

TIGHT BINDING BOOK

UNIVERSAL
LIBRARY

OU_162731

UNIVERSAL
LIBRARY

OSMANIA UNIVERSITY LIBRARY

Call No. 547

Accession No. 8702

Author P82 M Pope, F. G.

Title Modern Research in Organic

This book should be returned on or before the date last marked below.

Chemistry.

METHUEN'S TEXT-BOOKS OF SCIENCE

**MODERN RESEARCH
IN ORGANIC CHEMISTRY**

TEXT-BOOKS OF SCIENCE

- THE COMPLETE SCHOOL CHEMISTRY.** By F. M. OLDHAM, B.A. Sixth Ed., Revised. 4s. 6d.
- A TEXT-BOOK OF INORGANIC CHEMISTRY.** By G. SENTER. 6s. 6d.
- PRACTICAL CHEMISTRY.** Part I. By W. FRENCH, M.A. Fifth Ed. 1s. 6d.
- PRACTICAL CHEMISTRY.** Part II. By W. FRENCH, M.A., and T. H. BOARDMAN, M.A. 1s. 6d.
- A TEXT-BOOK OF PRACTICAL CHEMISTRY FOR TECHNICAL INSTITUTES.** By A. E. DUNSTAN and F. B. T. THOLE. 3s. 6d.
- AN INTRODUCTION TO QUANTITATIVE ANALYSIS.** By S. J. M. AULD. 5s.
- A CONCISE HISTORY OF CHEMISTRY.** By T. P. HILDITCH. 2s. 6d.
- ELEMENTARY CHEMICAL THEORY.** By J. M. WADMORE. 3s. 6d.
- PRELIMINARY PHYSIOLOGY.** By W. NARRAMORE. 3s. 6d.
- PLANT LIFE: Studies in Garden and School.** By HORACE F. JONES, F.C.S. 3s. 6d.
- AN ORGANIC CHEMISTRY FOR SCHOOLS AND TECHNICAL INSTITUTES.** By A. E. DUNSTAN, D.S.C. 2s. 6d.
- SECOND YEAR ORGANIC CHEMISTRY FOR SCHOOLS AND TECHNICAL INSTITUTES.** By F. B. T. THOLE, B.S.C. 2s. 6d.
- QUALITATIVE ORGANIC ANALYSIS.** By F. B. T. THOLE, B.S.C. 1s. 6d.
- MODERN RESEARCH IN ORGANIC CHEMISTRY.** By F. G. POPE. 7s. 6d.
- A FIRST YEAR PHYSICAL CHEMISTRY.** By T. P. HILDITCH. 2s.
- OUTLINES OF PHYSICAL CHEMISTRY.** By GEORGE SENTER, D.S.C. (Lond.), PH.D. Third Ed., Revised. 5s.
- PHYSICO-CHEMICAL CALCULATIONS.** By JOSEPH KNOX. 2s. 6d.
- ELEMENTARY SCIENCE FOR PUPIL TEACHERS.** Physics section by W. T. CLOUGH, A.R.C.S. Chemistry section by A. E. DUNSTAN. 2s.
- EXAMPLES IN PHYSICS.** By C. E. JACKSON, M.A. Second Ed. 2s. 6d.
- FIRST YEAR PHYSICS.** By C. E. JACKSON, M.A. Second Ed. 1s. 6d.
- EXAMPLES IN ELEMENTARY MECHANICS: Practical, Graphical and Theoretical.** By W. J. DOBBS, M.A. 5s.
- PRACTICAL MECHANICS.** By SIDNEY H. WELLS. Fifth Ed. 3s. 6d.
- A HANDBOOK OF PHYSICS.** By W. H. WHITE. 7s. 6d.
- TECHNICAL ARITHMETIC AND GEOMETRY.** By C. T. MILLIS, M.I.M.E. Second Ed. 3s. 6d.

TEXT-BOOKS OF TECHNOLOGY

- ELECTRIC LIGHT AND POWER.** By E. E. BROOKS, B.S.C., and W. H. N. JAMES, A.R.C.S. Second Ed. 4s. 6d.
- ENGINEERING WORKSHOP PRACTICE.** By C. C. ALLEN. 3s. 6d.
- CARPENTRY AND JOINERY.** By F. C. WEBBER. Sixth Ed. 3s. 6d.
- BUILDERS' QUANTITIES.** By H. C. GRUBB. 4s. 6d.
- REPOUSSÉ METAL WORK.** By A. C. HORTH. 2s. 6d.
- AN INTRODUCTION TO THE STUDY OF TEXTILE DESIGN.** By ALFRED F. BARKER. 7s. 6d.
- HOW TO MAKE A DRESS.** By J. A. E. WOOD. Fifth Ed. 1s. 6d.
- MILLINERY, THEORETICAL AND PRACTICAL.** By CLARE HILL. Fifth Ed. 2s.
- INSTRUCTION IN COOKERY.** By A. P. THOMPSON. 2s. 6d.

**MODERN RESEARCH
IN
ORGANIC CHEMISTRY**

BY

F. G. POPE

B.SC. (LOND.), F.C.S.

WITH 261 DIAGRAMS

**METHUEN & CO. LTD.
36 ESSEX STREET W.C.
LONDON**

First Published in 1912

CONTENTS

	PAGE
INTRODUCTION	vii
LIST OF ABBREVIATIONS	xii
CHAP. I. THE POLYMETHYLENES	1
II. THE TERPENES AND CAMPHORS	39
III. THE URIC ACID OR PURINE GROUP	101
IV. THE ALKALOIDS	125
V. THE RELATION BETWEEN THE COLOUR AND CON- STITUTION OF CHEMICAL COMPOUNDS	200
VI. SALT FORMATION, PSEUDO-ACIDS AND BASES	222
VII. THE PYRONES	245
VIII. KETENS, OZONIDES, TRIPHENYLMETHYL	275
IX. THE GRIGNARD REACTION	297
INDEX OF AUTHORS	317
INDEX OF SUBJECTS	320

INTRODUCTION

IN the course of the past century the study of organic chemistry has been pursued with an energy which has not been exceeded in any department of science, and, by sustained effort, not only has a better insight been obtained into processes of life, but many branches of industry have been revolutionized. It is common knowledge that much of the distinction between Inorganic and Organic Chemistry was broken down by Wöhler's discovery of the artificial production of urea in 1828, and although the breach in the barrier between the two branches of the science has been continually widened, the convenience of a division into inorganic and organic chemistry is such, that the study of the carbon compounds would probably remain distinct, even if it were not necessitated by the extreme complexity of the subject. At the same time, the organic chemist avails himself to an increasing extent of physical methods of research, and the use of organic derivatives in solving problems of inorganic chemistry, especially those relating to valency and spatial arrangement, becomes continually more widespread. Organic chemistry, in the stricter sense of the term, still offers a vast number of problems for solution; with the rapid progress made, the problems of one decade become the commonplaces of the next, and it is worth while to take an occasional general survey, considering the lines in which immediate progress is probable.

In the eighteenth century the chief recognized characteristics of organic compounds were that they contained aqueous and combustible principles. Lavoisier's explanation of combustion directed the attention of chemists to the fact that organic compounds always contain carbon, and generally hydrogen in addition; these elements furnish carbonic acid and water respectively when

viii MODERN RESEARCH IN ORGANIC CHEMISTRY

the compounds in question are burnt. Following up this discovery, Lavoisier devised a method for the determination of carbon in organic compounds, and somewhat later collected the water formed during combustion by absorbing it with a deliquescent salt. Considerable ingenuity was expended during the early part of the nineteenth century in perfecting the methods of organic analysis, and it soon became possible to determine the composition of a carbon compound with the accuracy attained in a mineral analysis.

The increasing number of organic compounds of known composition rendered the introduction of some system necessary. At a relatively early date, Dumas and Boullay compared the ethyl compounds with the addition products formed by ammonia; ethyl alcohol was the hydrate of "bicarburetted hydrogen," $C_2H_4.H_2O$, and analogous to aqueous ammonia, $NH_3.H_2O$; ethyl chloride and ammonium chloride were regarded respectively as the hydrochlorides of bicarburetted hydrogen and ammonia, and similar comparisons were instituted between other ethyl and ammonium compounds.

The idea of compound radicals was introduced by Lavoisier and Guyton de Morveau at a time when sugar was supposed to be the neutral oxide of a hydrocarbon radical, whilst oxalic acid was the higher acidic oxide obtained on oxidation with nitric acid. In 1832, Liebig and Wöhler published their research on the radical of benzoic acid; not only was it shown that *benzoyl* formed an integral part of a large series of compounds, but the fact was recognized that oxygen might be a constituent of a compound radical. A year or two later Liebig pointed out that order might be introduced amongst the compounds derived from alcohol if ether were looked on as the oxide of a radical "ethyl"; alcohol would then be the hydrate of this oxide, whilst the various ethers (or esters, as they are now called) are the analogues of metallic salts. Dumas adopted the idea of compound radicals, which also appealed in many of its aspects to Berzelius; the discovery of substitution processes had, however, at first a retarding influence. With a fuller understanding of the manner in which substitution

takes place and the introduction of the theory of types, the way was paved for the idea of molecular structure, and research in this direction made rapid progress after the complete recognition of Avogadro's law.

In the development which led to the adoption of molecular and structural formulæ, Frankland, Gerhardt, Hofmann, Laurent, Odling, Williamson, and Wurtz were specially prominent; to Kekulé must be assigned the credit of having first recognized the tetravalency of carbon, a similar view being put forward by Couper shortly afterwards.

The idea of the tetravalency of carbon led Kekulé to his conception of the structure of the aromatic compounds (1865), and although various modified formulæ have been proposed for benzene, the original idea that the six carbon atoms are members of one closed ring still holds its own. By 1870 the essential foundations of structural organic chemistry had been laid, and meanwhile the structure of the aromatic compounds had assumed large proportions, an added incentive to the work being found in the possibility of obtaining commercially valuable products. Rarely has an industry contributed so greatly to the advancement of science as in the case of the artificial organic dyestuffs.

During the next two decades the preparation of new organic compounds and the synthesis of natural products occupied the attention of the greater number of organic chemists, and some remarkable successes were achieved. Alizarine and indigo were obtained artificially; towards the end of the "eighties" the constitution of glucose was ascertained with some degree of certainty, and the synthesis of various sugars by Emil Fischer must give rise to as much admiration to-day as when the researches were first published.

Meanwhile other classes of naturally occurring compounds had been extensively investigated, and the derivatives of uric acid, caffeine, etc., from the (at that time) hypothetical parent substance, purine, assured. It was not, however, until Emil Fischer had virtually concluded his sugar work that he turned his attention to the purine group once more, and in a series of brilliant researches

synthesized the most important naturally occurring derivatives, the previous syntheses of uric acid by Horbaczewski and Behrend in no way lessening the value of the results obtained. Fischer's researches on the constitution of the sugars, the purine compounds, and the products of the hydrolysis of the proteins, followed up by the syntheses of so many substances of these groups, has afforded a sound basis for biological chemistry.

Another group of compounds, the terpenes, had also attracted much attention, and camphor had been shown to possess a closely related structure. Despite the useful experimental material accumulated by the researches of Armstrong, Tilden, Wallach, and others, the constitution of these compounds remained uncertain, Bredt's happy idea of the structure of camphor led to renewed effort, and in a few years the constitution of most of the natural hydrocarbons and cyclic ketones was settled. Syntheses in the terpene series are largely due to W. H. Perkin; for not only has he achieved the actual artificial production of such compounds, but the methods by which the formation of closed carbon chains can be effected are chiefly the results of his work. The chemistry of this series of compounds owes not a little to chemical industry, the synthesis of artificial perfumes having proved a remunerative field industrially.

The alkaloids have occupied many workers since the early days of organic chemistry, and at the present time the structure of a large number of these substances is known with accuracy, or with a considerable degree of probability; at the same time the examination of natural organic dyestuffs has led to much systematic research concerning compounds whose molecule contains a pyrone ring.

Whilst all this strictly organic work was in progress, other investigators followed a different line, endeavouring to trace relationships between the physical properties of substances and their chemical constitution. In the early days of this type of work, inorganic substances received possibly rather more than their fair share of attention; it might perhaps be contended that latterly the pendulum had swung too far in the other direction.

Certainly organic compounds offer one immense advantage : there is usually no doubt either as to the molecular weights or the arrangement of linkages in the substances under investigation. Prosecution of researches of this character has led to striking advances ; our ideas as to the arrangement of atoms in space and the rearrangement of structure which often occurs on salt formation have undergone considerable change. Workers in this branch of science are occasionally unduly optimistic, but the success which has attended some of the attempts to refer properties to constitution, notably in the cases of molecular volume and molecular refraction, can only act as a greater incentive to work. Organic chemists have achieved much, and as the habit of simply recording the melting-points and analytical data of new compounds dies out, it will be more clearly recognized what an enormous field of work lies in front of us.

