation of the polypeptides has shown that each amino-acid in a given chain occurs at regular intervals.

Closely related to the proteins are their degradation products (*albumoses*, *propeptones*, *peptones*, and *polypeptides*) which are successively formed when proteins are hydrolysed with the aid of digestive enzymes (pepsin, trypsin, etc.) or chemical reagents; the final products of hydrolysis, as already stated, are mainly complex mixtures of various amino-acids.

Tests for Proteins.—Most proteins are coloured red by a hot solution of mercuric nitrate containing traces of nitrous acid. This solution (*Millon's* reagent) is prepared by dissolving one part by weight of mercury in two parts of concentrated nitric acid and diluting the solution with twice its volume of water; after some time the supernatant liquid is decanted for use. When a protein is warmed with nitric acid, it gives a yellow colour, which becomes bright orange on the addition of ammonia (*xanthoproteic* reaction). These two tests are given by all proteins (the majority) which contain aromatic amino-acids.

When an excess of potash solution is added to a protein, and then a few drops of copper sulphate solution, a red to violet colouration is produced; this test is called the *biuret* reaction, because its results resemble those given under similar conditions by biuret.

When a protein, or one of its more complex degradation products (above), is warmed with an aqueous solution of ninhydrin (p. 556), it gives a deep-blue colouration (compare amino-acids, p. 618).

In the present state of knowledge, any systematic classification of the proteins is hardly possible, although they may be divided into (*a*) simple, (*b*) conjugated proteins. The simple proteins may then be further subdivided into (*a*) fibrous, (*b*) globular. The former, such as fibroin (from silk) and keratin (from hair), consist of long polypeptide chains, whereas the globular proteins are probably much more complex and consist of more or less spherical molecules. Simple proteins may be further classified by making use of slight differences in their physical properties such as solubility in water, dilute aqueous solutions of inorganic salts, acids, or alkalis ; in their coagulability or otherwise under various conditions and in their behaviour towards certain enzymes.

The *conjugated* proteins, such as haemoglobin, are composed not only of complex protein matter, but also of a small proportion of some *relatively* simple substance which, after gentle hydrolysis, may be separated from the protein and sometimes isolated in a crystalline condition.

The structures of a few of these constituents (*prosthetic* groups) of conjugated proteins have been determined and they have even been synthesised as described in Part III ; only a brief and elementary account of some of the proteins, other than albumin, met with in daily life, is given here.

Caseinogen (*casein*) is contained in milk, in the form of a soluble calcium salt. When milk turns sour, as the result of lactic fermentation (p. 172), or is treated with an acid, the calcium salt is decomposed and impure caseinogen is precipitated as a curd, together with some of the fat, while the milk-sugar (lactose) remains in the aqueous solution (whey). The caseinogen may be purified by dissolving it in very dilute alkali and reprecipitating it with very dilute acetic acid.

Rennet, an aqueous extract prepared from the stomach of the calf, also has the property of curdling milk, and is used for this purpose in making junket, in the manufacture of cheese, and in precipitating casein for the preparation of plastics.

The curd in this case is different from that obtained with acids and is regarded as the insoluble calcium salt of a decomposition product of caseinogen, called *casein*, which is produced from

caseinogen, in the presence of calcium salts, by an enzyme, *rennin*, contained in the rennet.

Caseinogen has an acidic character and dissolves in dilute alkalis; it contains about 0·85% of phosphorus, but otherwise resembles albumin and other proteins in composition. On hydrolysis casein gives all the amino-acids previously described except glycine, and its molecule must be of great complexity.

Oxyhaemoglobin and haemoglobin. The red corpuscles of the blood contain a pigment, which is a conjugated protein of extreme importance. In arterial blood, this pigment is loosely combined with oxygen and is in the form of *oxyhaemoglobin*, but as it is circulated through the animal body, its oxygen is utilised for the vital processes of the organism and it is converted into *haemoglobin*; the venous blood, of a duller colour, then passes to the lungs, where the haemoglobin takes up oxygen and again becomes oxyhaemoglobin. Oxyhaemoglobin, therefore, is the oxygen carrier of the body.

These transformations may also be brought about outside the animal system. When oxyhaemoglobin, in aqueous solution, is brought under greatly reduced pressure, or treated with weak reducing agents, it loses oxygen and is converted into haemoglobin, which is rapidly reconverted into oxyhaemoglobin on exposure to the air. When carbon monoxide is led into its aqueous solution, oxyhaemoglobin loses its oxygen and combines with the monoxide to form *carbonic oxide haemoglobin*, which forms bluish-red crystals. This compound, unlike haemoglobin, is not capable of absorbing and giving up oxygen—a fact which explains the very poisonous action of carbon monoxide. Oxyhaemoglobin, haemoglobin, and carbonic oxide haemoglobin, are all crystalline and all show characteristic absorption spectra, by which they are easily identified and distinguished from one another.

Oxyhaemoglobin may be prepared as follows: The red corpuscles are separated from the plasma of the blood centrifugally and the thick suspension so obtained is treated with ether, which causes the cells to burst. The aqueous solution is then separated in the same way, mixed with alcohol, exposed to oxygen and cooled to −20°, whereon the oxyhaemoglobin is deposited in crystals; it may be purified by recrystallisation from ice-cold alcohol.

Oxyhaemoglobin forms light-red rhombic prisms, which dissolve readily in water and are reprecipitated by alcohol; it was the first

protein to be obtained in a crystalline form. Its percentage composition is much the same as that of ovalbumin (except that oxyhaemoglobin contains about 0·33% of iron) and leads to the empirical formula, $C_{738}H_{1166}O_{208}N_{203}S_2Fe$; on the assumption that one molecule of haemoglobin contains one atom of iron, the calculated molecular weight would be roughly 16,500, but the ultracentrifugal method of determination gives M.W. = 68,000 approximately, a figure which would indicate that the lower value must be multiplied by about four.

Haemin and **Haematin.** The conjugated chromoprotein, haemoglobin, consists of about 94% of protein (globin) and 6% of pigment (*haem*[1]). When oxyhaemoglobin or dried blood is warmed with dilute acetic acid in the presence of sodium chloride, it is decomposed into protein and *haemin*, $C_{34}H_{32}O_4N_4FeCl$, the chloride of haematin, which separates in reddish-brown crystals when the mixture is cooled; these crystals, treated with alkali, give brownish-red flocks of *haematin*, $C_{34}H_{32}O_4N_4Fe\cdot OH$. This formation of haemin and haematin serves as a very delicate test for blood.

Chlorophyll is the green colouring matter of plants; its prosthetic group may be extracted from dried leaves, which contain about 0·8%, with the aid of 90% aqueous alcohol or acetone containing about 20% of water, and thus obtained as a green, wax-like substance. This product is a mixture of two nearly related compounds, distinguished as chlorophyll *a*, $C_{55}H_{72}O_5N_4Mg$, and chlorophyll *b*, $C_{55}H_{70}O_6N_4Mg$, respectively, approximately in the ratio $3a:b$; it is noteworthy that magnesium is an essential constituent of these compounds, just as iron is an essential constituent of haemoglobin.

The function of chlorophyll in the vegetable kingdom is to absorb light energy and use it to transform carbon dioxide from the air, with the liberation of oxygen, into one or more primary products, from which (with the addition of other elements) the various components of plants are generated. According to Baeyer's theory the dioxide is first reduced to formaldehyde, which then undergoes polymerisation (as it is known to do) into sugars; from the latter, starches and celluloses might be produced by the action of enzymes. It is very unlikely, however, that the reactions involved are as simple as suggested, but they are, as yet, little understood.

[1] In haem the iron is in the ferrous state, whereas in haemin and haematin it is ferric.

Chlorophyll, like haemoglobin, shows a characteristic absorption spectrum, and the absorption spectra and other properties of certain chlorophyll derivatives are almost identical with those of certain derivatives of haemoglobin. As the function of haemoglobin is to absorb oxygen, while that of chlorophyll is to set free oxygen from carbonic acid, this close relationship between the two compounds is of great interest.

It has been proved after years of strenuous endeavour, on the part of many skilled workers, that chlorophyll and haemin are very closely related in structure, and as a brilliant climax the latter has been synthesised (Part III).

Gelatin is closely related to the proteins ; it may be obtained by the action of hot water on the protein, *collagen*, which is contained in white fibrous connective tissue.

Clean cartilage, skin, etc., is treated for some time with milk of lime, washed, carefully freed from lime with hydrochloric acid and again washed : it is then heated with water at 55–80°, the filtered solution evaporated at 70–80° and the gelatin, usually in thin, almost colourless sheets, dried at 20° in a vacuum. More impure, coloured extracts, mainly obtained from bones, are used as glue.

Gelatin is a hard, almost transparent, horn-like substance, which is insoluble in alcohol, ether, and practically so in cold water, but dissolves readily in hot water, yielding a solution which sets to a jelly (*gelatinises*) as it cools. When, however, the aqueous solution is boiled during some hours, the property of gelatinising is entirely lost. Gelatin forms an insoluble compound with tannic acid, and the object of the process of tanning is to convert the gelatin of the hides into this hard, insoluble compound, by steeping the skins in tannic acid solution. Gelatin is also rendered insoluble in water when it is treated with formaldehyde. When heated with dilute sulphuric acid, gelatin breaks down, much in the same way as do the proteins, yielding glycine, hydroxyproline, proline, alanine, leucine, and many other amino-acids.

Gelatin is extensively used for making edible jellies and photographic films.

Hormones

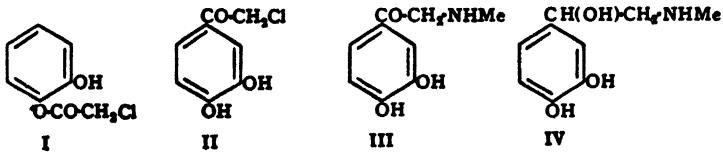
Certain small organs of the body, which at one time seemed to have no particular function, are now known to produce internal secretions, which do not pass to other parts of the body through

definite channels, but are absorbed directly from the gland into the blood system. The secretions of such ductless or *endocrine* glands contain substances, named **hormones** (Gr. *hormōn*, an impulse) by Starling, which are most extraordinarily active, and play a highly important part in exciting or moderating the action of other organs; the deficiency or excess of a hormone in the body leads to serious or fatal results. Three of the better-known hormones are described below; of these, adrenaline and thyroxine, especially the former, are very simple substances, compared with many animal products, their constitutions are known, and they have been synthesised.