J. T. HEWITT

ABBREVIATIONS USED IN THE BIBLIOGRAPHY

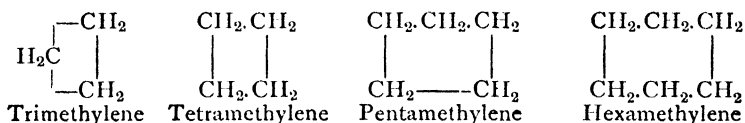
ABBREVIATION	FULL TITLE
<i>Amer. Chem. Jour.</i>	American Chemical Journal.
<i>Ann.</i>	Justus Liebig's Annalen der Chemie.
<i>Ann. Chim. Phys.</i>	Annales de Chimie et de Physique.
<i>Arch. Pharm.</i>	Archiv. der Pharmazie.
<i>B. A. Rep.</i>	British Association Reports.
<i>Ber.</i>	Berichte der deutschen chemischen Gesellschaft.
<i>Bull. Soc.</i>	Bulletin de la Société chimique de France.
<i>C. R.</i>	Comptes rendus hebdomadaires des Séances de l'Académie des Sciences.
<i>Gazz.</i>	Gazzetta chimica italiana.
<i>J. Amer. Chem. Soc.</i>	Journal of the American Chemical Society.
<i>Jour. Chem. Soc.</i>	Transactions of the Chemical Society.
<i>Jour. prak. Chem.</i>	Journal für praktische Chemie.
<i>Jour. Russ. phys. chem. G.</i>	Journal of the Physical and Chemical Society of Russia.
<i>Monats.</i>	Monatshefte für Chemie und verwandte Theile anderer Wissenschaften.
<i>Phil. Mag.</i>	Philosophical Magazine.
<i>Proc. Chem. Soc.</i>	Proceedings of the Chemical Society.
<i>Z. f. Elektrochem.</i>	Zeitschrift für Elektrochemie.
<i>Z. f. phys. Chem.</i>	Zeitschrift für physikalische Chemie.

MODERN RESEARCH IN ORGANIC CHEMISTRY

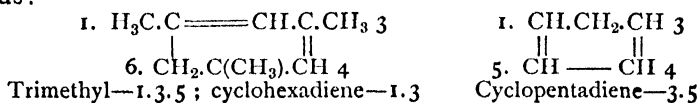
CHAPTER I

THE POLYMETHYLENES

THE isolation of trimethylene in 1882 by Freund led to the opening up of a vast field of research, since it showed that a series of cyclic compounds existed which could not be regarded as simple derivatives of benzene. The simple hydrocarbons of the group consist of three or more methylene groups united so that they form a closed chain, the names given to the various members (*e.g.* trimethylene, tetramethylene, etc.) denoting the number of methylene groups associated together in the particular ring so designated, thus:—



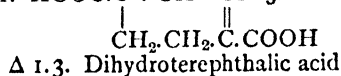
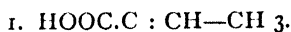
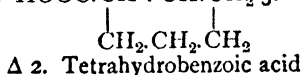
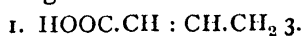
although under a more systematic scheme of nomenclature they are spoken of as *cyclopropane*, *cyclobutane*, *cyclopentane*, etc. The unsaturated members of the series are best named according to the Geneva system in which the suffix *-ane* is replaced by *-ene*, *-diene*, or *-triene*, according to the number of double linkages present in the molecule, the position of such double linkages being shown by the numerals immediately following the suffix, thus:—



As an alternative method for denoting the position of the double

2 MODERN RESEARCH IN ORGANIC CHEMISTRY

linkages, Baeyer's symbol Δ is occasionally used, being placed in front of the name of the compound and immediately followed by one or more numerals indicating the position of the double linkages in the molecule—

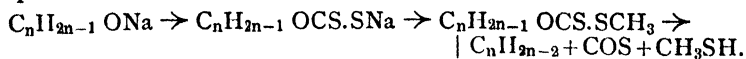


In the production of the polymethylene compounds it is found that the five and six membered rings are the most stable of the series, and are preferentially formed. The reason for this greater stability was first shown by Baeyer in his "Spannung's Theorie," which refers the phenomena to stereo-chemical data. In this theory, Baeyer accepts the generally received laws as to the affinities of the carbon atom, and adds the following assumption: "The four valencies of a carbon atom act along the direction joining the centre of a tetrahedron with the corners of the tetrahedron, and make, with one another, angles of $109^\circ.28'$. The direction of the attraction can, however, experience a deviation, and this gives rise to a tension which increases with the magnitude of the deviation." Applying this principle to the polymethylene compounds, it is obvious that the deviation must vary with the particular group considered, and it is possible to calculate the deviation in the various cases if one assumes each axis to experience an equal displacement. Thus in C_2H_4 , with one double bond, each must undergo a deviation $\frac{1}{2} (109^\circ.28') = 54^\circ.44'$; in C_3H_6 (trimethylene), which can be considered as possessing the equilateral triangle configuration for the plane of its carbon atoms, the deviation must be $\frac{1}{2} (109^\circ.28' - 60^\circ) = 24^\circ.44'$, whilst in tetramethylene, pentamethylene, hexamethylene, and heptamethylene the respective deviations will be $\frac{1}{2} (109^\circ.28' - 90^\circ) = 9^\circ.44'$; $\frac{1}{2} (109^\circ.28' - 108^\circ) = 0^\circ.44'$; $\frac{1}{2} (109^\circ.28' - 120^\circ) = -5^\circ.16'$; $\frac{1}{2} (109^\circ.28' - 128^\circ.34') = -9^\circ.33'$. Consequently the deviation, and therefore the strain, is least in the penta- and hexamethylene compounds, and these should be the most stable. This theory fits in very well with the observed facts; thus ethylene, which forms the weakest ring, is immediately acted upon by bromine and even iodine, while the trimethylene ring is

readily attacked by hydrobromic acid, and even by bromine in the presence of sunlight. Tetramethylene derivatives are, on the other hand, more stable, whilst the penta- and hexamethylene derivatives are remarkably stable, and show little or no tendency to rupture of the molecule.

GENERAL METHODS OF PREPARATION

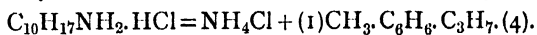
The hydrocarbons of the series may be obtained by the action of sodium on the alkylene dibromides, which have not the halogen atoms attached to the same or to neighbouring carbon atoms. Cyclic ketones, by conversion into alcohols, and then into the corresponding iodo-derivatives, also yield hydrocarbons when these halides are reduced by means of zinc and acid (Wislicenus). In the cyclohexane series some members may be obtained by the direct reduction of the benzene hydrocarbons with sodium and alcohol, or the method of Sabatier and Senderens may be employed, in which case the vapour of the benzene hydrocarbon is passed along with hydrogen, over reduced nickel, at a temperature of 180-250° C. In the preparation of unsaturated hydrocarbons, the important xanthogenic ester method of Tschugaeff may be used, in which case the cyclic monohydric alcohol is converted into the sodium derivative (or preferably the potassium derivative), and this is then transformed into the sodium xanthogenate by the direct action of carbon bisulphide. On treatment with an alkyl iodide the xanthogenic ester is produced, and on distillation decomposes with formation of the unsaturated hydrocarbon, which is then generally purified from final traces of sulphur compounds by redistillation over sodium. The reaction takes place thus:—



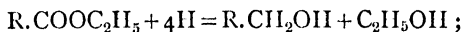
In some cases the elimination of water from a cyclic alcohol can be carried out either by heating the alcohol with anhydrous oxalic acid or with potassium bisulphate, with the consequent formation of the unsaturated hydrocarbon; or the hydrochloride of a cyclic amine may be distilled when it decomposes, in some cases with elimination of ammonium chloride and formation of

4 MODERN RESEARCH IN ORGANIC CHEMISTRY

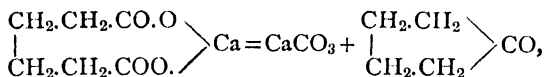
the hydrocarbon. In this way Baeyer obtained carvestrene from vestrylamine hydrochloride and from carylamine hydrochloride.



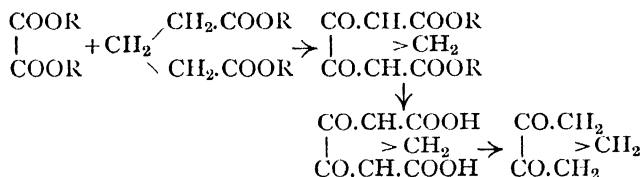
The methods employed in the formation of the alcohols of the series are essentially the same as those adopted in the formation of the aliphatic alcohols, namely, the replacement of halogen in halogen derivatives of the hydrocarbons by the hydroxyl group by means of silver oxide and water, or by the use of silver acetate followed by hydrolysis of the ester produced; by the reduction of ketones; by Bouveault and Blanc's recently discovered method of the reduction of esters by sodium and alcohol,



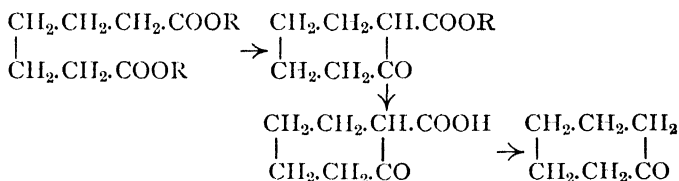
by the action of nitrous acid on the cyclic amines, and by the addition of the elements of water to the unsaturated cyclic hydrocarbons, the latter reaction being brought about in many cases simply by boiling the hydrocarbon with dilute sulphuric acid. Wagner has also made the important discovery that dihydric alcohols of the series may be obtained in very good yield when the unsaturated compounds are oxidized by means of a very dilute solution of potassium permanganate in the presence of a dilute solution of the alkaline hydroxides at low temperature. For the methods of preparation of the ketones we are indebted to the researches of J. Wislicenus, who showed that the distillation of the calcium salts of the higher dibasic acids of the oxalic series gave rise to these substances, calcium adipate for example, yielding keto-pentamethylene,



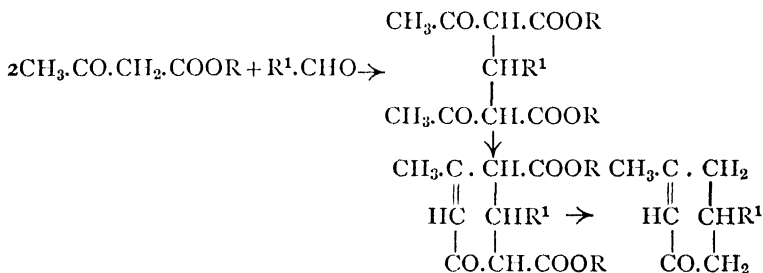
whilst calcium pimelate and calcium suberate yield keto-hexamethylene and ketoheptamethylene respectively, although in these two latter cases the yield is not so good as in the former case; and to Dieckmann, who condenses ethyl oxalate with the esters of dibasic acids in the presence of sodium ethoxide, the resulting esters on hydrolysis and elimination of carbon dioxide yielding diketones.



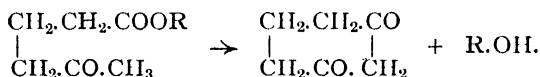
A somewhat similar reaction takes place on treatment of the esters of acids of the adipic and pimelic series with sodium.



As alternative methods, Knoevenagel has shown that the condensation of aceto-acetic ester with aldehydes leads to the formation of unsaturated ketonic acid esters, from which the corresponding ketones may be obtained by saponification and elimination of carbon dioxide.