***l*-Adrenaline,** $C_9H_{13}O_3N$ (adrenine, epinephrine), is the hormone produced in the very small organs known as the suprarenal or adrenal glands, and was obtained in a crystalline form by Aldrich and by Takamine in 1901. When injected into the blood system, it causes a contraction of the arteries and a very considerable increase in the blood pressure, the effect of a dose of 0·001 mg. given to a cat being recognisable.

Adrenaline is a crystalline, laevorotatory, secondary base (m.p. 216°), sparingly soluble in water, but readily soluble in caustic alkalis; its phenolic character is shown by its behaviour towards alkalis, and also by the fact that, like catechol, it gives an intense green colouration with ferric chloride. It is decomposed by boiling hydriodic acid, giving methylamine, and it affords protocatechuic acid (p. 602) when it is fused with alkalis; when it is exhaustively methylated and the decomposition product of the quaternary hydroxide is then oxidised, *veratric acid* (p. 612) is formed.

From these and other facts the structural formula (IV) was assigned to adrenaline, and was fully established by the following synthesis: Catechol, treated with chloroacetyl chloride, gives catechol chloroacetate, (I), which with phosphorus oxychloride undergoes isomeric change into 4-*chloroacetylcatechol*, (II); this product, with an excess of methylamine, is converted into a crystalline, substituted ketone, *adrenalone*, (III), which is reduced with aluminium amalgam and water to dl-*adrenaline*, (IV):



The *dl*-base is then converted into its hydrogen tartrate, which is fractionally crystallised from methyl alcohol; the *l*BdA salt is thus separated, and the base, obtained from it, is identical in every respect with *l*-adrenaline.

The *d*-base, which remains as hydrogen tartrate in the mother-liquors, is readily racemised by hydrochloric acid, and from the *dl*-compound thus formed further quantities of the *l*-base are obtained. The physiological activity of *d*-adrenaline is only about $\frac{1}{15}$th of that of the *l*-base.

***l*-Thyroxine,** $C_{15}H_{11}O_4I_4N$, occurs combined with a protein in the thyroid gland, the defective development of which was found to be associated with cretinism and myxoedema, whereas its abnormal enlargement was observed in cases of goitre; preparations of the thyroid glands of animals, administered by the mouth, were proved to have a very beneficial effect on patients suffering from cretinism and myxoedema, so that a relation between the gland and these diseases was clearly established.

In 1896 Baumann made the surprising discovery that the thyroid contained combined iodine, and twenty years later a crystalline iodo-compound was isolated from it by Kendall; minute doses of this compound, which he named *thyroxine*, were found to have the same beneficial effect on the above-mentioned diseases as large quantities of the gland-substance.

The molecular formula of thyroxine was determined by Harington, who also showed that, on reduction with hydrogen in alkaline solution in the presence of colloidal palladium, the iodine was displaced by hydrogen, giving a primary base, *desiodothyroxine*, $C_{15}H_{15}O_4N$.

The structure of desiodothyroxine was then shown to be (I) as follows: (*a*) On exhaustive methylation, followed by the decomposition of the quaternary salt, (I), gave an unsaturated acid, (II), which on oxidation was converted into an aldehyde, (III), or the corresponding acid:

I $HO \cdot C_6H_4 \cdot O \cdot C_6H_4 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$

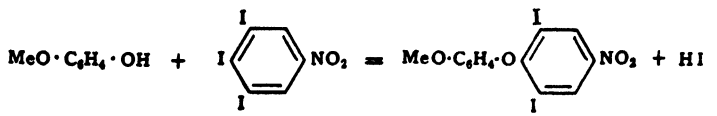
II $MeO \cdot C_6H_4 \cdot O \cdot C_6H_4 \cdot CH{:}CH \cdot COOH$

III $MeO \cdot C_6H_4 \cdot O \cdot C_6H_4 \cdot CHO$

(*b*) When fused with potash, desiodothyroxine, (I), was converted into quinol, a phenol, $HO \cdot C_6H_4 \cdot O \cdot C_6H_4 \cdot CH_3$ (derived from phenyl-*p*-tolyl ether), *p*-hydroxybenzoic acid, oxalic acid and ammonia.

The constitutions of these various degradation products of desiodothyroxine having been determined, and collateral evidence as to the positions of the iodine atoms in thyroxine having been obtained, it was possible to assign to the latter the structure (VI); this formula was finally established by the synthesis of thyroxine, accomplished by Harington and Barger, and now used for the commercial preparation of the hormone:

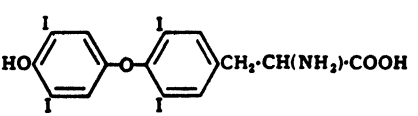
3:4:5-*Tri-iodonitrobenzene* is prepared by treating *p*-nitroaniline with iodine chloride and then displacing the 1-amino-group of the resulting 2:6-di-iodo-4-nitroaniline by iodine in the usual manner. This compound reacts with p-*methoxyphenol* in the presence of anhydrous potassium carbonate, giving a methoxynitrodi-iodo-derivative of diphenyl ether, (IV).



IV

The nitro-group in this compound is successively transformed into $-NH_2$, $-N_2X$, —CN, and —CHO by the usual methods, and the aldehyde thus obtained is converted into (V) by the azlactone method (p. 617) with accompanying demethylation; finally this saturated *dl*-amino-acid is treated with potassium tri-iodide in ammoniacal solution and is thus converted into β-[3:5-di-iodo-4-(3:5-di-iodo-4-hydroxyphenoxy)]-phenyl-α-aminopropionic acid, (VI):

V $HO\cdot C_6H_4\cdot O\cdot C_6H_2I_2\cdot CH_2\cdot CH(NH_2)\cdot COOH$

VI 

This *dl*-acid has been resolved and gives an *l*-acid, identical with thyroxine in physical, chemical, and physiological properties.

Insulin is a hormone, which is secreted by the islet cells (*islets of Langerhans*) of the pancreas of man and of animals, and is of great physiological importance. It has been known for many years that the removal of the pancreas brings on the symptoms of *diabetes*

mellitus, and it seemed very probable, therefore, that this disease was closely connected with some deficiency in that organ; it was not, however, until 1922 that Banting and Best succeeded in separating from the pancreas a stable preparation which, when injected into the system, was found to diminish the proportion of glucose in the blood, and to produce a wonderful improvement in the condition of patients suffering from diabetes.

'Men declining quickly or slowly through stages of weakness and pain to early death have been brought within a few days back to full working powers; sufferers carried to hospital, actually dying of diabetes, already helpless and unconscious, have been resuscitated as by some magic, and have been brought back almost at once to normal life by help of this remedy.'[1]

The preparation, or the hormone contained in it, which produces these effects was named *insulin* by its discoverers.

A crystalline preparation of insulin, which is laevorotatory, was isolated by Abel, who assigned to it the empirical formula, $C_{45}H_{69}O_{14}N_{11}S$; it is a protein and on hydrolysis affords a complex mixture of many amino-acids. The structure of insulin has been elucidated by a brilliant series of investigations by Sanger and his co-workers.

Other important animal hormones are described later (Part III); hormones also occur in the vegetable kingdom (auxins) and one of these has already been mentioned (p. 593).

Vitamins

The work of many investigators, extending over a very long period, gradually led to the conclusion that normal health depended not only on the quantity of food which is consumed, and the composition of its main components, but also on some factor or factors quite unknown.

Scurvy, for example, which in days gone by was rife among sailors during long voyages, was prevented to a greater or less extent by the addition of lemon-juice to the men's rations. Much later it was found that *beri-beri*, a disease common in the East, was due to a diet of cleaned or polished rice, and could be cured by adding an alcoholic extract of the polishings to the food of the sufferer. From

[1] Report of Medical Research Council.

the alcoholic extract of the polishings, there was obtained a highly potent, nitrogenous material which was called '*vitamine*' by Funk, but this preparation was a mixture, and its active component was not isolated.

In 1906, it was shown by Hopkins that although a mixed diet of ordinary food consisting of carbohydrates, fats, proteins, and mineral matter, may be sufficient for normal nutrition, a diet of the same substances, after they have been 'purified,' may be totally inadequate and give rise to various diseases; he also proved that fresh milk contains something, other than the components just mentioned, which is essential to a growing animal.

It was then found that many other food-stuffs, such as butter, egg-yolk, wheat-germ, orange-juice, fresh vegetables, etc., also contain some very active components which are essential to normal health; these unknown compounds, called *accessory food factors* by Hopkins, were afterwards named *vitamins*, and were distinguished as vitamin A, B, C, etc., according to their effects, or to the results produced by their absence. Later on, it was found that certain active extracts or preparations which had been regarded as *a* vitamin were mixtures of active substances, each of which had a specific physiological effect; these components, of vitamin B for example, were then distinguished as B_1, B_2, and so on.

Vitamin A enables an organism to resist infection and restores the growth of young animals suffering from a diet deficient in this vitamin; it does not occur as such in vegetable food, but is produced in the body from *carotenoids* which are found in many plants, such as carrots, spinach, tomatoes, etc., and also in cod-liver oil.

When about 0·1 g. of an oil or fat, dissolved in chloroform, is added to about 2 c.c. of a 30% solution of antimony trichloride in chloroform, a blue colouration is obtained in the presence of vitamin A, but this test is also given by certain other substances.

Vitamin B (a mixture of B_1 and B_2) is present in rice-polishings, yeast, liver, and many vegetables; its absence from a diet brings on *beri-beri* and retarded growth.

Vitamin C is contained in many vegetables, notably in *paprika*, and in lemon-juice, the latter of which has long been used as an antiscorbutic or preventive of scurvy. It is a crystalline, optically active compound, $C_6H_8O_6$, and is also called *ascorbic acid*.

Vitamin D_2, $C_{28}H_{43}\cdot OH$ (*calciferol*), is concerned with the

calcification of bones and teeth; its absence causes rickets. It occurs in cod-liver oil, which was used in medicine as a cure for rickets long before vitamins were discovered; it is also present in notable proportions in the liver oils of halibut and other fish, and in whale-oil.

It is so potent that the effect on bone formation of a daily dose of only 1/400,000 mg. during 14 days can be detected. Calciferol is formed when *ergosterol* is exposed to ultra-violet light. The latter occurs in yeast and ergot[1] and is closely related to *cholesterol*, which is present in the human skin; it is thought that the well-known beneficial effect of sunlight in cases of rickets is due to the production of vitamin D_2 in the body from one or more of such sterols.