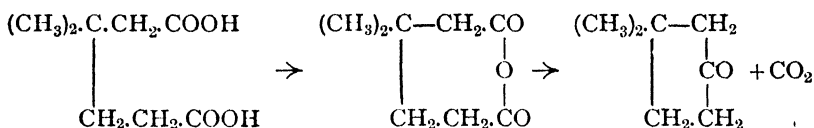
and Vörländer, by the action of sodium ethoxide on esters of δ -ketonic acids, has obtained diketones of the hexamethylene series



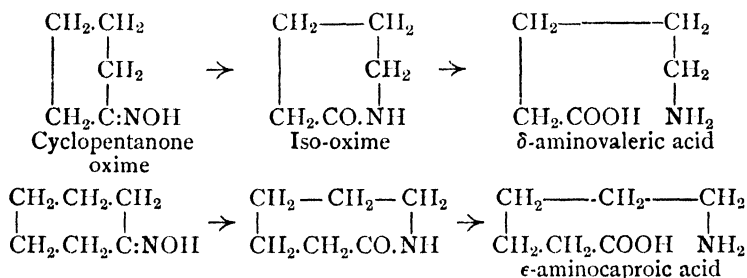
Blanc has recently shown that cyclic ketones may be obtained from the corresponding adipic or pimelic acids by heating them with acetic anhydride, and subsequently distilling the anhydrides which are so formed, thus, for example, under these conditions $\beta\beta$ -dimethyl adipic acid yields dimethyl-1,1-cyclopentanone-4,

6 MODERN RESEARCH IN ORGANIC CHEMISTRY

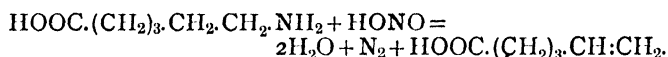
and $\beta\beta$ -dimethyl pimelic acid yields dimethyl-1,1-cyclohexanone-5.



In connection with these cyclic ketones, Wallach has made the interesting observation that the oximes of the saturated members of the series are readily converted into iso-oximes by a Beckmann transformation, and these latter, on treatment with hydrochloric acid, then yield amino-acids, thus from cyclopentanone oxime, δ -aminovaleric acid is formed, whilst cyclohexanone oxime in the similar manner is converted into ϵ -aminocaproic acid, the mechanism of the reaction being represented thus:—

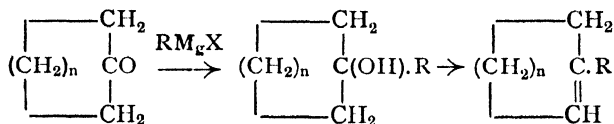


These acids may be (by the action of sodium nitrite on their hydrochlorides) transformed into unsaturated acids, in which the double bond is furthest removed from the carboxyl group, thus ϵ -aminocaproic acid under these conditions will yield hexene-5-acid.

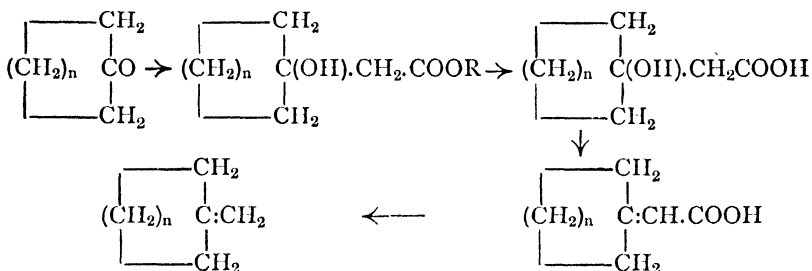


A similar series of transformations is obtained in the case of the complex cyclic ketones of the terpene series.

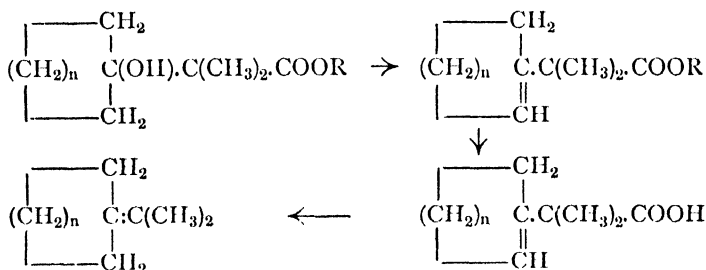
In the course of further observations on the cyclic ketones, Wallach has also shown that they condense quite readily with the Grignard reagent to form tertiary alcohols, which readily split out a molecule of water and form unsaturated hydrocarbons containing the double linkage in the cyclic nucleus, thus:—



If, however, the conditions be somewhat modified, and the ketone be condensed with the ethyl ester of bromoacetic acid and zinc, and the resulting hydroxy-cyclo carboxylic acid be then heated with potassium bisulphate, an unsaturated acid is produced which on distillation yields an unsaturated hydrocarbon containing a semicyclic ethylenic linkage, thus :—



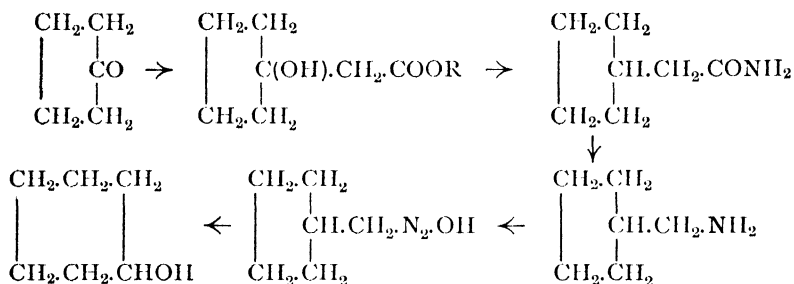
An interesting case occurs if the ethyl ester of α -bromoisobutyric acid be used instead of the bromoacetic ester, for the hydroxy ester produced can only give a cyclic unsaturated ester by loss of water, but if this ester be hydrolyzed, and the resulting acid be then distilled, a wandering of the ethylenic linkage takes place and a semicyclic ethylenic compound is formed.



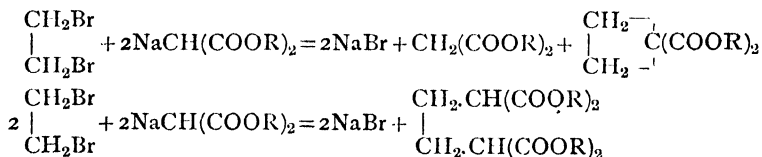
Wallach has further shown (1907) that in the series of cyclic ketones it is possible to pass from one series to another (*e.g.* from cyclopentanone to cyclohexanone, etc.) by the following process. The cyclic ketones condense with bromo-acetic ester to give

8 MODERN RESEARCH IN ORGANIC CHEMISTRY

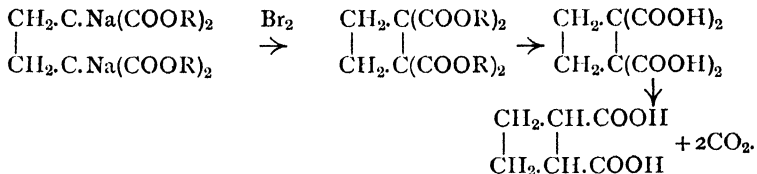
hydroxy esters, from which, by the action of hydrobromic acid and then reduction, the cyclic derivatives of acetic acid are formed. These acids may be converted into the corresponding amines by the Hofmann reaction, and from the nitrites of these amines, by the action of acids, products are obtained from which on boiling, nitrogen is eliminated, and the resulting compound, when hydrolyzed, yields an alcohol of the next higher system, which may be oxidized in the usual manner to a ketone, thus :—



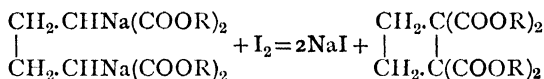
In the formation of acids and their esters we are chiefly indebted to the brilliant researches of W. H. Perkin, junr., who showed that the dihalogen paraffins condense readily with sodio-malonic ester or sodio-aceto-acetic ester to give esters of acids of the polymethylenes. The first reaction examined by Perkin was the condensation of ethylene dibromide with the ester, and here it was found that the reaction proceeded in two directions, one leading to the formation of an ester of trimethylene dicarboxylic acid and the other to tetraethyl butane tetracarboxylate, thus :—



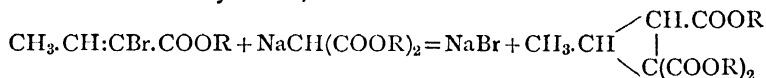
In the case of the second reaction, the resulting compound may be converted into a tetramethylene derivative by the action of bromine on its disodio-derivative, the resulting ester on hydrolysis yielding a tetracarboxylic acid which, when heated, loses carbon dioxide and yields tetramethylene dicarboxylic acid.



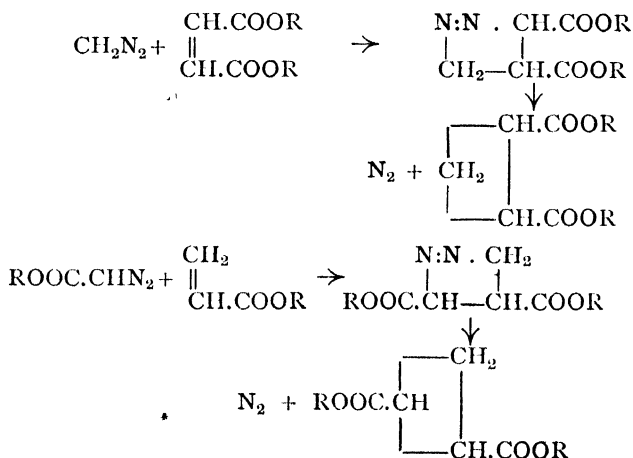
Again, Perkin has shown that by the action of halogens (preferably iodine) on the disodio derivatives of various esters (*e.g.* tetraethyl butane carboxylate), the esters of polymethylene acids are obtained.



Other methods of preparation of acids of the trimethylene series have been worked out by Michael, who has shown that sodiomalonic ester condenses readily with α -halogen derivatives of unsaturated fatty acids, thus:—

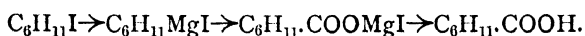


and by Buchner, who, by the condensation of diazomethane or diazoacetic ester with the esters of unsaturated acids, obtained pyrazoline carboxylic acids which, on heating, decompose with evolution of nitrogen, and the consequent formation of acids of the trimethylene series.

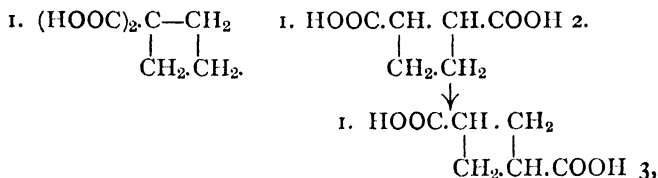


10 MODERN RESEARCH IN ORGANIC CHEMISTRY

In the hexamethylene series Zelinsky has shown that the Grignard reaction is applicable for the preparation of acids when the monobromo, or monoiodo substitution derivatives of the hydrocarbons are used. These halogen derivatives are brought into contact with magnesium in the usual way in ether solution and the resulting magnesium iodide or chloride on treatment with dry carbon dioxide and subsequent decomposition with dilute sulphuric acid yields the hexamethylene carboxylic acid

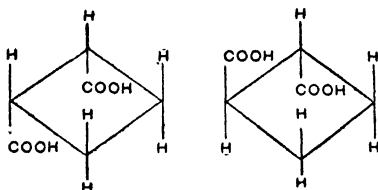


In the polymethylene compounds no cases of isomerism are met with in the monosubstituted derivatives, but in the di- and poly-substituted derivatives isomerism due to the position of the substituent in the molecule is possible, thus in the tetramethylene series the following dicarboxylic acids are possible:—

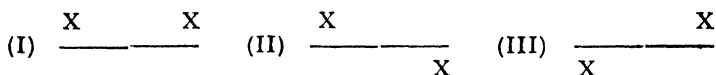


namely, the 1.1, 1.2 and 1.3 acids, the carboxyl groups occupying the positions shown. Again, some disubstituted derivatives are found to exist in stereo-isomeric forms, due to the spatial configuration of the molecule, thus in the case of the tetramethylene-1.2-dicarboxylic acid two forms are known, namely, the *cis*-acid, which melts at 137-138° C., and the *trans*-acid, which melts at 131° C. This isomerism can be accounted for in the following manner by considering that the plane of the paper represents the plane in which the carbon atoms of the ring lie, when the carboxyl groups may be considered as both being in the same plane either above or below the plane of the paper, or one may be in the plane above that of the paper and one in the plane below that of

the paper. This explanation leads to the following pictorial representation of the acids :—



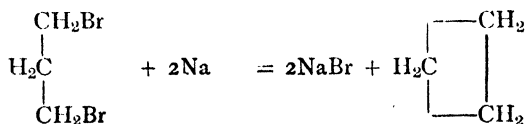
The former is known as the *cis*-acid, the latter as the *trans*-acid. A very neat method of representing these cases of isomerism has been devised by *Aschan*, who represents the plane of the carbon atoms of the ring as a straight line, and denotes the substituted hydrogen atoms by the letters X, Y, Z. Thus, for the dicarboxylic acids of the trimethylene series, if the carboxyl groups are represented by X, we have the following possibilities—



where (I) would represent the internally compensated active form of the acid, whilst (II) and (III), which are mirror images, represent the active forms of the acids. The configuration (I) is that of the *cis*-acid, (II) being that of the *trans*-acid, and since the artificially prepared *trans*-acids are optically inactive it is probable that they consist of racemic mixtures of (II) and (III).

In dealing with the various groups, only those compounds will be mentioned which possess an historical interest, or which are of importance as decomposition products of other series.

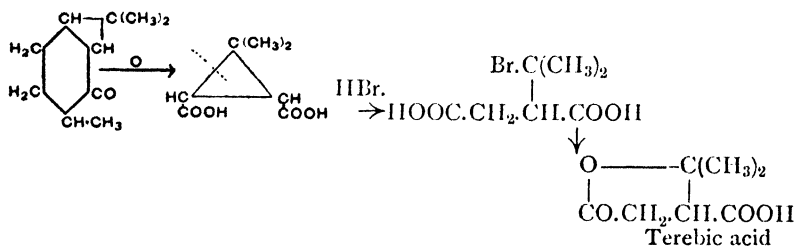
Cyclopropanes.—Of this series, cyclopropane itself and caronic acid are perhaps the most important members. The hydrocarbon was obtained by Freund in 1882, and was the first synthetic cyclic hydrocarbon to be prepared, containing less than six atoms of carbon. It was prepared by heating trimethylene bromide with sodium, the reaction taking place as follows :—



12 MODERN RESEARCH IN ORGANIC CHEMISTRY

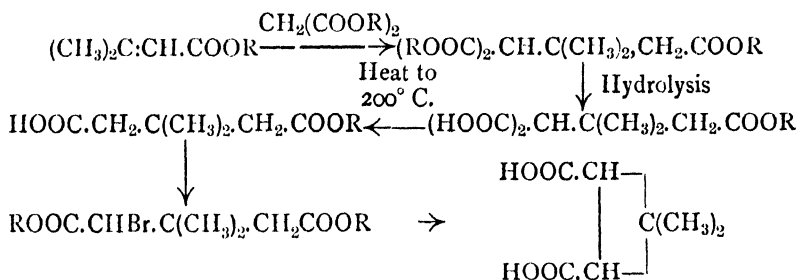
At ordinary temperature and pressure it is a gas which shows a marked difference in chemical behaviour from the isomeric propylene, for whereas the latter rapidly absorbs bromine with formation of propylene dibromide $\text{CH}_3\cdot\text{CHBr}\cdot\text{CH}_2\text{Br}$, cyclopropane is attacked very slowly and then yields trimethylene bromide. Again, hydriodic acid reacts with cyclopropane to form normal propyl iodide, whilst propylene, under similar conditions, yields isopropyl iodide. These reactions necessarily point to a difference in structure between cyclopropane and propylene, and are best explained by giving to the former the cyclic grouping of the carbon atoms.

Caronic acid $(\text{CH}_3)_2\cdot\text{C}_3\text{H}_2\cdot(\text{COOH})_2$ is a dimethyl cyclopropane dicarboxylic acid, which was first obtained by Baeyer from the oxidation of carone with a warm solution of potassium permanganate. From the fact that hydrobromic acid converts caronic acid into the isomeric terebic acid, Baeyer considered that caronic acid must be a *gem*-dimethyl cyclopropane dicarboxylic acid,¹ the reactions above mentioned proceeding as follows:—



This structure for caronic acid was afterwards confirmed by W. H. Perkin, jun., and Thorpe, who showed that the ethyl ester of dimethylacrylic acid condenses with ethyl malonate to form ethyl dimethyl propane tricarboxylic ester. This ester when hydrolyzed yields the free acid, which, when heated, is converted into $\beta\beta$ -dimethyl glutaric acid. The α bromodimethyl ester of the latter acid, when warmed with alcoholic potash, is converted into a mixture of *cis*- and *trans*-caronic acid.

¹ The prefix "*gem*" is used to denote that two alkyl groups are attached to the same carbon atom.

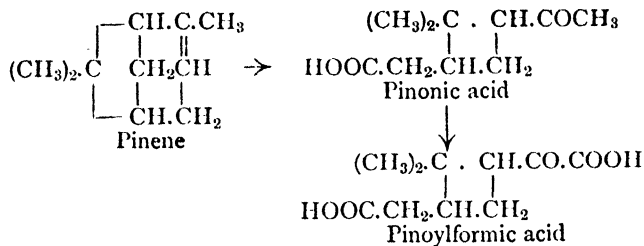


The two forms of the acid may be separated by means of their ammonium salts, that of the *cis*-form being much more soluble in hot alcohol than the corresponding salt of the *trans*-acid.

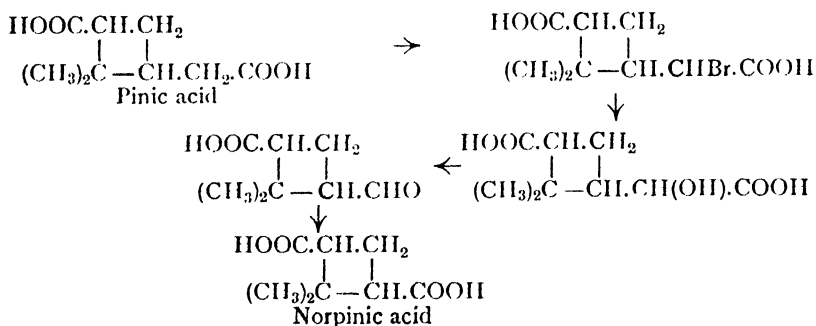
Cyclobutanes.—Many attempts were made by the earlier investigators to isolate the parent hydrocarbon of this group, all of which were unsuccessful until Willstätter, in 1907, showed that the unsaturated cyclobutene was capable of reduction by the Sabatier and Senderens method at comparatively low temperature. The hydrocarbon is a very volatile liquid, the vapour of which burns with a luminous flame. On further reduction by the above method at a temperature of 180-200° C. it yields *n*-butane. The cyclobutene required for the above reaction is produced by the distillation of trimethylcyclobutylammonium hydroxide (which is obtained by methylating cyclobutylamine in the usual manner), the process thus being an adaptation of Hofmann's "destructive methylation process" (see Alkaloids).

Among the other compounds belonging to this series may be mentioned *pinonic acid*, $\text{C}_{10}\text{H}_{16}\text{O}_3$, and *pinoylformic acid*, $\text{C}_{10}\text{H}_{14}\text{O}_5$, which are obtained when pinene, is oxidized with potassium permanganate at low temperature, the former acid being the chief product of the action, the latter being obtained in the form of its bisulphite compound from the mother liquor remaining after crystallization of the pinonic acid. Assuming Wagner's formula for pinene, the formation of pinonic acid and pinoylformic acid may be represented thus :—

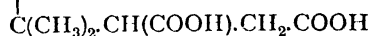
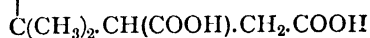
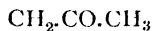
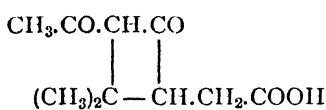
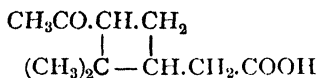
14 MODERN RESEARCH IN ORGANIC CHEMISTRY



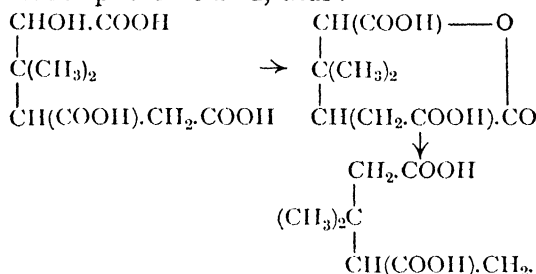
By oxidation of pinonic acid with sodium hypobromite *pinic acid* $\text{C}_9\text{H}_{14}\text{O}_4$ is obtained, the grouping $-\text{CH.CO.CH}_3$ being transformed into $-\text{CH.COOH}$, with elimination of bromoform. This acid readily forms a bromo-derivative which, by the action of caustic baryta, passes into the corresponding hydroxyl derivative. The latter compound on boiling its aqueous solution with lead peroxide is oxidized to an aldehyde acid, which, on further oxidation with potassium permanganate, is transformed into *norpinic acid* $\text{C}_9\text{H}_{12}\text{O}_4$, thus:—



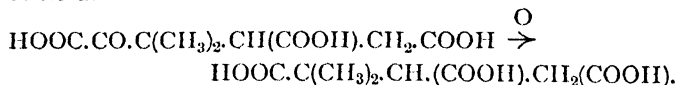
By the oxidation of pinonic acid with chromic acid mixture the tetramethylene ring is broken and two acids, namely, *isoketocamphoric acid*, $\text{C}_{10}\text{H}_{16}\text{O}_5$ and *isocamphoronic acid*, $\text{C}_9\text{H}_{14}\text{O}_6$, are obtained. Such an oxidation may be explained by the following scheme:—



In a similar manner pinoylformic acid on oxidation with bleaching powder is converted into *ketoisocamphoronic acid* $\text{HOOC.CO.C}(\text{CH}_3)_2\text{.CH(COOH).CH}_2\text{.COOH}$, which on reduction with sodium amalgam gives the lactone of α -hydroxyisocamphoronic acid, and the latter on reduction gives a quantitative yield of isocamphoronic acid, thus:—

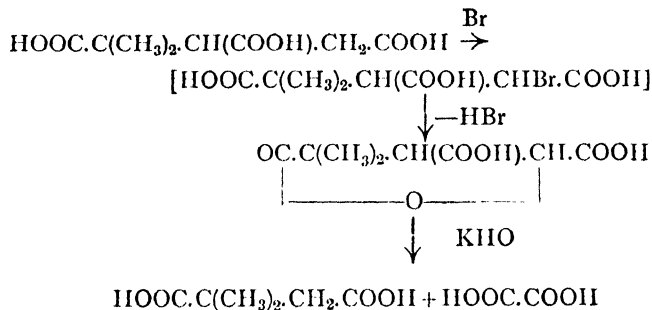


The ketoisocamphoronic acid obtained above when oxidized with lead peroxide yields the dimethyltricarballic acid $\text{C}_8\text{H}_{12}\text{O}_6$, which was obtained by Tiemann and Semmler from the action of a concentrated alkaline solution of potassium permanganate on pinonic acid.



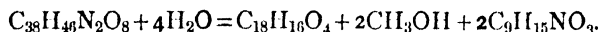
The determination of the constitution of this dimethyltricarballic acid is of fundamental importance since the formulation of pinonic acid and its derivatives depend entirely upon it. It was settled by A. v. Baeyer, who heated the acid with phosphorous tribromide and bromine, and then fused the resulting lactonic acid with caustic potash, when oxalic acid and asymmetrical dimethyl-succinic acid were obtained.

16 MODERN RESEARCH IN ORGANIC CHEMISTRY



It was also ascertained that the dimethyltricarballic acid contained no malonic acid grouping, and consequently the formula given above must be correct. Thus dimethyltricarballic acid, isocamphoronic acid, and ketoisocamphoronic acid contain two methyl groups linked to one and the same carbon atom, from which it follows that the pinic acid series contains the same grouping.

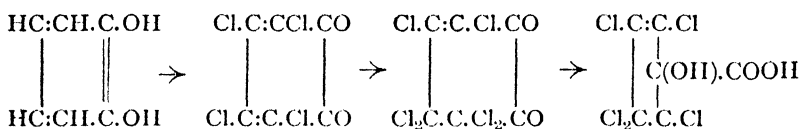
The truxillic acids $\text{C}_{18}\text{H}_{16}\text{O}_4$, which are derived from the alkaloid truxilline, are diphenylcyclobutane dicarboxylic acids. They are formed when truxilline is boiled with hydrochloric acid, the alkaloid breaking down into ecgonine, methyl alcohol, and truxillic acid



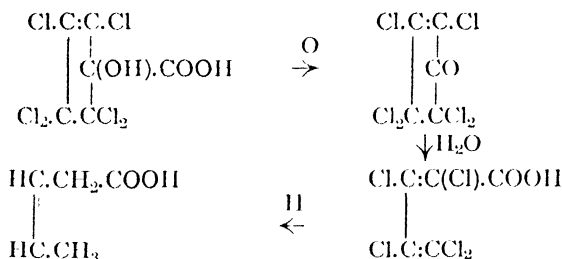
Their constitution was determined by Liebermann, who showed that they are polymers of cinnamic acid, into which they readily pass on distillation. They are stable towards potassium permanganate. The α - and β -truxillic acids, which are simultaneously formed in the hydrolysis of truxilline, are separated by means of their barium salts, that of the α -acid being soluble in water and that of the β -acid being insoluble. The α -acid has been synthesized by the oxidation of diphenyl-2,4-cyclobutane-bis-methylene malonic acid with potassium permanganate, the latter acid resulting when cinnamic aldehyde, malonic acid, and quinine are left in contact for some days.