Vitamin E is contained in wheat-germ and its absence brings about sterility.

Vitamin K is concerned in the clotting of blood and its absence from the diet lengthens the time required for blood clotting; it occurs in hog's liver fat and green vegetables.

It is thought that all vitamins originate in the vegetable kingdom, and that those present in animal products (eggs, butter, cod-liver oil, etc.) have been produced in the body from vegetable food.

Vitamins may be compared with hormones and with enzymes, since a minute quantity of any member of one of these groups is capable of bringing about, within the body, chemical changes which are essential to normal life.

Penicillin

The significant observation by Fleming in 1929, that during its growth *Penicillium notatum Westling* produced something which hindered or prevented the normal development of some bacteria, led to his discovery of a highly important medicinal substance, but it was not until 1940 that a stable preparation of the active material was isolated by Florey and Chain.

Since that time the results of intense investigations, carried out in collaboration by individual and grouped workers,[2] in this country and the U.S.A. have shown that the antibacterial action of the mould culture is due to organic matter, which Fleming named

[1] A fungus found on the seeds of certain plants, notably rye.

[2] So many biochemists, chemists, physicists, medical men and others have taken part in the development of Fleming's discovery, that it would be invidious to mention particular names other than those already given.

penicillin, and of which several varieties are now known. These closely related compounds, some of which have been isolated as crystalline salts, contain nitrogen and sulphur, as well as C, H and O; they are heterocyclic structures, $C_9H_{11}O_4N_2SR$, the constitutions of which are described later (Part III).

Penicillin is of outstanding importance in medicine owing to its high bacteriostatic action, accompanied by its very low toxicity, if any, to man; it is even more valuable than the sulphanilamide drugs for the treatment of diphtheria, meningitis, anthrax, etc.: unfortunately it is readily decomposed in the animal body. It is now prepared for medicinal use on the large scale, but its extraction from the culture fluid is no easy task.

Penicillin, so far as is known, is in no way related to any vitamin; it is described here as an important compound of general interest.

CHAPTER 42

DYES AND THEIR APPLICATION

ALTHOUGH most organic compounds are colourless, a relatively few, almost exclusively aromatic, are intensely coloured substances, among which representatives of almost every shade occur; all the principal dyes used at the present day, in fact, are aromatic compounds, the primary source of which is coal-tar—hence the well-known expression 'coal-tar colours.' The first of such dyes, *mauve* or *mauveine*, discovered by Perkin (in 1856), was obtained by the oxidation of crude aniline; for this reason those subsequently prepared from other coal-tar components were also called 'aniline dyes.'

That a dye must give rise to colour is, of course, obvious, but a coloured substance is not necessarily a dye, in the ordinary sense of the word, unless it is also capable of fixing itself, or of being fixed, on the fabric to be dyed, in such a way that the colour is not removed when the fabric is rubbed, or washed with water; azobenzene, for example, is highly coloured, but it is not a dye, because it does not fulfil the second condition.

Now, when a piece of *silk* or *wool* is soaked in a solution of picric acid, it is dyed yellow, as the colour is retained when the material is washed with water. When, however, a piece of *calico* or other *cotton* material is treated in the same way, the picric acid is washed out and the fabric is not dyed. A given substance, therefore, may be a dye for certain materials, but not for others; silk and wool are dyed by picric acid, but cotton is not—a behaviour which is repeatedly met with in the case of other colouring matters.

Now, materials such as wool, cotton, silk, rayon, etc., consist of minute hollow or solid fibres, the walls of which, like parchment paper and certain membranes, allow of the passage of water and of dissolved crystalloids by diffusion, but not that of colloid substances, or, of course, of matter in coarse suspension. If, therefore, picric acid were present in a fibre, *as* picric acid, it should be extracted from this fibre by water; since, in the case of silk and wool, this does not occur, it may be assumed that the picric acid has combined

with some substance in the fibre, and has thus been converted into a yellow compound, which is insoluble in water.

The nature of the insoluble products which are thus formed when a material is dyed is not known, but there are reasons for supposing that certain components of the fibre unite with the dye to form an insoluble product. This seems probable from the fact that nearly all dyes, which thus fix themselves directly on the fabric, are either basic, acidic, or amphoteric in character. Azobenzene, as already mentioned, is not a dye, probably because it is a neutral substance; if, however, some group, such as an amino-, alkylamino-, or hydroxyl radical, which possesses basic or acidic properties, is introduced into the molecule of azobenzene, then the resulting derivative may be a dye, apparently because it has the property of combining with the components of certain fibres.

Again, certain dyes—as, for example, rosaniline—are salts of bases, which are themselves colourless, and yet some materials may be dyed by mere immersion in the *colourless* solutions of these bases, and the same colour is obtained as with the coloured salt (that is, the dye); this can be easily explained on the assumption that some component of the fibre combines with the colourless base, forming with it a salt of the same colour as the dye. Some fibres, especially those of silk and wool, contain both acidic and basic components, and are often dyed directly both by basic and by acidic dyes; cotton (cellulose), on the other hand, which is free from salt-forming groups, does not combine with either type of dye except in rare cases.

In spite of facts such as these, this explanation of dyeing may not account for the phenomena in all cases, and the dye may be merely adsorbed, giving a solid solution.

Mordants and Lakes

Since the fixing of a dye within the fibre is probably the result of its conversion into some insoluble compound, it seems reasonable to suppose that, even if a colouring matter does not combine with any component of the fibre, it might still be employed as a dye, provided that, after it had passed into the substance of the fibre, it could be there converted into some insoluble product; this principle is applied in the case of many dyes, and the compounds used to fix them in the fibre are termed *mordants*.

Dyes, therefore, may be roughly divided into two classes with respect to their behaviour towards a *given* fabric: (*a*) *Direct* or *substantive* dyes, which fix themselves on the fabric, and (*b*) *Indirect* or *adjective* dyes, which do so only with the aid of a mordant. These terms are merely relative; a dye may be *direct* with respect to wool and silk, *indirect* with respect to cotton, a general behaviour illustrated above in the case of picric acid.

Mordants are substances which (usually after having undergone some preliminary change) combine with dyes, forming insoluble coloured compounds; the colour of the dyed fabric, in such cases, depends on that of the compound thus produced, and not on that of the dye itself, so that by using different mordants different shades or colours are often obtained.

As an example of dyes of the second class, alizarin may be taken, as its applications illustrate very clearly the use of mordants.

When a piece of calico is soaked in an aqueous solution of alizarin, it is coloured *yellow*, but the colour is not fixed, and is easily removed with the aid of soap and water. When, however, a piece of calico, which has been previously *mordanted* with a suitable aluminium salt (below), is treated in the same way, it is dyed a fast *red*, because the alizarin has combined with aluminium hydroxide in the fibre to form a red insoluble substance; if the calico had been mordanted with a ferric salt, it would have been dyed a fast *dark violet*.

A substance such as alizarin, which can thus be used for the production of different colours, is termed a *polygenetic* dye; one which gives one colour only is a *monogenetic* dye.

Compounds very frequently employed as mordants are certain inorganic salts of iron, aluminium, chromium (alums) and tin; also some of their organic salts, such as acetates and thiocyanates, from which an insoluble metallic hydroxide or basic salt can be easily formed by hydrolysis with water.

The process of mordanting cotton involves two operations: firstly, the fabric is passed through, or soaked in, a solution of the mordant, in order that its fibres may become impregnated with the metallic salt; secondly, the fabric is treated in such a way that the salt is decomposed within the fibres, and there converted into some insoluble compound.

The second operation, the fixing of the mordant, so that it will not be washed out when the fabric is brought into the dye-bath, is

accomplished in many ways. One method is to pass the mordanted material through a solution of some weak alkali (ammonia, sodium carbonate, lime), or of some salt, such as sodium phosphate or arsenate, which reacts with the metallic salt in the fibre, forming an insoluble metallic hydroxide, or a phosphate, arsenate, etc. Another method, applicable in the case of mordants which are salts of *volatile acids*, consists in exposing the treated fabric to the action of steam, at a suitable temperature; under these conditions the metallic salt is hydrolysed, the acid volatilises with the steam, and an insoluble hydroxide or basic salt remains in the fibre.

In the case of silk and woollen fabrics, the operations of mordanting and fixing the mordant are commonly carried out simultaneously, by merely soaking the materials in a boiling dilute solution of the mordant; under these conditions the metallic salt is hydrolysed in the fibre, and the product is there retained in an insoluble form; silk is sometimes merely soaked in a cold, concentrated solution of the mordant, and then washed with water to hydrolyse the metallic salt.

In cases where only parts of the fabric are to be dyed, as, for example, in *calico-printing*, a solution of a suitable mordant may be mixed with the dye, together with some thickening substance, such as starch, dextrin, or gum, which prevents the mordant and dye from spreading; the mixture is then printed on the fabric, which is afterwards steamed, whereon the metallic hydroxide, which is produced within the fibre, combines with and fixes the dye.

All these processes have the same object, namely to deposit within the fibre some insoluble compound, which, when afterwards treated with a solution of a suitable dye, forms a coloured substance, stable in the light and towards soap and water.

The coloured substances produced by the combination of a dye with a metallic hydroxide are termed *lakes*, and those dyes which form lakes belong to the class of *acid* dyes.

Tannin is an example of a different type of mordants—namely, of those which are employed with *basic dyes*, such as malachite green (p. 661) and rosaniline (p. 663). The fabric is mordanted by being passed first through a solution of tannin, and then through a weak solution of tartar emetic, or stannic chloride; the tannin is thus changed into an insoluble antimony or tin tannate, which combines with the basic dye, giving an insoluble colloidal product, and thus fixes it in the fibres.

Leuco-compounds and Vat-Dyes

Many organic dye-stuffs may be transformed into colourless compounds on reduction, and when the reduction product can be readily reconverted into the dye by oxidation, it is called a *leuco-compound*.

When an insoluble dye yields a *soluble* leuco-compound, it may be applied to fabrics in a special manner, as, for example, in the case of indigo-blue. Indigo-blue, $C_{16}H_{10}O_2N_2$ (p. 681), is insoluble in water, but on reduction it is converted into a leuco-compound, $C_{16}H_{12}O_2N_2$, known as *indigo-white*, which is soluble in aqueous alkalis. In dyeing with indigo, an alkaline solution of indigo-white is prepared by reducing indigo, suspended in water, with a suitable reagent, and the fabric is then passed through this solution, whereon the indigo-white diffuses into the fibres through their walls; on subsequent exposure to the air, the indigo-white is reconverted into indigo-blue by oxidation, and the insoluble dye is thus fixed in the fabric. Indigo is an important example of the class of *vat-dyes*, which have the very great advantage of not requiring any mordant.