18 MODERN RESEARCH IN ORGANIC CHEMISTRY

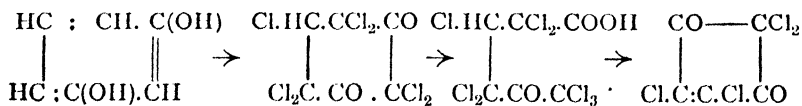
Catechol similarly on chlorination yields a tetrachloro-ortho-benzoquinone, which on further chlorination forms a hexachloro-derivative from which, by warming with water, a hydroxy-cyclopentane carboxylic acid is obtained.



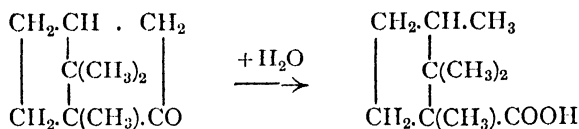
That the acid formed possesses this constitution is shown by the facts that on oxidation it yields a ketone which, by the action of alkalis, is converted into perchlorovinylacrylic acid, from which ethylidene propionic acid is obtained by reduction.



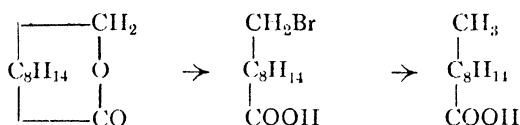
In the same way resorcinol, when chlorinated in glacial acetic acid solution, forms a heptachlororesorcinol, which on treatment with chlorine and water is transformed into trichloro-acetyl pentachlorobutyric acid. The latter acid when boiled with water is decomposed with elimination of hydrochloric acid and carbon dioxide, and consequent formation of a tetrachloro-diketo cyclopentene.



Many of the decomposition products of the camphor compounds are derivatives of the cyclopentane series, and as such will be considered in the following pages. Campholic acid, $\text{C}_{10}\text{H}_{18}\text{O}_2$, is a tetramethyl cyclopentane carboxylic acid, which is formed by the prolonged heating of a solution of camphor in xylene, with sodium, or by the action of bases with camphor



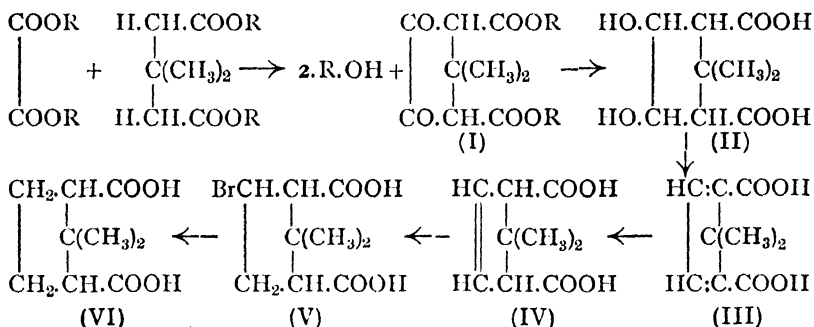
This structure of the acid is confirmed by the synthesis of the acid by Haller and Blanc in 1900 from campholid, which readily adds on the elements of hydrobromic acid, yielding a bromo-campholic acid which on reduction is transformed into campholic acid.



Nitric acid oxidizes it readily to camphoric acid, $\text{C}_8\text{H}_{14}(\text{COOH})_2$, and to camphoronic acid, $\text{C}_6\text{H}_{11}(\text{COOH})_3$, whilst when heated with soda lime it is converted into the unsaturated hydrocarbon campholene.

Apocamphoric acid, $\text{C}_8\text{H}_{14}\text{O}_4$, is a lower homologue of camphoric acid and was first obtained by Marsh and Gardner by the elimination of carbon dioxide from the camphoric acid ($\text{C}_9\text{H}_{14}\text{O}_6$) which they obtained from the action of nitric acid on camphene. It is also produced in the oxidation of bornyl chloride with nitric acid, and its constitution has been definitely determined by its synthesis in 1901 by Komppa. In this synthesis the dimethyl ester of $\beta\beta$ -dimethyl glutaric acid is condensed with oxalic ester in the presence of sodium ethoxide to form diketoapocamphoric ester (I), which on reduction yields the corresponding dihydroxyapocamphoric acid (II). The latter acid, when heated for some time with hydriodic acid and red phosphorus, yields an unsaturated acid (III). This acid, on further reduction with sodium and amyl alcohol, is transformed into another unsaturated acid the constitution of which is most probably to be represented by the formula (IV). On heating this acid with hydrobromic acid and glacial acetic acid, a saturated bromo-compound (V) is obtained, from which by reduction with zinc dust and acetic acid, apocamphoric acid (VI) finally results.

20 MODERN RESEARCH IN ORGANIC CHEMISTRY



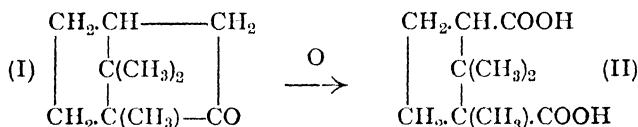
The acid on treatment with acetyl chloride and alkali is decomposed into its two stereoisomeric components, the *cis*-acid being transformed into its anhydride, which can be separated from the unaltered *trans*-acid by shaking up with sodium carbonate solution.

Camphoric acid, $\text{C}_{10}\text{H}_{16}\text{O}_4$, a trimethylcyclopentane dicarboxylic acid, is one of the longest known of the alicyclic compounds. It was apparently first obtained by Kosegarten in 1785, by the oxidation of camphor with nitric acid. The acid of above composition is found to exist in six different forms, namely, the *d*, *l*, and racemic forms, and the *d*, *l*, and racemic forms of the corresponding isocamphoric acid, the active varieties of which are prepared from *l* and *d*-camphoric acid respectively when these latter are heated for some time with acids or with water to high temperatures. The most important of these acids is the *d*-camphoric acid, obtained by the oxidation of camphor with nitric acid.



It crystallizes in prisms (melting at 187°C .), and is converted into its anhydride by the action of acetyl chloride. It is readily oxidized by potassium permanganate, yielding oxalic acid and a dibasic acid, $\text{C}_8\text{H}_{12}\text{O}_5$ (known as Balbiano's acid), together with small quantities of camphanic, camphoronic, and trimethyl succinic acid. On reduction with hydriodic acid it yields α,β -trimethyl glutaric acid, which points to the grouping $\text{HOOC.C}(\text{CH}_3)_2.\text{C}(\text{CH}_3)_2.\text{C.COOH}$ in the molecule.

Owing to the unsymmetrical positions of the $-(\text{COOH})$ groups in the molecule, two series of acid esters are known, one containing the grouping $-\text{CH}.\text{COOR}$, designated as *ortho*-esters, which result from the action of sodium alcoholates on camphoric anhydride or on heating the anhydride with alcohols, the other, containing the grouping $-\text{C}(\text{CH}_3)-\text{COOR}$, and known as *allo*-esters, which are produced when the neutral esters are heated for a short time with alcoholic potash. The constitution of camphoric acid has been definitely settled by its synthesis at the hands of Komppa in 1903,¹ although previously to this a general idea of its structure was known through the work of Bredt and others. The investigations of Bredt, based on the decomposition of camphoronic acid, led him to assign the formula (I) to camphor, from which it follows that camphoric acid must be represented by formula (II).

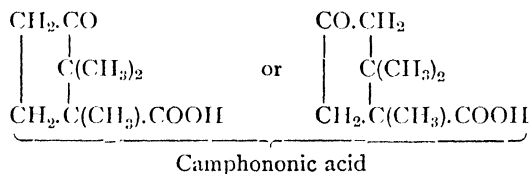
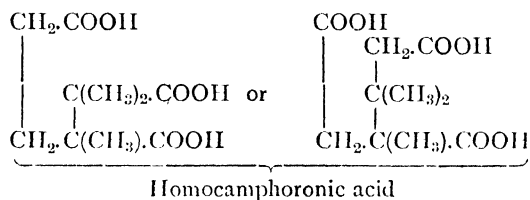


Further confirmation of the above-given structure is shown (a) by the formation of $\alpha\beta\gamma$ -trimethyl glutaric acid, $\text{HOOC}.\text{CH}(\text{CH}_3).\text{C}(\text{CH}_3)_2.\text{CH}_2.\text{COOH}$ (see above), and (b) that camphoric acid must be a substituted glutaric or adipic acid, and consequently its next higher homologue, homocamphoric acid, whose calcium salt yields camphor (a ring ketone) on distillation, must be either a substituted adipic or pimelic acid, since experience shows that only acids of these types give ring ketones on distillation of their salts. Again, since α -oxycamphoric acid readily lactonizes to form a γ -lactone (camphanic acid), it follows that a dibasic acid whose α -oxyderivative yields a γ -lactone must be a glutaric acid derivative. Further, camphoric acid contains a trimethyl cyclopentane ring, since Lapworth has shown that α -dibromocamphor is readily converted by silver nitrate into homocamphoronic acid, $\text{C}_7\text{H}_{13}(\text{COOH})_3$, an open chain tribasic acid, the anhydride of which on heating is converted into cam-

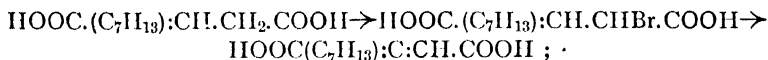
¹ See footnote, p. 94.

22 MODERN RESEARCH IN ORGANIC CHEMISTRY

phononic acid, $C_9H_{14}O_3$, a monobasic ketonic acid formed by the elimination of carbon dioxide from the anhydride, and consequent closing of the ring. On oxidation, camphononic acid yields camphoronic acid (*i.e.* $\alpha\alpha,\beta$ -trimethyl carballylic acid, $(CH_3)_2C(COOH) \cdot (CH_3) \cdot C(COOH) \cdot CH_2 \cdot COOH$), consequently camphononic acid must contain three methyl groups; and since another carbon atom is present as $-COOH$, this leaves a residue of five carbon atoms, one of which is present as a keto-group. These must represent a five-carbon ring nucleus, since the cyclic ketonic acid (camphononic acid) is obtained from the open chain tribasic acid (homocamphoronic acid), and the formation of ring ketones with less than five atoms of carbon has not as yet been observed. Homocamphoronic and camphononic acids must thus be—



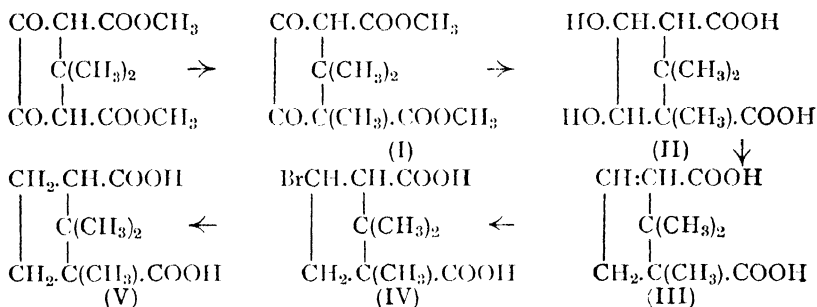
Again, homocamphoric acid on bromination yields an α -bromo-derivative from which, by removal of the elements of hydrobromic acid, dehydrohomocamphoric acid is obtained,



and since the oxidation of dehydrocamphoric acid yields camphononic acid, $HOOC(C_7H_{13}) : CO$, it follows that homocamphoric acid and camphoric acid contain the same cyclic nucleus as camphononic acid.

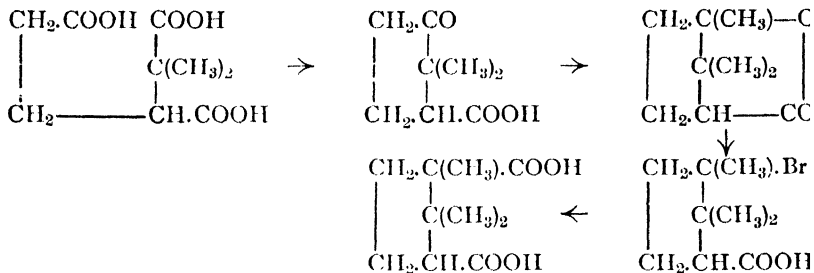
A complete synthesis of camphoric acid was carried out in 1903 by Komppa, from diketoapocamphoric ester (see p. 20).