Another method of dyeing, of increasing importance, applicable in the case of azo-dyes, is the direct formation of an insoluble dye-stuff within the fibres, by the process of coupling, as described later (p. 673). In this process, as in vat-dyeing, since the dye-stuff is produced within the fibres, the presence of a particular basic or acidic group in the dye is unnecessary and the coloured product may be a direct dye to all fibres.

So many dyes are known that only a few of the more typical are described in the following pages, and some important groups are not even mentioned, partly because of the complexity of their members, but principally because their description would not illustrate any new principle.

Basic Triphenylmethane Derivatives

Triphenylmethane, $(C_6H_5)_3CH$ (p. 421), is the parent hydrocarbon, from which various brilliant *basic* dyes, such as *malachite green*, *pararosaniline*, and *rosaniline*, are derived.

The various di-and tri-*p*-amino-derivatives of this and related hydrocarbons may be regarded as *leuco-bases*, since, on oxidation, they afford products, the salts of which are used as dyes; the

latter, however, are not vat-dyes, as they are soluble in water and require the use of mordants.

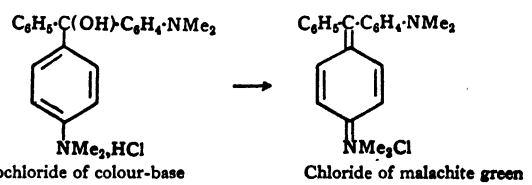
The leuco-base of malachite green, for example, is pp'-*tetramethyldiaminotriphenylmethane* (I), which, on oxidation, is converted into the *colour-base*, pp'-*tetramethyldiaminotriphenyl carbinol* (II),

I $C_6H_5 \cdot CH < \begin{matrix} C_6H_4 \cdot NMe_2 \\ C_6H_4 \cdot NMe_2 \end{matrix}$ II $C_6H_5 \cdot C(OH) < \begin{matrix} C_6H_4 \cdot NMe_2 \\ C_6H_4 \cdot NMe_2 \end{matrix}$

The colour-base, like the leuco-base, is colourless and yields colourless or only slightly coloured salts with cold acids; when warmed with acids, however, such compounds lose the elements of water and give the dyes,

$$\underset{\text{Base of malachite green}}{C_{23}H_{26}N_2O} + HCl = \underset{\text{Chloride of malachite green}}{C_{23}H_{25}N_2Cl} + H_2O.$$

This conversion of the colourless into the coloured salt may be represented in the following manner:



Hydrochloride of colour-base — Chloride of malachite green

and similar changes may be assumed to take place in the formation of the pararosaniline and rosaniline dyes, which may also be represented by corresponding quinonoid structures.

Malachite green is manufactured by heating a mixture of benzaldehyde (1 mol.) and dimethylaniline (2 mol.) with hydrochloric acid,

$$C_6H_5 \cdot CHO + \begin{matrix} C_6H_5 \cdot NMe_2 \\ C_6H_5 \cdot NMe_2 \end{matrix} = C_6H_5 \cdot CH < \begin{matrix} C_6H_4 \cdot NMe_2 \\ C_6H_4 \cdot NMe_2 \end{matrix} + H_2O.$$

The colourless, crystalline leuco-base, *pp'*-tetramethyldiaminotriphenylmethane, when treated with lead dioxide and hydrochloric acid, is oxidised to the (colourless) colour-base, *pp'*-tetramethyldiaminotriphenyl carbinol, which is converted into the dye by boiling it with an acid, such as oxalic acid. Commercial malachite green is (usually) the oxalate, $2C_{23}H_{24}N_2, 3C_2H_2O_4$, which forms deep-green crystals, and is readily soluble in water.

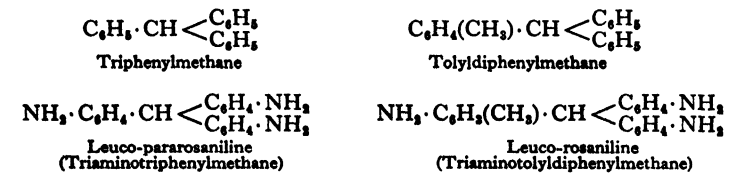
Malachite green dyes silk and wool directly an intense dark-bluish green, but cotton must first be mordanted with tannin and tartar emetic.

Laboratory Preparation of Malachite Green. Dimethylaniline (10 parts) and benzaldehyde (4 parts) are heated with finely powdered, *anhydrous* zinc chloride (8 parts) in a porcelain basin on a water-bath, during 4 hours, in the course of which the mixture is frequently stirred. The product is submitted to distillation in steam, to remove any benzaldehyde or dimethylaniline; the insoluble leuco-compound is then washed with water, dissolved in the minimum quantity of boiling alcohol, and the filtered solution left to crystallise overnight. The deposit, mixed with further quantities of leuco-base, obtained by concentrating the filtrate, is washed with a little alcohol and dried.

The leuco-base (10 g.) is dissolved in concentrated hydrochloric acid (14 c.c.) and water (900 c.c.), and a paste of the theoretical quantity of finely divided lead dioxide[1] with about 5 parts of water is rapidly stirred into the solution, cooled to 0°. A few minutes later the lead is precipitated with a solution of sodium sulphate, and the filtered liquid is treated with a concentrated solution of zinc chloride (10 g.) and finally with a saturated solution of sodium chloride, until the precipitation of the zinc double salt, $3C_{23}H_{25}N_2Cl$, $2ZnCl_2$, $2H_2O$, is practically complete.

Many dyes, closely allied to malachite green, are prepared by condensing benzaldehyde with other tertiary alkylanilines; diethylaniline, for example, gives *brilliant green*, whereas *acid green* is obtained from ethylbenzylaniline.

Pararosaniline and *rosaniline* are important dyes, which, like malachite green, are based on a triphenylmethane structure. Whereas, however, malachite green is a derivative of *diamino*triphenylmethane, the pararosanilines and the rosanilines are *triamino*-derivatives of triphenyl- or of tolyldiphenyl-methane respectively:



[1] The quality of the lead dioxide is important and should be determined beforehand.

$NH_2 \cdot C_6H_4 \cdot C(OH) < \begin{matrix} C_6H_4 \cdot NH_2 \\ C_6H_4 \cdot NH_2 \end{matrix}$ Pararosaniline base (Triaminotriphenyl carbinol)

$NH_2 \cdot C_6H_3(CH_3) \cdot C(OH) < \begin{matrix} C_6H_4 \cdot NH_2 \\ C_6H_4 \cdot NH_2 \end{matrix}$ Rosaniline base (Triaminotolyldiphenyl carbinol)

$ClNH_2 : C_6H_4 : C < \begin{matrix} C_6H_4 \cdot NH_2 \\ C_6H_4 \cdot NH_2 \end{matrix}$ Pararosaniline chloride

$ClNH_2 : C_6H_3(CH_3) : C < \begin{matrix} C_6H_4 \cdot NH_2 \\ C_6H_4 \cdot NH_2 \end{matrix}$ Rosaniline chloride

In all these compounds each of the amino-groups is in the *para*-position (*pp'p''*) to the methane carbon atom.

Pararosaniline is derived from *triaminotriphenyl carbinol*, a base which is prepared by oxidising a mixture of *p*-toluidine (1 mol.) and aniline (2 mol.) with arsenic acid, or nitrobenzene,

$$NH_2 \cdot C_6H_4 \cdot CH_3 + 2C_6H_5 \cdot NH_2 + 3O = NH_2 \cdot C_6H_4 \cdot C(OH) < \begin{matrix} C_6H_4 \cdot NH_2 \\ C_6H_4 \cdot NH_2 \end{matrix} + 2H_2O.$$

Probably the *p*-toluidine is first oxidised to *p*-aminobenzaldehyde, which condenses with the aniline (as in the formation of leuco-malachite green) giving leuco-pararosaniline; this compound is then oxidised to the pararosaniline colour-base, triaminotriphenyl carbinol, which is converted into the quinonoid dye by warming it with acids,

$$HCl, NH_2 \cdot C_6H_4 \cdot C(OH) < \begin{matrix} C_6H_4 \cdot NH_2 \\ C_6H_4 \cdot NH_2 \end{matrix} = ClNH_2 : C_6H_4 : C < \begin{matrix} C_6H_4 \cdot NH_2 \\ C_6H_4 \cdot NH_2 \end{matrix} + H_2O.$$

The salts of pararosaniline have a deep magenta colour, and are soluble in warm water; they dye silk, wool, and cotton under the same conditions as those described in the case of malachite green; pararosaniline, however, is not so largely used as rosaniline.

Rosaniline, *fuchsine*, or *magenta*, is a methyl substitution product of pararosaniline, and the colour-base is produced by the oxidation of equal molecular proportions of aniline, *o*-toluidine, and *p*-toluidine (with nitrobenzene, arsenic acid, etc.), just as the pararosaniline base is formed from aniline (2 mol.) and *p*-toluidine (1 mol.),

$$\underset{p\text{-Toluidine}}{NH_2 \cdot C_6H_4 \cdot CH_3} + \underset{\text{Aniline}}{\overset{o\text{-Toluidine}}{\begin{matrix} C_6H_4Me \cdot NH_2 \\ C_6H_5 \cdot NH_2 \end{matrix}}} + 3O = \underset{\text{Rosaniline base}}{NH_2 \cdot C_6H_4 \cdot C(OH) < \begin{matrix} C_6H_3Me \cdot NH_2 \\ C_6H_4 \cdot NH_2 \end{matrix}} + 2H_2O.$$

The salts of the rosaniline base with one equivalent of an acid, as, for example, the chloride, $C_{20}H_{20}N_3Cl,4H_2O$, form crystals which show an intense green metallic lustre ; they dissolve in warm water, giving deep-red solutions, which dye silk, wool, and cotton a brilliant magenta colour, under the same conditions as in the case of malachite green. These salts and those of pararosaniline may be represented by quinonoid structures, corresponding with those of malachite green.

The structural formulae of the basic triphenylmethane dyes are founded on that of 4:4′-dihydroxybenzophenone, which has been determined as follows : Anisaldehyde (*p*-methoxybenzaldehyde) is treated with potassium cyanide and the resulting *anisoin* (compare benzoin, p. 501) is oxidised to *anisil* ; this diketone, (I), undergoes the benzil-benzilic acid change (Part III) giving *anisilic acid*, (II),

I $MeO\cdot C_6H_4\cdot CO\cdot CO\cdot C_6H_4\cdot OMe \longrightarrow$
II $MeO\cdot C_6H_4\cdot C(OH)(COOH)\cdot C_6H_4\cdot OMe,$

which on oxidation yields *dimethoxybenzophenone*. In all these substances the two methoxyl groups are in the 4:4′-positions.

Now benzaldehyde condenses with aniline in the presence of zinc chloride to give diaminotriphenylmethane,

$$Ph\cdot CHO+2C_6H_5\cdot NH_2 = Ph\cdot CH(C_6H_4\cdot NH_2)_2+H_2O ;$$

by the usual method this compound is converted into dihydroxytriphenylmethane, which, fused with alkali, gives 4:4′-dihydroxybenzophenone. The two amino-groups of the diaminotriphenylmethane are therefore in the *p*-positions to the methane carbon atom.

p-Nitrobenzaldehyde condenses with aniline to give nitrodiaminotriphenylmethane, which, on reduction, affords leucopararosaniline ; on the assumption that the condensation of nitrobenzaldehyde and aniline proceeds in the same way as that of benzaldehyde and aniline, the *p*-orientation of all three amino-groups in pararosaniline is proved.

Derivatives of Pararosaniline and Rosaniline. The hydrogen atoms of the three amino-groups in pararosaniline and rosaniline may be displaced by alkyl groups, by methods analogous to those used in the manufacture of the alkylanilines ; alkyl and aryl derivatives of the two dyes may also be obtained in other ways (below).

The substitution of methyl groups for hydrogen in the molecule

of rosaniline, which is a brilliant red dye, brings about a change in colour—first to reddish-violet, and then to bluish-violet, as the number of alkyl groups increases. This change is more marked when ethyl groups are introduced, and still more so when benzyl or phenyl radicals are substituted for hydrogen; in the latter case, pure blue dyes are produced. In fact, by varying the number and character of the substituents, almost any shade from red to blue can be obtained.

Methyl violet appears to consist principally of the chloride of *pentamethyl*pararosaniline.

It is manufactured by warming dimethylaniline with copper sulphate, sodium chloride, phenol, and a little water during 6–8 hours; atmospheric oxidation occurs and formaldehyde is evolved, but little is known of the other reactions which take place. The powdered product is extracted with, and then dissolved in, hydrochloric acid, and cautiously treated with sodium sulphide to precipitate copper; the filtered solution is finally evaporated to dryness.

It is readily soluble in alcohol and hot water, forming beautiful violet solutions, which dye silk, wool, and cotton under the same conditions as in the case of malachite green. It is extensively used in the manufacture of copying inks, ribbons for typewriters, pencils, and for colouring methylated spirit, etc.

Crystal violet is the chloride of *hexamethyl*pararosaniline, and is manufactured by heating dimethylaniline with carbonyl chloride (phosgene) in the presence of anhydrous zinc chloride.

pp′-*Tetramethyldiaminobenzophenone* (*Michler's* ketone) is first formed, and then condenses with dimethylaniline, giving the colour-base of crystal violet,

$$NMe_2 \cdot C_6H_4 \cdot CO \cdot C_6H_4 \cdot NMe_2 + C_6H_5 \cdot NMe_2 = HO \cdot C(C_6H_4 \cdot NMe_2)_3.$$

Colour-base of crystal violet

Its applications and properties are similar to those of methyl violet.

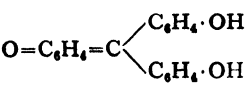
When rosaniline is heated with aniline and some acid, such as acetic, benzoic, or oxalic acid, phenyl groups displace the hydrogen atoms of the amino-groups just as in the formation of diphenylamine from aniline and aniline hydrochloride. Here, as in the case of the alkyl derivatives of rosaniline, the colour of the product depends on how many phenyl groups have been introduced into the molecule; the mono- and di-phenyl derivatives are reddish-violet and bluish-

violet respectively, whereas the triphenyl compound is a pure blue dye, known as *aniline blue*.

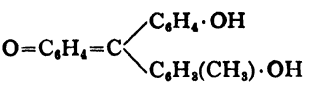
Aniline blue, $(C_6H_5 \cdot NH \cdot C_6H_4)_2C{:}C_6H_3(CH_3){:}NH(C_6H_5)Cl$ (triphenylrosaniline chloride), is very sparingly soluble in water, and for use as a dye it had to be dissolved in alcohol. In order to avoid this difficulty, it is treated with anhydrosulphuric acid, and thus converted into a mixture of sulphonic acids, the sodium salts of which, *alkali blue*, *water blue*, etc., are readily soluble in water.

In dyeing silk and wool the material is first dipped into an alkaline solution of the salt (whereby a light-blue tint is obtained) and is then immersed in dilute acid to liberate the blue sulphonic acid. Cotton is dyed in the same way, but must first be mordanted with tannin.

The tri-hydroxy-derivatives of triphenyl carbinol and of tolyldiphenyl carbinol, which correspond with the tri-amino-compounds described above, may be obtained by treating the latter (the colour-bases of pararosaniline and of rosaniline) with nitrous acid, and then heating the solutions of the diazonium salts. The products, *aurin* and *rosolic acid* respectively, correspond with the pararosaniline and rosaniline dyes in constitution :



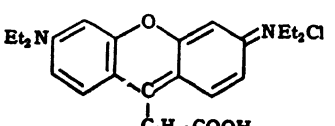
Aurin



Rosolic acid

They are of little use as dyes, owing to the difficulty of fixing them on the fabric.

Rhodamines. When phthalic anhydride is condensed with dialkyl derivatives of *m*-aminophenols, it gives tetra-alkyldiamino-compounds closely related to the fluoresceins (below). The salts of these bases are beautiful red to bluish-violet, strongly fluorescent dyes, which may be represented by quinonoid structures, as below :



Acid Triphenylmethane Derivatives

The **phthaleins** and **fluoresceins,** like malachite green and the rosanilines, are derivatives of triphenylmethane, but they are *acid* dyes and only the latter are of any considerable commercial value.

The phthaleins are dihydroxy-substitution products of *phthalophenone*, a lactone formed from *triphenylcarbinol-o-carboxylic acid*,

$$CO<\begin{matrix}-C_6H_4-\\ OH\quad HO\end{matrix}>C(C_6H_5)_2 = CO<\begin{matrix}C_6H_4\\ -O-\end{matrix}>C(C_6H_5)_2+H_2O.$$

Phthalophenone is prepared by treating a mixture of phthalyl chloride (p. 521) and benzene with aluminium chloride,

$$CO<\begin{matrix}C_6H_4\\ -O-\end{matrix}>CCl_2+2C_6H_6 = CO<\begin{matrix}C_6H_4\\ -O-\end{matrix}>C(C_6H_5)_2+2HCl.$$

It crystallises in needles, melts at 115°, and dissolves in alkalis, yielding salts of triphenylcarbinol-*o*-carboxylic acid.

Phenolphthalein, $C_{20}H_{14}O_4$ (dihydroxyphthalophenone), is prepared by heating phthalic anhydride (3 parts) with phenol (4 parts) and anhydrous zinc chloride (5 parts), at 115–120°, during about eight hours,

$$CO<\begin{matrix}C_6H_4\\ -O-\end{matrix}>CO+2C_6H_5\cdot OH = CO<\begin{matrix}C_6H_4\\ -O-\end{matrix}>C(C_6H_4\cdot OH)_2+H_2O;$$

the product is extracted with boiling water (about 75 parts) and the residue is recrystallised from aqueous alcohol.

Phenolphthalein separates from alcohol in crystals, and melts at about 254°; it dissolves in dilute alkalis, giving solutions which have a deep-pink colour, owing to the formation of coloured salts, but on the addition of acids (or of concentrated alkali) the colour vanishes, hence the use of phenolphthalein as an indicator (p. 686). It is, however, of no value as a dye.

The conversion of colourless phenolphthalein into an intensely coloured salt may be ascribed to its transformation into a quinonoid compound, just as in the case of malachite green (compare p. 686),

$$CO<\begin{matrix}C_6H_4\\ -O-\end{matrix}>C<\begin{matrix}C_6H_4\cdot OH\\ C_6H_4\cdot OH\end{matrix} \longrightarrow COONa\cdot C_6H_4\cdot C(OH)<\begin{matrix}C_6H_4\cdot OH\\ C_6H_4\cdot OH\end{matrix} \longrightarrow$$
$$COONa\cdot C_6H_4\cdot C(C_6H_4\cdot ONa):C_6H_4:O+H_2O.$$

Fluorescein, $C_{20}H_{12}O_5$, is produced by heating phthalic anhydride with resorcinol,

$$CO<\begin{matrix}C_6H_4\\ -O-\end{matrix}>CO+2C_6H_4<\begin{matrix}OH\\ OH\end{matrix} =$$
$$CO<\begin{matrix}C_6H_4\\ -O-\end{matrix}>C<\begin{matrix}C_6H_3(OH)\\ C_6H_3(OH)\end{matrix}>O+2H_2O.$$

Many important dyes are prepared by this last method from benzidine and substitution products of this base, such as *tolidine*, *dianisidine*, *diphenetidine*,[1] and since the bis-diazo-derivatives react readily with one molecule, but only slowly with a second molecule, of the amino- or phenolic compound, it is relatively easy to prepare many dis-azo-dyes, $A \cdot N_2 \cdot C_6H_4 \cdot C_6H_4 \cdot N_2 \cdot B$, in which A and B represent the same or different substituted aromatic nuclei.

The first dye thus obtained from benzidine was *congo red*, and the compounds of this group, of which some hundreds are known, are classed as dyes of the congo group; they are *direct* dyes to (unmordanted) cotton, and were the first dyes, having this important property, to be discovered. They are much used in the dyeing of wood, paper, leather, etc., as well as fabrics.

Congo red, produced by coupling diphenylbis-diazonium chloride with naphthionic acid is one of the important compounds of this class. Its sodium salt,

$$SO_3Na \cdot (NH_2)C_{10}H_5 N{:}N \cdot C_6H_4 \cdot C_6H_4 \cdot N{:}N C_{10}H_5(NH_2) \cdot SO_3Na,$$

is a scarlet powder, which on the addition of acid turns blue.