This was methylated in the ordinary manner, and from the mixture of reaction products a diketocamphoric ester (I) was isolated. On reduction with sodium amalgam this furnishes a dihydroxycamphoric acid (II), which by heating for some time with hydriodic acid and amorphous phosphorus, is transformed into the unsaturated racemic dehydrocamphoric acid (III). This acid readily combines with hydrobromic acid to form β -bromocamphoric acid (IV), which on reduction with zinc dust and acetic acid yields mesocamphoric acid (V). The meso-acid was split by the action of acetyl chloride into the anhydride of a *cis*-acid, and a *trans*-acid which was not capable of yielding an anhydride. The *cis*-anhydride is identical with the anhydride of racemic camphoric acid, and the *trans*-acid is identical with racemic isocamphoric acid.

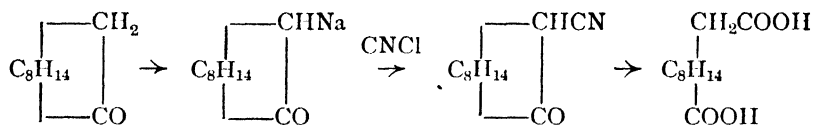


W. H. Perkin, junr., has recently (1906) synthesized camphoric acid starting from $\alpha\alpha$ -dimethylbutane- $\alpha\beta\delta$ -carboxylate, the sodium salt of which on treatment with acetic anhydride yields a dimethyl cyclopentanone carboxylic acid. The ester of this acid on treatment with magnesium methyl iodide is converted into α -campholactone. The latter compound by the action of fuming hydrobromic acid yields a bromotrimethyl cyclopentane carboxylic acid, which on shaking with potassium cyanide and hydrocyanic acid and subsequent heating yields an acid that passes on boiling with acetic anhydride into *i*-camphoric anhydride, from which the camphoric acid can be prepared in the usual manner. Unfortunately, the yield of acid obtained is very poor.

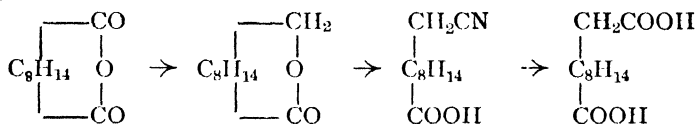
24 MODERN RESEARCH IN ORGANIC CHEMISTRY



Homocamphoric acid $\text{C}_{11}\text{H}_{18}\text{O}_4$, the higher homologue of camphoric acid, was first obtained by Haller by the hydrolysis of cyanamphor,

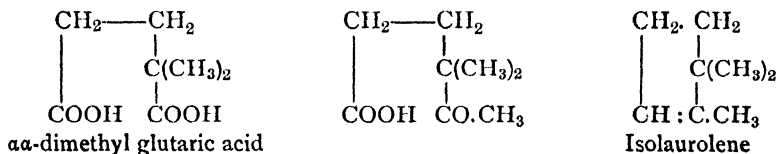


and later from camphoric anhydride by reduction to campholide, from which, by the addition of potassium cyanide, homocamphoric nitrile is obtained, the hydrolysis of the latter yielding homocamphoric acid.

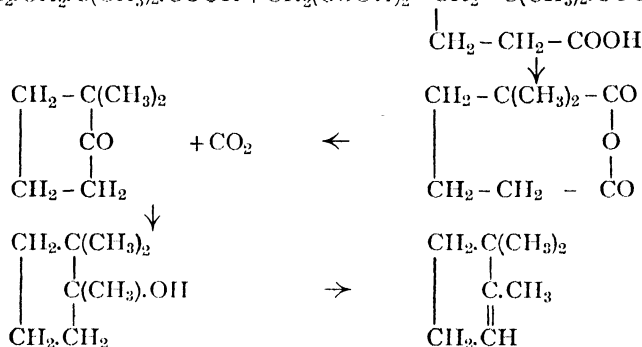
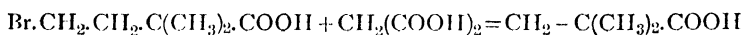


The distillation of its calcium or barium salt gives camphor (see Cap. II).

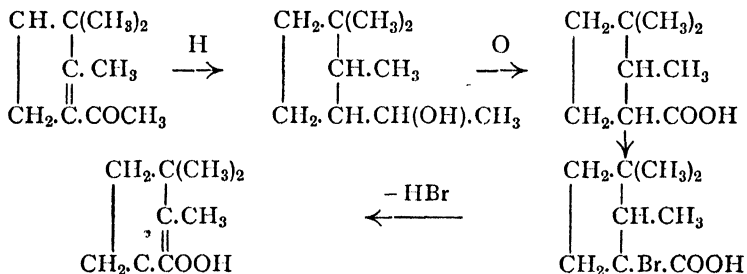
Isolaurelene, C_8H_{14} , is an unsaturated hydrocarbon of the cyclopentane series, which was obtained by Blanc on heating isolaurenic acid to 300°C ., $\text{C}_8\text{H}_{13} \cdot \text{COOH} = \text{CO}_2 + \text{C}_8\text{H}_{14}$. On oxidation with potassium permanganate it yields a dimethylhexanone carboxylic acid, and with potassium hypobromite $\alpha\alpha$ -dimethyl glutaric acid. These results indicate that the hydrocarbon should possess the annexed formula.



This has been confirmed recently (1906) by Blanc, who has synthesized the hydrocarbon, starting from γ -bromo- $\alpha\alpha$ -dimethyl butyric ester, which on condensation with malonic ester yields $\alpha\alpha$ -dimethyl adipic acid. This acid on treatment with acetic anhydride yields an anhydride which on distillation is converted into dimethylcyclopentanone, and from this by the action of the Grignard reagent the tertiary alcohol, trimethyl cyclopentanol, is obtained. The alcohol when distilled under diminished pressure readily loses a molecule of water and forms isolaurolene.

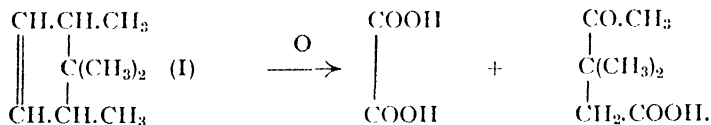


This series of reactions also leads to a synthesis of isolauronic acid, since isolaurolene on treatment with acetyl chloride in the presence of aluminium chloride gives a ketone, which is then reduced to the corresponding secondary alcohol. Oxidation of this alcohol with nitric acid yields dihydroisolauronic acid, and if this acid be then brominated and the elements of hydrobromic acid be eliminated from the resulting bromo-compound, isolauronic acid, $\text{C}_9\text{H}_{14}\text{O}_2$, is obtained.

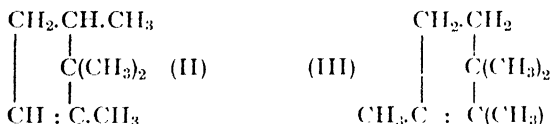


26 MODERN RESEARCH IN ORGANIC CHEMISTRY

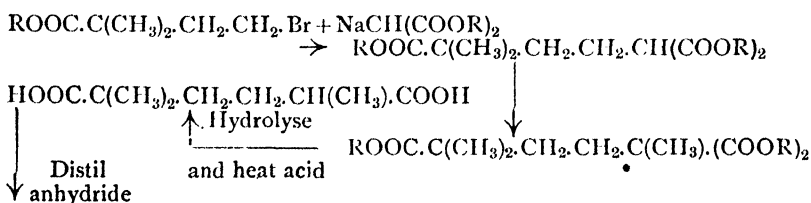
Campholene, C_9H_{16} , is also an unsaturated hydrocarbon of the cyclo-pentane series, and is obtained by the distillation of calcium α -campholenate or on heating β -campholenic acid with caustic soda. On oxidation with potassium permanganate it yields oxalic acid and dimethyl lævulinic acid, which led Tiemann to ascribe to it the following structure, and resulting decomposition on oxidation :—

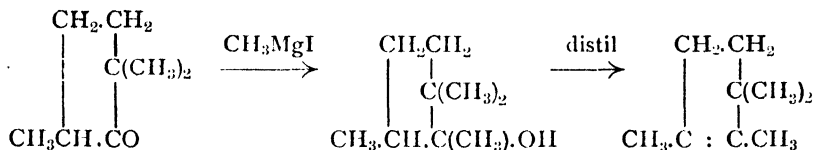


Bredt had at an earlier date given a different configuration (II), based on the preparation of the hydrocarbon from campholic acid and α -campholenic acid, whilst Bouveault and Blanc, on account of its preparation from β -campholenic acid, gave, in 1899, the formula represented in (III).

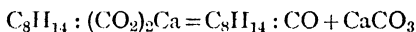


This last constitution appears to be the correct one, since campholene has been obtained synthetically in 1907 by Blanc in the following manner. The ethyl ester of γ -bromo- $\alpha\alpha$ -dimethyl butyrate, on condensation with ethyl sodiomalonate, yields the ethyl ester of β -methylpentane- $\beta\epsilon\epsilon$ -tricarboxylic acid. This ester is then methylated, the methylated product hydrolyzed, and the resulting acid heated, when $\alpha\alpha\delta$ -trimethyl adipic acid is formed. The anhydride of this acid on distillation yields 1,1,4-trimethyl cyclopentanone-5, from which, by means of the Grignard reagent, the corresponding tertiary alcohol is obtained. This alcohol on distillation loses water and gives campholene, thus :—

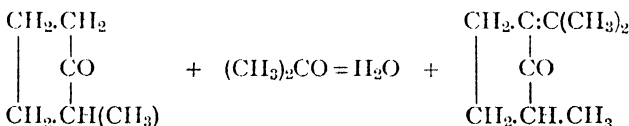




Camphorporone, $\text{C}_9\text{H}_{14}\text{O}$, which is obtained on distilling calcium camphorate, is a keto-cyclopentane derivative—

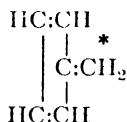


Its constitution follows, from its synthesis by Bouveault, by the action of sodium ethoxide on α -methylcyclopentanone and acetone, and consequently it must be a methylisobutylene cyclopentanone :—



The reverse process takes place when camphorporone is heated with solid caustic potash. It combines directly with hydroxylamine to form a hydroxylamino derivative, the group $>\text{C}=\text{C}(\text{CH}_3)_2$ being transformed into $>\text{CH}-\text{C}(\text{NHOH})(\text{CH}_3)_2$, such a reaction being shown by Harries and Roeder to be characteristic of this type of unsaturated ketone.

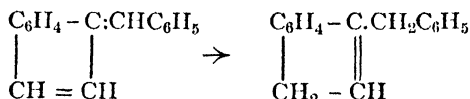
The fulvenes are a series of unsaturated hydrocarbons of a deep yellow or red colour, which were first obtained by Marckwald on condensing aldehydes with indene, and later by Thiele by the condensation of cyclopentadiene with aldehydes and ketones in the presence of sodium ethoxide. They may thus be considered as derivatives of the as yet unknown hydrocarbon fulvene, in which it may be noted that



one has a system of linkages comparable with that in benzoquinone, that is to say, a grouping of a chromophoric character. The fulvenes derived from the ketones and cyclopentadiene are more stable than those derived from the aldehydes and the hydrocarbon. Thiele has shown that those fulvenes which

28 MODERN RESEARCH IN ORGANIC CHEMISTRY

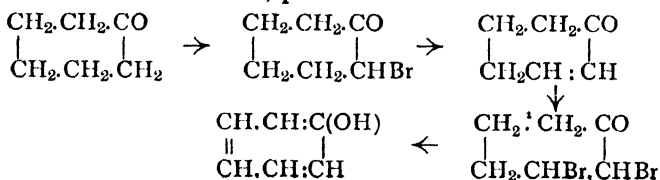
possess a phenyl or carboxyl group attached to the carbon atom C* are readily reduced by the aluminium mercury couple and yield colourless derivatives, benzylidene indene, for example, yielding benzyl indene.



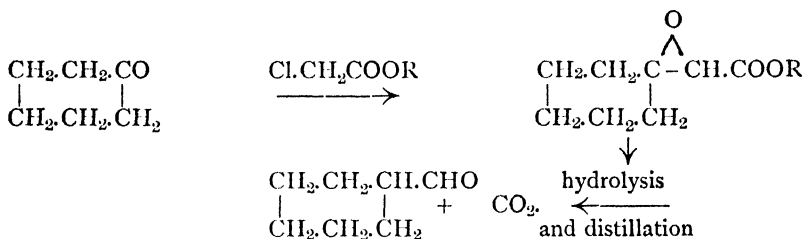
This reduction seems also to depend on the presence of the cyclopentadiene ring, since bis-diphenylene ethylene is reducible, whilst tetraphenyl ethylene is not.