Tolidine, and to a greater extent dianisidine, give rise to bluer shades of red than does benzidine, with naphthionic acid, and when the bis-diazotised bases are coupled with phenolic instead of with amino-sulphonic acids, blue, instead of red dye-stuffs are obtained, as will be seen from the following table:

Name of dye	Bis-diazotised base	Compound, or compounds, coupled with the bis-diazotised base
Congo red (scarlet)	Benzidine	Naphthionic acid + Naphthionic acid
Benzopurpurin 4B (blue red)	Tolidine	Naphthionic acid + Naphthionic acid
Benzopurpurin 10B (blue red)	Dianisidine	Naphthionic acid + Naphthionic acid
Congo corinth B (violet)	Tolidine	Naphthionic acid + α-Naphtholsulphonic acid
Azo-blue (blue violet)	Tolidine	α-Naphtholsulphonic acid + α-Naphtholsulphonic acid
Benzoazurine G (pure blue)	Dianisidine	α-Naphtholsulphonic acid + α-Naphtholsulphonic acid

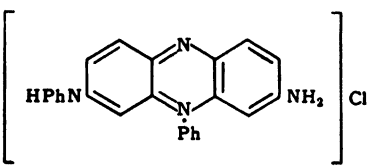
[1] *Tolidine*, $NH_2 \cdot MeC_6H_3 \cdot C_6H_3Me \cdot NH_2$, *dianisidine* (*dimethoxybenzidine*), and *diphenetidine*, $NH_2 \cdot (OEt)C_6H_3 \cdot C_6H_3(OEt) \cdot NH_2$, are produced from *o*-nitrotoluene, *o-nitroanisole*, and *o-nitrophenetole* respectively, by reactions similar to those by which benzidine is produced from nitrobenzene; when their salts are treated with nitrous acid, they yield bis-diazonium compounds, just as does benzidine.

Various Colouring Matters

Naphthol yellow, $C_{10}H_5(NO_2)_2 \cdot OH$ (2:4-dinitro-1-naphthol), is obtained by the action of nitric acid on α-naphtholmono- or di-sulphonic acid, the sulphonic group or groups being displaced during nitration. The dye is the sodium salt, $C_{10}H_5(NO_2)_2 \cdot ONa$; it is readily soluble in water, and dyes silk and wool directly an intense golden yellow.

When α-naphtholtrisulphonic acid is nitrated, only two of the sulphonic groups are eliminated, and the resulting substance, $C_{10}H_4(NO_2)_2(OH) \cdot SO_3H$, is the sulphonic acid of naphthol yellow. This dye, **naphthol yellow S,** is used in the form of its potassium salt, $C_{10}H_4(NO_2)_2(OK) \cdot SO_3K$, which gives yellow shades, faster to light than those of naphthol yellow.

Mauveine, $C_{27}H_{24}N_4$, HCl (*mauve*), is only of historical interest (p. 656) and was first obtained by oxidising a salt of commercial aniline (containing toluidine) with potassium dichromate; from pure aniline, Perkin obtained *pseudomauveine*, of which mauveine



Pseudomauveine

is a trimethyl derivative. These compounds were at one time used for colouring penny stamps, but are no longer of any practical importance.

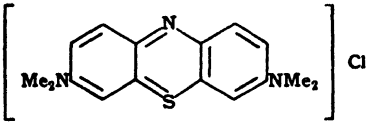
Aniline black is a highly complex insoluble compound, which is produced when an aniline salt is oxidised with sodium dichromate and an acid; the presence of traces of copper or vanadium salts, or of a ferrocyanide, hastens the oxidation, which may even be brought about with atmospheric oxygen in the presence of a trace of *p*-phenylenediamine, as well as that of a copper salt. On oxidation with potassium dichromate and sulphuric acid, aniline black gives quinone, and its molecule probably consists of aniline residues, which have combined with the loss of nuclear hydrogen, forming chains of quinonoid complexes. Aniline black is an important fast dye, especially for cotton, and being insoluble, it must be produced within the fibres of the material.

Methylene blue, $C_{16}H_{18}N_3ClS$, was first prepared by the oxidation of *p*-aminodimethylaniline with ferric chloride, in the presence of hydrogen sulphide.

p-Nitrosodimethylaniline is reduced in strongly acid solution with zinc-dust, or with hydrogen sulphide, and the solution of *p*-aminodimethylaniline, which is so obtained, is treated with ferric chloride in the presence of an excess of hydrogen sulphide. The intensely blue solution, thus produced, is mixed with salt and zinc chloride, which precipitate the colouring matter as a zinc double salt.

Methylene blue is readily soluble in water, and is important because it dyes cotton, mordanted with tannin and tartar emetic, a beautiful blue, which is very fast to light and soap, but it is not much used in dyeing silk or wool; it is extensively employed in staining biological preparations.

The structure of methylene blue (as the chloride) is related to that assigned to pseudomauveine, and is shown below,



Primuline is a mixture of two or more compounds manufactured by heating *p*-toluidine with sulphur and then sulphonating the product. The first change leads to the formation of *dehydrothiotoluidine*,

$$2CH_3\cdot C_6H_4\cdot NH_2+4S = CH_3\cdot C_6H_3\begin{cases}N\\ S\end{cases}C\cdot C_6H_4\cdot NH_2+3H_2S,$$

which then reacts with *p*-toluidine (1 mol.) and sulphur (4 atoms) to form *bis-dehydrothiotoluidine*,

$$CH_3\cdot C_6H_3\begin{cases}N\\ S\end{cases}C\cdot C_6H_3\begin{cases}N\\ S\end{cases}C\cdot C_6H_4\cdot NH_2,$$

and more complex compounds; the mixture is then sulphonated in order to substitute a $-SO_3H$ group for hydrogen of the $-C_6H_4-$ complex. The sodium salts of the sulphonic acids dye cotton directly a greenish-yellow shade, and are of little importance; but when the dyed fabric is afterwards treated with nitrous acid, and the

resulting diazonium salts are coupled with various phenolic compounds, yellow, orange, red, etc., *ingrain* azo-dyes (p. 674) are obtained.

Diazotised primuline is decomposed by light; when an impregnated material is exposed under a negative and then 'developed' with a phenol, the depth of colour due to the formation of an azo-compound varies according to the extent to which the decomposition of the diazonium salt has occurred.

Indigo, $C_{16}H_{10}O_2N_2$, is a natural dye which has been used from the earliest times. It was obtained from the leaves of the indigo plant (*Indigofera tinctoria*) and from woad (*Isatis tinctoria*), which contain *indican*, $C_8H_6ON \cdot C_6H_{11}O_5$, a colourless, crystalline glucoside of indoxyl (p. 593). When the leaves are macerated with water fermentation sets in, and the glucoside is hydrolysed into glucose and indoxyl; on exposure to the air the indoxyl in solution undergoes atmospheric oxidation, and indigo (*indigotin*) separates as a blue scum.

It is a dark-blue crystalline substance which, especially when rubbed, shows a copper-like lustre. It is insoluble in water and most other solvents, but dissolves readily in hot aniline, from which it may be crystallised.

Alkaline reducing agents, such as sodium hydrosulphite, convert indigotin into its leuco-compound, *indigo-white*, which, in contact with the air, is rapidly reconverted into indigo-blue (indigotin), a property made use of in dyeing with this substance (p. 660); fuming sulphuric acid dissolves indigotin, with the formation of *indigo-disulphonic acid*, $C_{16}H_8O_2N_2(SO_3H)_2$, the sodium salt of which is used as a dye under the name 'indigo carmine.'

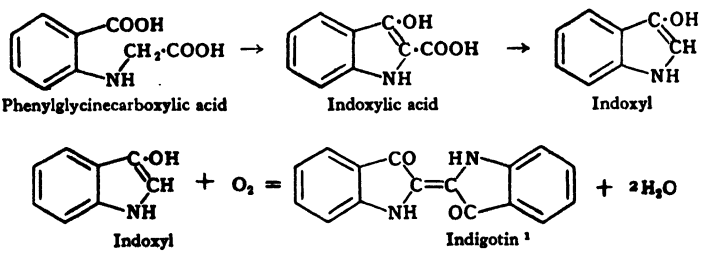
Owing to its importance in the dye industry, indigo naturally attracted a good deal of attention, and as the result of laborious research on the part of many chemists, its constitution was established about 1880, chiefly by the work of Baeyer and his pupils. During his investigations, Baeyer succeeded in preparing indigotin artificially by various reactions, two of which have already been described (pp. 501, 529), but it was not until about 1900 that successful processes for the manufacture of indigotin had been worked out in Germany; since that time synthetic indigotin has gradually displaced the natural product of the indigo plantations.

One of these processes was based on the discovery by Heumann

that indigotin could be obtained by fusing phenylglycine (phenylaminoacetic acid) with caustic alkali in the presence of air. The yield was very poor, but was much improved by the use of phenylglycine-*o*-carboxylic acid instead of phenylglycine. Since, moreover, this substance could be obtained from naphthalene, a cheap and abundant raw material, Heumann's improved process for the manufacture of indigo was then successfully carried out as follows: Naphthalene is oxidised to phthalic anhydride (p. 521), which is converted into phthalimide (p. 521) and then by treatment with sodium hypochlorite into anthranilic acid (p. 518); this, with chloroacetic acid gives phenylglycine-*o*-carboxylic acid,

$$C_6H_4{<}^{COOH}_{NH_2}+Cl\cdot CH_2\cdot COOH = C_6H_4{<}^{COOH}_{NH\cdot CH_2\cdot COOH} + HCl,$$

which is converted into indoxyl by fusion with caustic alkali. The oxidation of the indoxyl to indigo is then completed by dissolving the fused mass in water and passing air through the solution:



Phenylglycinecarboxylic acid — Indoxylic acid — Indoxyl

Indoxyl — Indigotin [1]

It was discovered later that by using sodamide instead of alkali in the fusion, a good yield of indoxyl could be obtained from phenylglycine instead of phenylglycine-*o*-carboxylic acid; as the former is easily made by the hydrolysis of its *nitrile*, which can be prepared from aniline and a mixture of sodium cyanide and formaldehyde sodium bisulphite,

$$C_6H_5\cdot NH_2+HCN+CH_2O = C_6H_5\cdot NH\cdot CH_2\cdot CN+H_2O,$$

this process has largely superseded the earlier method.