Cyclohexanes.—Many of the members of this group will be considered under Terpenes (Cap. II), more particularly those derived from methyl-1-isopropyl-4-cyclohexane or hexahydro-cymene, $\text{C}_{10}\text{H}_{20}$, which may be looked upon as the parent substance of many of the monocyclic terpenes. This hydrocarbon may be obtained by the reduction of menthyl chloride with sodium and alcohol, or by the reduction of limonene, cymene, etc., with hydrogen in the presence of reduced nickel by the Sabatier and Senderens method.

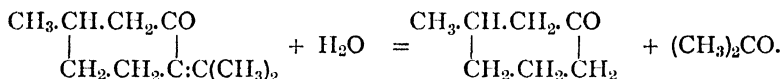
The ketones are perhaps the most important derivatives of this series, since some of them are closely related to the monocyclic terpenes. Cyclohexanone, $\text{C}_6\text{H}_{10}\text{O}$, the first member of the series, was obtained by Wislicenus by the distillation of calcium pimelate. It has also been obtained by the electrolytic reduction of phenol, and recently the process has been reversed in such a way that the intermediate products could be isolated, showing the gradual transition from the saturated ring system to the ordinary aromatic ring system. In this change the ketone is brominated, and hydrobromic acid is eliminated from the resulting bromo-compound. The unsaturated hexenone so formed, readily takes up two atoms of bromine, and if now hydrobromic acid be removed from the dibromide, phenol is obtained.



Cyclohexanone condenses readily with monochloroacetic ester in the presence of sodium ethoxide to form a glycide ester which on hydrolysis yields the free acid. This acid on distillation in vacuo loses carbon dioxide and is converted into hexahydrobenzaldehyde.

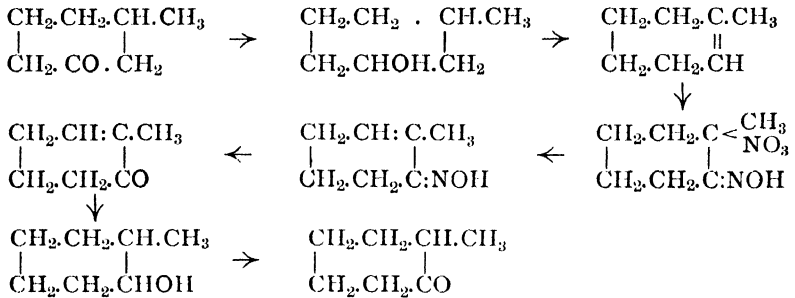


Of the three possible methylcyclohexanones, the methyl-1-cyclohexanone-3 is the most important, since it arises from the hydrolysis of pulegone.

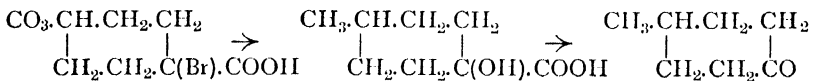


The product obtained in this way represents the α -form, whilst the racemic variety is obtained by the distillation of the calcium salt of β -methyl pimelic acid. On oxidation with nitric acid, both varieties yield a mixture of α - and β -adipic acids. Successive treatment with sodamide and the alkyl iodides converts it into homologues to menthone. Wallach has shown that it may be converted into the isomeric methyl-1-cyclohexanone-2, by the following series of reactions. The cyclohexanol formed by reduction, loses water when heated with phosphorus pentoxide, and is converted into methyl cyclohexene, the nitrosate of which, when heated with sodium methoxide, yields two isomeric oximes, and from these on hydrolysis one and the same methylhexenone is formed. This hexenone is then reduced by sodium and alcohol to the cyclohexanol from which the ketone is obtained by oxidation.

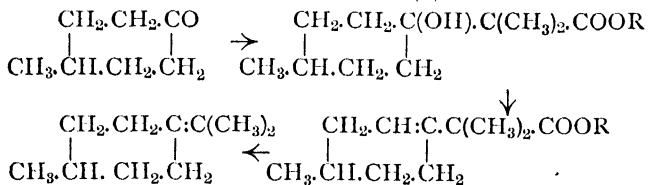
30 MODERN RESEARCH IN ORGANIC CHEMISTRY



Methyl-1-cyclohexanone-4 acquires a theoretical interest since Perkin has shown that with the Grignard reagent it can be converted into tertiary menthol. The starting-point in this transformation is α -bromohexahydroparatoluic acid, which is decomposed by sodium carbonate into Δ .1-tetrahydroparatoluic acid and α -hydroxyhexahydroparatoluic acid, the latter being converted into the cyclohexanone by the action of dilute sulphuric acid.



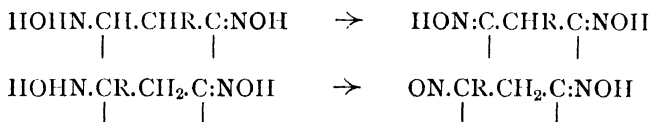
On condensation with magnesium isopropyl iodide and subsequent hydrolysis it is converted into tertiary menthol. Wallach has also shown that on treatment with isobutyric acid and zinc it is converted into an oxy-ester which loses water easily, and if the resulting unsaturated ester be hydrolyzed and the free acid heated, carbon dioxide is eliminated and *i*- Δ .4(8)-menthene is obtained.



It may be mentioned in passing that two types of cyclohexenones exist, namely the $\alpha\beta$ and $\beta\gamma$ hexenones, the isomerism depending on the position of the double linkage, thus—

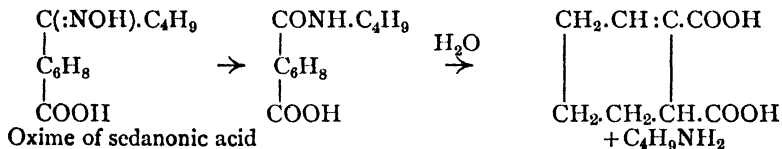


These two groups show characteristic differences in their behaviour to reagents, the $\alpha\beta$ compounds, for example, on reduction with zinc and alcoholic potash, yielding saturated ketones and also bimolecular compounds, in which two molecules are linked together through the β -carbon atom, whilst the $\beta\gamma$ compounds are unaffected. Again, the $\beta\gamma$ series react in the normal manner with hydroxylamine to form oximes, whilst the $\alpha\beta$ series form oxamino-oximes, the group $-\text{CH}=\text{CH}-\text{CO}-$ becoming $-\text{HC}(\text{NHOH})-\text{CH}_2-\text{C}(:\text{NOH})-$. These oxamino compounds may also be of two different types, depending on whether the group $-\text{NHOH}$ is united to a secondary or a tertiary carbon atom, and for this reason show a characteristic behaviour on oxidation. Those of the former type on oxidation yield colourless dioximes, whilst the latter yield nitroso compounds which give the usual characteristic blue solutions; thus—

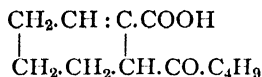


Two naturally occurring compounds of the cyclohexane series are sedanonic acid, $\text{C}_{12}\text{H}_{18}\text{O}_3$, and sedanolic acid, $\text{C}_{12}\text{H}_{20}\text{O}_3$, which were found by Ciamician and Silber in the higher boiling fractions of celery oil. The constitution of these substances has been worked out in the following manner. On reduction with sodium amalgam, both yield the same product, an alcohol acid, $\text{C}_{12}\text{H}_{22}\text{O}_3$ (orthohydroxyamyl hexahydrobenzoic acid), consequently both contain the same carbon nucleus. Again, sedanonic acid behaves as an unsaturated ketonic acid, and its oxime readily undergoes the Beckmann transformation on warming with concentrated sulphuric acid, yielding *n*-butyl tetrahydrophthalamic acid, which is easily hydrolyzed to *n*-butylamine and Δ .2-tetrahydrophthalic acid. And since potassium permanganate oxidizes sedanonic acid to oxalic, glutaric, and *n*-valeric acids, it follows that the ethylene linkage must be next to the carboxyl group. Thus one has

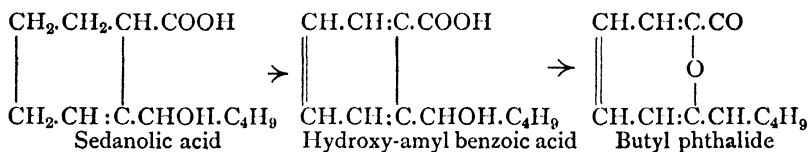
32 MODERN RESEARCH IN ORGANIC CHEMISTRY



whence sedanonic acid must be orthovaleryl- Δ -1-tetrahydrobenzoic acid.

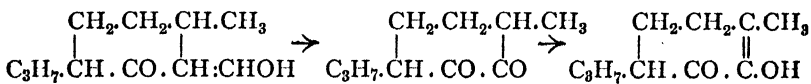


Again, sedanonic acid is readily oxidized by alkaline potassium permanganate to ortho-hydroxyamyl benzoic acid, which readily passes into its lactone butyl phthalide; and since it possesses the same carbon nucleus as sedanonic acid, it is to be considered as an ortho-hydroxyamyl- Δ .5-tetrahydrobenzoic acid, the latter series of changes taking place thus:—

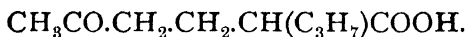


Sedanonic acid readily splits out a molecule of water between the -COOH- and -OH groups, and passes into its lactone sedanolid, $\text{C}_{12}\text{H}_{18}\text{O}_2$, a colourless thick oil which is the odoriferous constituent of celery oil.

Diosphenol, $\text{C}_{10}\text{H}_{16}\text{O}_2$, which is found in the essential oil of Bucco leaves, is an unsaturated ketone alcohol of the cyclohexane series. It was formerly thought to be a hydroxyaldehyde, but its synthesis from hydroxymethylene menthone has shown that it must be regarded as a hydroxy-ketone. Oxymethylene menthone is readily oxidized by ozone to the corresponding methyl-1-isopropyl-4-cyclohexane-dione-2.3, which, on treatment with acids or alkalis, rearranges itself to diosphenol, thus:—



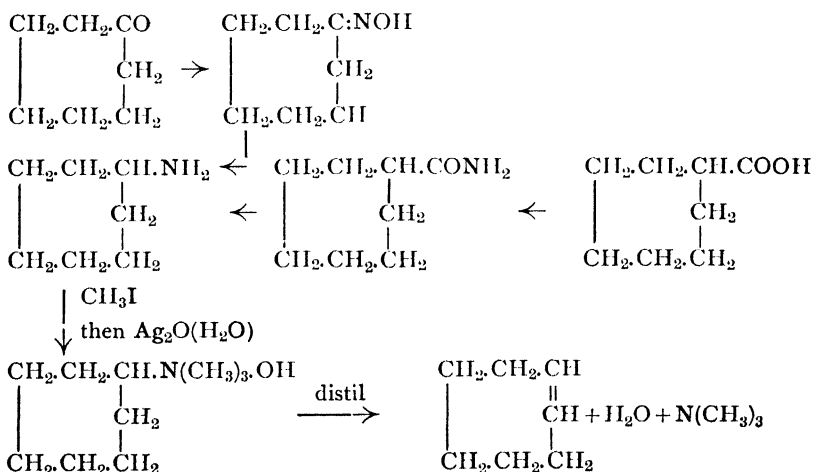
On reduction it gives paramenthane-diol-2.3, whilst ozone oxidizes it to α -isopropyl- γ -acetyl butyric acid,



When heated in a sealed tube with hydrochloric acid it gives an almost quantitative yield of thymol.

Cycloheptanes—In this group the most important derivatives are those which have been obtained by the breaking down of the tropine molecule, a series of unsaturated hydrocarbons and their derivatives being produced according to the conditions of experiment. Many of these compounds have been synthesized in recent years by Willstätter.

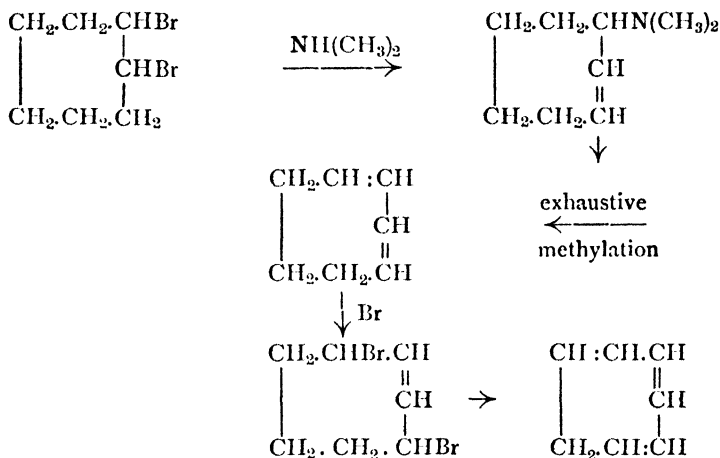
Cycloheptane C_7H_{12} results when suberone oxime is reduced to cycloheptane amine, which is then subjected to the destructive methylation process of Hofmann (see *Alkaloids*), or as an alternative cycloheptane carboxylic acid, which is obtained in the breaking down of the hydroecgonidine molecule (see *Alkaloids*), may be converted into its amide, which on treatment with bromine and alkali yields cycloheptane amine.