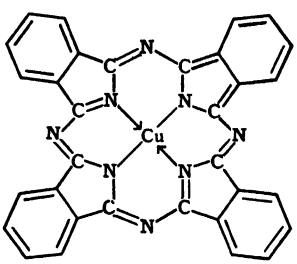
Many derivatives of indigotin, such as its halogen substitution products, and *thioindigotin* (a compound in which each of the >NH

[1] In Baeyer's formula for indigotin the two CO groups were shown in the *cis*-position; it is now known that they are in the *trans*-position to one another as here.

groups of indigotin has been displaced by an atom of sulphur) are now manufactured and used as vat-dyes.

Phthalocyanines

The metallic phthalocyanines are very important organic pigments. Their discovery was due to the formation of patches of a blue substance in some phthalimide, which had been prepared by passing ammonia into phthalic anhydride, contained in an iron pan. Linstead and his co-workers then showed that this blue compound was *iron phthalocyanine*, and prepared analogous pigments by heating o-*cyanobenzamide* with a metal or an appropriate salt; of these, *copper phthalocyanine*, the structure of which is shown below, is now manufactured by heating phthalonitrile, $C_6H_4(CN)_2$, with copper at 220–270°, and is known as **Monastral fast blue,** B.S.



This compound sublimes at 550° under reduced pressure, is insoluble in, and unchanged by, acids and alkalis, and is very fast to heat and to light; it can be sulphonated and thus converted into a soluble product, used as a *dye* for paper.

Monastral fast green, G.S., is a derivative of copper phthalocyanine in which all the sixteen hydrogen atoms are displaced by atoms of chlorine. **Lead phthalocyanine** is also green: with acids it gives the metal free phthalocyanine.

The metallic phthalocyanines are not dyes, but pigments; they are used as paints or enamels for colouring wall-paper, leather, cloth, linoleum, rubber, plastics, etc.

Colour and Constitution of Dyes

A compound is coloured when it absorbs some only of the rays of the visible spectrum, that is to say when its absorption spectrum

in the visible region shows one or more dark lines or bands. A compound will appear red, for example, if it absorbs all colours but red, i.e. all those rays which comprise the complementary colour to red (blue-green).

The part of the spectrum to which the eye is sensitive, however, is only a small fraction of the whole and a colourless substance may show a marked absorption just outside the visible region. The complete *absorption spectrum* of a compound is determined by the structure of the latter, and two substances which differ only slightly in structure may absorb respectively the one in, say, the ultra-violet and the other in the visible region ; thus one will appear colourless and the other coloured. Furthermore, unless the colour of a compound is accurately defined in terms of the wave-lengths of the absorbed rays, two substances which appear to be the same, or nearly the same colour, may differ widely in absorption and hence in structure. Clearly, therefore, any attempts to correlate colour with structure, except in the cases of very closely related compounds, are beset with difficulties, and it is only by considering the complete relationship between structures and absorption spectra that a solution of the problem is possible.

Nevertheless the great development of the dyeing industry, in which so many chemists were concerned, led to much discussion of the cause of colour, and certain generalisations which received wide acceptance were put forward. Thus the fact that aromatic azo-compounds, but not other types which contain nitrogen, are highly coloured, led to the inference that here colour is due to the unsaturated —N:N— group (combined with two aromatic nuclei). This group was therefore termed a *chromophore* or colour producer.

It was also observed that when certain radicals such as —OH, $—NH_2$, —NHR, $—NR_2$ are present in the molecule of an azo-compound the colour, attributed to the chromophore, was often materially altered in shade ; such groups were termed *auxochromes*, or auxiliaries in colour production.

An auxochrome has usually basic or acidic properties ; the neutral parent compound was thus enabled to combine with acids, or bases, and with, or even without, the aid of a mordant could often be fixed in fibres (p. 657).

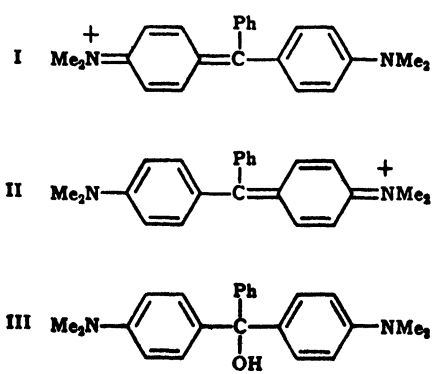
Among aromatic compounds consisting of carbon, hydrogen and oxygen only, *o*- and *p*-quinones stood out as coloured (yellow)

compounds, but were transformed into colourless ones by reduction. These facts led Armstrong (about 1888) to suggest that colour here is due to the quinonoid structures of the molecules. It was, however, difficult to distinguish any particular portion of such structures as chromophores or even to define precisely the term quinonoid, since one or both the >C=O groups of quinones may be displaced by >C=C< or >C=N—, or modified in various other ways without the disappearance of colour; on the other hand a few such modified quinonoid structures (e.g. quinonimines) are colourless. Nevertheless Armstrong's quinonoid theory was a very useful generalisation which led to an acceptable revision of the constitutional formulae at that time assigned to various dyestuffs.

The further study of dyes and organic compounds in general, as well as the production of new types of coloured compounds, have only emphasised the difficulty of correlating colour and structure, and the problem, now largely in the hands of mathematicians, is not yet solved.

Current views attribute important roles in the production of colour both to resonance and/or hydrogen bonding, particularly in those cases in which a molecule contains suitable benzenoid and quinonoid rings.

Thus, the hydrochloride of the colour base of a triphenylmethane dyestuff, for example, shows only the resonance of the benzene rings, and is colourless or only slightly coloured, but the quinonoid dye can undergo much more complex resonance between the two identical contributory forms, which in the case of malachite green, are shown in (I) and (II):



When the dye is treated with alkali, the deep colour slowly fades, as the mesomeric cation changes into the colour base (III), which is no longer quinonoid.

In crystal violet (IV), all three nuclei can take part in the resonance, but when a strong acid is added, salt formation takes place at an additional dimethylamino-group (V); the resonance, thus restricted to two nuclei, is now similar to that of malachite green, and the

IV $Me_2\overset{+}{N}=C_6H_4=C<\begin{matrix}C_6H_4\cdot NMe_2\\C_6H_4\cdot NMe_2\end{matrix}$

V $Me_2\overset{+}{N}=C_6H_4=C<\begin{matrix}C_6H_4\cdot \overset{+}{N}HMe_2\\C_6H_4\cdot NMe_2\end{matrix}$

VI $Me_2\overset{+}{N}=C_6H_4=C<\begin{matrix}C_6H_4\cdot \overset{+}{N}HMe_2\\C_6H_4\cdot \underset{+}{N}HMe_2\end{matrix}$

colour passes from the original violet to green. With more acid, the third dimethylamino-group is changed (VI), all interannular resonance is entirely prevented, although resonance of two of the benzene nuclei is still possible, and the colour changes to orange. Similar variations in colour, caused by the suppression of resonance, can be brought about by converting the dimethylamino-groups into quaternary ammonium salts.

In the case of aurin, the identical contributory forms may be the anions:

$$\bar{O}\cdot C_6H_4\cdot C(C_6H_4\cdot OH):C_6H_4:O$$
$$O:C_6H_4:C(C_6H_4\cdot OH)\cdot C_6H_4\cdot\bar{O}$$

The colour changes of phenolphthalein are attributed to its conversion, on the addition of alkali, into a divalent ion (I), which can show a complex resonance of the same type as that of aurin.

I $\begin{matrix}\bar{O}\cdot C_6H_4\\ \bar{O}OC\cdot C_6H_4\end{matrix}\!\!>\!C:C_6H_4:O$

II $\begin{matrix}HO\cdot C_6H_4\\ \bar{O}OC\cdot C_6H_4\end{matrix}\!\!>\!C:C_6H_4:O$

III $\begin{matrix}\bar{O}\cdot C_6H_4\\ \bar{O}OC\cdot C_6H_4\end{matrix}\!\!>\!C(OH)\cdot C_6H_4\cdot\bar{O}$

The univalent ion (II), to which the colour was formerly ascribed, should be colourless. With a large excess of alkali the pink colour of phenolphthalein disappears ; this result may be ascribed to the formation of the additive compound (III), in which interannular resonance is impossible. Similarly the colours of fluorescein and its derivatives are ascribed to a divalent anion in which resonance can occur.

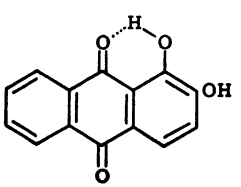
As an example of an azo-dye, the case of helianthin may be considered. The sodium salt, methyl orange (IV), contains only the azo-chromophore and is relatively feebly coloured ; the addition of an acid converts it into a highly coloured cation, in which resonance between (V) and (VI) is possible :

IV $\bar{O}_3S \cdot C_6H_4 \cdot N{:}N \cdot C_6H_4 \cdot NMe_2$

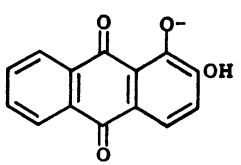
V $HO_3S \cdot C_6H_4 \cdot NH \cdot N{:}C_6H_4{:}\overset{+}{N}Me_2$

VI $HO_3S \cdot C_6H_4 \cdot \overset{+}{N}H{:}N \cdot C_6H_4 \cdot NMe_2$

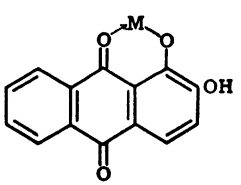
Alizarin can show hydrogen bonding in the free state (I), resonance as its sodium salt (anion, II), or chelation in the form of a lake (III), and it is immaterial whether the second hydroxyl group undergoes salt formation or not.



I



II



III

Speculations on similar lines to the above may also be made in the case of naphthol yellow, the rhodamines, benzoflavine, mauveine, methylene blue, indigo, phthalocyanines and other dyes.

NOTE ON THE IDENTIFICATION OF ORGANIC COMPOUNDS

Practice in the identification of organic compounds in the laboratory is of great help to the student in his theoretical work, and also trains his powers of observation; conclusions based on inaccurate observations are, of course, fatal to success.

Only a very small proportion of carbon compounds can be identified by qualitative tests; a larger number can be referred to their type or class, but for the vast majority—which are therefore unsuitable for such purposes—the qualitative and quantitative methods, described in Chapter 1, would have to be adopted.

The substances usually chosen for such exercises—to which alone this note applies—may be broadly classed in two groups:

I. Those which can be identified in their given condition, as, for example, some of the simpler halogen derivatives, alcohols, aldehydes, ketones, and acids, as well as a few of the commoner sugars and glycosides; certain aromatic hydrocarbons, nitro- and amino-compounds, phenols, acids and alkaloids.

II. Those which must first be hydrolysed to give recognisable compounds of group I, as, for example, esters, amides, and anilides. Salts, mineral or otherwise, may be classed in either group (p. 691).

The methods of examination have little in common with those of inorganic qualitative analysis; no tables are (or should be) used, and no fixed procedure is necessarily adopted. A few simple tests, occupying a few minutes only, serve as a guide to further investigation, but the interpretation of the results, throughout the whole of the work, requires some considerable theoretical knowledge.

The colour and smell of the given compound are noted. Only a very few (nitro-compounds, quinones) are coloured, but many commercial products, especially bases, are yellow or brown owing to the presence of impurities. Many types of compounds (hydrocarbons, halogen compounds, ketones, aldehydes, phenols, acids, and esters) have a more or less distinctive class, or individual, odour, the recognition of which is greatly improved by practice.

The following tests may then be made [1]:

1. The substance is heated (*a*) on a nickel spatula or platinum wire, (*b*) in an ignition or test-tube, (*c*) on a crucible lid (but not necessarily in all these ways or in the given order). If it burns with a feebly luminous flame, it is probably rich in oxygen (e.g. methyl alcohol, oxalic acid, glycerol); a smoky flame indicates a high proportion of carbon (aromatic compounds generally) or the presence of halogen (often a green-edged flame). If it distils, a very rough observation of its boiling-point may be made (with about 0·5 c.c. or g. in a test-tube) by holding a thermometer bulb in the vapour; a boiling-point below 81° shows the absence of all aromatic compounds (benzene boils at 81°). If it decomposes, all the above-named types of group I which contain only *one* distinctive group are excluded; decomposition, without appreciable charring, generally indicates simple aliphatic compounds, containing more than one substituent (urea, oxalic acid) and also salts of amines. If charring occurs the presence of more complex substances (hydroxy-acids, sulphonic acids, sugars, glycosides, alkaloids, etc.) is indicated, and, in general, compounds of high molecular weight. If, after prolonged ignition, there is a non-combustible residue, the substance is a metallic salt; those of simple acids (formic, acetic, oxalic, benzoic) do not char appreciably. The identification of salts is described on p. 691.

2. The substance is treated with cold water (note comparative density; almost all halogen compounds are denser). If it is readily or moderately soluble (footnote, p. 162), the presence of one or more —OH, —COOH, —CO·NH_2, —SO_3H, —NH_2, —CHO, or >CO groups is indicated, but the solubility must be considered in conjunction with the results of (1). If, for example, the compound decomposes when it is heated, it cannot owe its solubility to *one* of these groups only (except —SO_3H); on the other hand it might be sparingly soluble and yet contain one of these groups in combination with a hydrocarbon radical (such as C_5H_{11}— or C_6H_5—) of fairly high molecular weight. Hydrocarbons, ethers, halogen compounds, nitro-derivatives, and most esters (p. 187) are very sparingly soluble in water.

[1] In most cases, say 0·05–0·1 g. or c.c. of the substance is ample, but where products of hydrolysis have to be examined, say 0·5 g. or c.c. or more may be required.

3. The substance is treated with a cold (say 5–10%) solution of (*a*) sodium carbonate, (*b*) caustic soda, (*c*) hydrogen chloride, in any order. If it is more readily soluble in (*a*) than in water, it is probably an acid, anhydride, or nitrophenol (yellow); even so, effervescence *may* not be detected if the substance dissolves very slowly, as the carbon dioxide may form bicarbonate, but may generally be observed when the compound is added to a *hot* solution. If it is more readily soluble in (*b*) than in (*a*), it is probably a phenol. If more soluble in (*c*) than in (*a*) or (*b*), it is very probably a base (or a *salt*, p. 691). From an alkaline (*a* or *b*) or acid (*c*) solution, the compound may *generally* be precipitated on the addition of an excess of acid or alkali as the case may be.

The results of these few simple tests *considered as a whole*, in the case of substances of group I, will often give some definite indication, which can then be followed up.

Example. An odourless solid decomposes when it is heated, leaving no residue, but does not char. Its decomposition products are not recognised by their smell. The substance is readily soluble in cold water, and dissolves in sodium carbonate solution with effervescence. It cannot be a simple monocarboxylic acid, but it might be a hydroxy- or dicarboxylic acid, and further tests are made for common compounds of these types.

Example. A liquid has a ' basic ' smell, distils at 175–185°,[1] is only moderately soluble in water and aqueous alkali, but dissolves readily in diluted (1:1) hydrochloric acid, and is precipitated from the (sufficiently concentrated) solution on the addition of an alkali. It is therefore a base (not a common alkaloid), and tests are immediately made to find out whether it is a primary, secondary, or tertiary base and whether it is an aromatic or an aliphatic compound (pp. 221, 449, 458).

Example. A liquid, smelling like ' carbolic acid,' distils at 178–188°[1]; it is only moderately soluble in cold water, and in sodium carbonate solution, but dissolves readily in caustic soda and is precipitated from the (sufficiently concentrated) solution on the addition of an acid. It is probably a phenol, and is tested further with ferric chloride and by Liebermann's reaction (p. 481).

Example. An odourless solid, distils at a high temperature (above 200° apparently); it is readily soluble in cold water, and when treated with a solution of sodium carbonate the liquid begins to

[1] An approximate result, observed in a test-tube experiment.

turn yellow, and darkens rapidly when shaken (in contact with the air). Probably a di- or poly-hydric phenol (pp. 490-92).

When the above tests (1–3), which may be carried out in any order, have failed to give any clue to its nature, the compound probably belongs to group II (amides, anilides, esters, etc.), and its examination may proceed as follows:

4. The substance is heated with a concentrated solution of caustic soda. If it is an ammonium salt or an amide (or a cyanide) ammonia will be evolved. The substance is then mixed with solid sodium carbonate and the mixture is moistened with water; an immediate evolution of ammonia shows an ammonium salt, the presence of which may have already been suspected from previous results. Amides (and cyanides) may be only very slowly hydrolysed by caustic soda (reflux apparatus); any acid which is formed is identified as described under esters (p. 188). A substituted amide (anilide) will give a primary or secondary base and the alkali salt of an acid; the base, which usually separates as an oil, may be extracted with ether; the acid is identified as before. Certain anilides are very stable towards boiling alkalis, and are more easily hydrolysed with boiling diluted (1:1) sulphuric acid; the free organic acid and a salt of the base are thus obtained.

The hydrolysis of esters, for their identification, has already been described (p. 187).

5. When at this stage no satisfactory clue has been obtained the substance may be tested for nitrogen, halogens, and sulphur (pp. 14-16). If nitrogen is found, and the compound is not one of the types already considered, it may be a nitro-derivative or some compound such as sulphanilic acid (p. 476) or hippuric acid (p. 512). A nitro-derivative can be reduced and the base may be identified. If a halogen is found, its nature is determined and, if necessary, the substance is heated with an aqueous-alcoholic solution of silver nitrate (pp. 74, 425). If sulphur is found, the compound may be an alkyl hydrogen sulphate (as a salt), a sulphonic acid, or a sulphonamide (which might not have been detected under 4); sulphonic derivatives are fused with alkalis and converted into phenols (p. 479).

6. *Salts.* If the substance is a salt of any kind some indications of this should have been obtained in one or more of the preceding tests. A metallic or ammonium salt may be treated with diluted sulphuric acid and the solution examined, as described under esters

(p. 188). Salts of organic bases (*which may be mistaken for organic acids*) are treated with an excess of alkali, and the liberated base is extracted with ether, if necessary ; the alkaline solution is examined for inorganic and organic acids.

7. If all the above tests have failed to give any definite information, the substance may be strongly heated with soda-lime or treated with phenylhydrazine (p. 460), concentrated sulphuric acid, or oxidising agents.

Example. A pleasant-smelling liquid (b.p. 55–65°)[1] is not appreciably soluble in water, alkalis, or acids, and does not *seem* to be changed when it is heated with these reagents. It is observed that its density is very much greater than that of water ; possibly a halogen compound. It is tested for halogens and proved to contain chlorine ; probably chloroform (p. 77).

Example. An odourless solid distils (b.p. above 200°). It is sparingly soluble in cold water, alkalis, and acids. When heated with caustic soda it seems to give a basic odour (not that of ammonia). Probably an anilide. It is boiled with diluted (1:1) sulphuric acid (reflux condenser), and after a short time the vapours in the flask are found to have an acid reaction and a smell of acetic acid. The heating is continued during, say, 30–60 minutes, and the volatile, readily soluble acid is identified ; the sulphuric acid solution is examined for an aromatic base.

Example. A liquid (distinct odour, but not recognised) burns with a smoky flame, boils at about 105–115°,[1] and is practically insoluble in, and apparently unchanged by, water, alkalis, or acids. Nitrogen, halogens, and sulphur are absent, but, in carrying out the test, it is seen that the boiling liquid and the sodium do not interact. Probably an aromatic hydrocarbon (toluene ?). Treated with a mixture of nitric and sulphuric acids, the substance, itself lighter than water, gives an oil denser than water. This product is treated with tin and hydrochloric acid, and the solution is examined for a primary aromatic base.

Example. An odourless solid, decomposes when it is heated, without charring, giving ammonia, and leaves no residue on ignition. It is sparingly soluble in cold water, dissolves in sodium carbonate with effervescence, but is not reprecipitated by acids. It does not give ammonia with damp sodium carbonate (see above). Boiled with caustic soda it gives ammonia. The acid in the alkaline solution is not precipitated on the addition of sulphuric acid, and

[1] See footnote, p. 690.

is non-volatile. Probably a dibasic acid, and is ultimately identified as oxalic acid. But the original compound cannot be oxamide; it might be $NH_2 \cdot CO \cdot COOH$, a very uncommon substance, but is probably a salt of some very simple basic amide, such as urea.

For the final identification of a solid or liquid a melting-point (and mixed melting-point) or boiling-point determination may, of course, be made in many cases, and a liquid may often be converted into some solid derivative of definite melting-point (pp. 149, 150, 461, 514).

PREPARATIONS

The following are some of the typical compounds for which methods of preparation are described in detail. Many others may be prepared with the aid of the experimental data which are given throughout the book.

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