This hydrocarbon yields a dibromide which condenses with dimethylamine to form dimethylaminocycloheptene, and the amino-compound by destructive methylation, and distillation of the corresponding ammonium hydroxide is converted into a cycloheptadiene-1-3, C_7H_{10} . This hydrocarbon in its turn, by the addition of bromine and subsequent heating of the dibromide

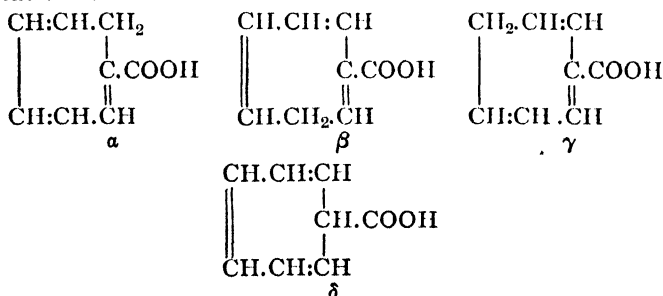
34 MODERN RESEARCH IN ORGANIC CHEMISTRY

with quinoline, was converted by Willstätter into cycloheptatriene C_7H_8 , which had first been obtained by Ladenburg (and called by him tropilidene) as a decomposition product of tropine.



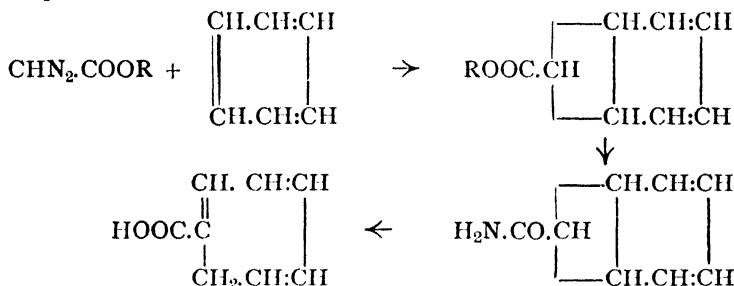
Further details of the related compounds will be given in the discussion of the constitution of tropine (p. 146).

The isophenylacetic acids may be mentioned here, since, according to the investigations of Buchner, they are to be regarded as cycloheptatriene carboxylic acids, although at one time regarded as being methylene dihydrobenzoic acids. All four possible isomers are known and have been assigned the following constitutions:—

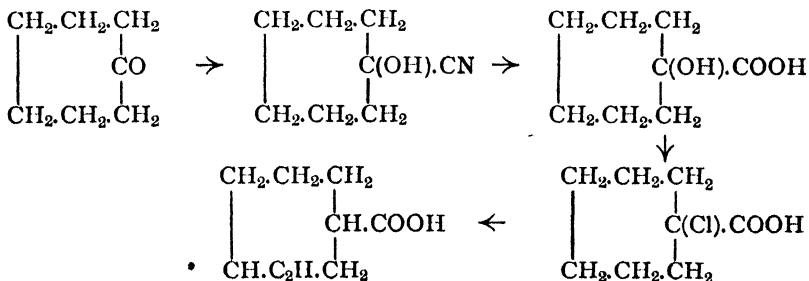


By the condensation of diazoacetic ester with benzene at about $130^\circ C.$, a ψ -phenylacetic ester is obtained which, on long standing with concentrated ammonia, is converted into ψ -phenylacetamide,

and from this latter compound by hydrolysis with caustic soda, the free α -isophenylacetic acid is obtained. The reactions may be expressed thus :—



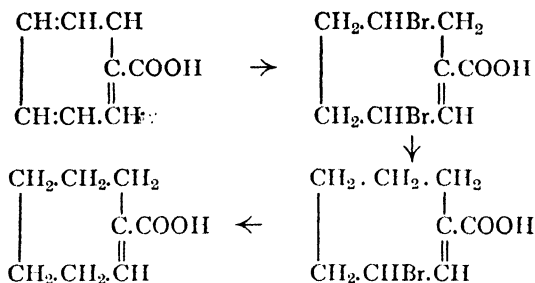
whilst if the ψ -phenylacetic ester be heated in an evacuated tube to 150° C., the ester of the isomeric β -acid is obtained, from which the free acid results on hydrolysis. This β -acid is also formed when the methiodide of ecgonine ethyl ester is hydrolyzed with dilute caustic alkali. The α -acid contains three double linkages, since it combines with six atoms of hydrogen and yields as ultimate reduction product the saturated hexahydroisophenylacetic acid $\text{C}_7\text{H}_{13}\text{COOH}$, and since this acid contains two less hydrogen atoms than the corresponding octane acid $\text{C}_7\text{H}_{16}\text{COOH}$ it must in all probability possess a cyclic structure. Again, the amide of this hexahydroisophenylacetic acid is identical with the amide of suberone carboxylic acid which results when suberone is condensed with hydrocyanic acid and the resulting nitrile is hydrolyzed to the hydroxy-acid. This acid on treatment with phosphorus pentachloride yields a chlorinated acid, from which suberone carboxylic acid is obtained by reduction.



Consequently, the α -isophenylacetic acid contains a seven carbon

36 MODERN RESEARCH IN ORGANIC CHEMISTRY

ring. The position of the double linkages is shown by the fact that the dihydrobromide of the α -acid on reduction, first by zinc dust and alcoholic hydrochloric acid, and finally by zinc dust and glacial acetic acid, gives Δ .1-cycloheptene carboxylic acid, which has been obtained synthetically.



The β -acid yields a dihydrobromide identical with that obtained from the α -acid, and so contains the same carbon nucleus. On reduction it yields Δ .2-cycloheptene carboxylic acid.

γ -Isophenylacetic acid is formed when the β -acid is heated for many hours with alcoholic potash, whilst the δ -acid is obtained by the action of silver oxide and water on the methiodide of anhydro-ecgonine ester, the intermediate product being decomposed by boiling with caustic alkali. On reduction it yields Δ .2-cycloheptene carboxylic acid.

Cyclo-octanes—Very few members of this group have as yet been isolated. ψ -Pelletierine, one of the alkaloids of the pomegranate, on destructive methylation yields a cyclo-octadiene C_8H_{12} as an unstable compound which rapidly polymerizes. A β -cyclo-octadiene of a much more stable character has been described, and is prepared from methyl granatine methiodide (see *Alkaloids*). When reduced by the Sabatier and Senderens method it yields cyclo-octane C_8H_{16} , a liquid with a strong camphor odour, and which on oxidation yields suberic acid.

Doebner has also prepared compounds, which are probably to be considered as cyclo-octadienes, by the distillation of β -vinylacrylic acid and cinnamylacrylic acid with anhydrous baryta.

BIBLIOGRAPHY

A very complete list of references to papers dealing with the Polymethylene compounds is given in Aschan's "Chemie d. alicyclischen Verbindungen." Of the subject matter dealt with in the text, the following list gives the more important papers.

- Spannung's Theorie** Baeyer, *Ber.* 1885, **18**, 2277.
- Préparations** . Wislicenus, *Ann.* 1893, **275**, 312.
 Tschugaeff, *Ber.* 1899, **32**, 3332
 Bouveault and Blanc, *C.R.* 1903, **136**, 1676 ; **137**, 60.
 Wagner, *Ber.* 1888, **21**, 1230, 3343.
 Dieckmann, *Ber.* 1897, **30**, 1470 ; 1899, **32**, 1930.
 Knoevenagel, *Ann.* 1894, **281**, 25 ; 1896, **288**, 321 ;
Ber. 1904, **37**, 4461.
 Vorlander, *Ber.* 1895, **28**, 2348.
 Wallach, *Ann.* 1900, **312**, 171 ; 1907, **353**, 318 ;
 1908, **360**, 26
 Blanc, *C.R.* 1907, **144**, 1356.
 Perkin, *Ber.* 1884, **17**, 54 ; 1888, **21**, 739 ; *Jour. Chem.*
Soc. 1888, **53**, 185 ; 1892, **61**, 36.
 Buchner, *Ber.* 1890, **23**, 701 ; *Ann.* 1895, **284**, 212.
 Aschan, *Ber.* 1902, **35**, 3389.
- Cyclopropanes** . Freund, *Monats.* 1882, **3**, 625.
 Perkin, *Journ. Chem. Soc.* 1899, **75**, 48.
- Cyclobutanes** . Willstätter, *Ber.* 1907, **40**, 3979.
 Baeyer, *Ber.* 1896, **29**, 326, 1907, 2775.
 Liebermann, *Ber.* 1888, **21**, 2342 ; 1889, **22**, 124.
 Rüber, *Ber.* 1902, **35**, 2411.
- Cyclopentanes** . Hantzsch, *Ber.* 1889, **22**, 1238.
 Haller and Blanc, *C.R.* 1900, **130**, 376.
 Komppa, *Ber.* 1901, **34**, 2472 ; 1903, **36**, 4332.
 Zincke, *Ber.* 1890, **23**, 3766 ; 1891, **24**, 912 ; 1893,
26, **34**, 498, 513 ; 1894, **27**, 733.
 Haller, *C.R.* 1896, **122**, 446.
 Lapworth, *Jour. Chem. Soc.* 1899, **75**, 986 ; 1900, **77**,
 1053.
 Perkin, *Jour. Chem. Soc.* 1906, **89**, 795.
 Blanc, *Ann. ch. phys.* 1899, (vii), **18**, 181 ; *C.R.* 1906,
142, 1084 ; 1907, **145**, 681.
 Tiemann, *Ber.* 1897, **30**, 594.
 Bredt, *Ber.* 1893, **26**, 3055.
 Bouveault, *Bull. Soc.* 1900, (iii), **23**, 160
 Harries, *Ber.* 1898, **31**, 1809 ; 1899, **32**, 1315.

38 MODERN RESEARCH IN ORGANIC CHEMISTRY

- Thiele, *Ber.* 1900, **33**, 666.
- Cyclohexanes** . Wallach, *Ann.* 1904, **329**, 368 ; *Ber.* 1906, **39**, 2504.
Perkin, *Proc. Chem. Soc.* 1905, **21**, 255.
Ciamician and Silber, *Ber.* 1897, **30**, 492, 501, 1419.
Semmler, *Ber.* 1906, **39**, 1158.
- Cycloheptanes** . Buchner, *Ber.* 1898, **31**, 2241.
Einhorn and Friedlander, *Ber.* 1893, **26**, 329, 1490.
- Cyclo-octanes** . Willstätter, *Ber.* 1907, **40**, 957.
Doebner, *Ber.* 1902, **35**, 2129 ; 1903, **36**, 4318.

CHAPTER II

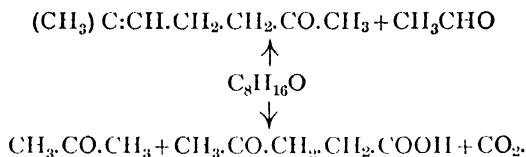
THE TERPENES AND CAMPHORS

THE terpene group of compounds consists of a series of cyclic hydrocarbons of the general formula $(C_5H_8)_n$ and the oxygenated substances which are chiefly of an alcoholic, aldehydic or ketonic nature, derived from them. The parent hydrocarbons are capable of division into distinct groups, and may be classified as (a) *Hemiterpenes*, which correspond to the molecular formula C_5H_8 ; (b) *Terpenes* proper, corresponding to $C_{10}H_{16}$; (c) *Sesquiterpenes* corresponding to $C_{15}H_{24}$, and (d) *Polyterpenes* corresponding to $(C_5H_8)_n$. In addition to the above groups of compounds, another series has been discovered in recent years, namely, that of the open chain olefine hydrocarbons $(C_5H_8)_2$ and the aldehydes, ketones, and alcohols derived from them.

In the following pages, the olefine terpene series will be considered first. The alcohols and aldehydes of this series are found to exist in many essential oils, more especially in oil of lemons, oil of oranges, and the oils of geranium, neroli, petit-grain, linaloe, coriander; lemon grass oil, and in Turkish and German rose oil. One of the most important derivatives of this series is *citral* (geranial) $C_{10}H_{16}O$, an aldehyde obtained largely from essence of lemon grass, from which it may be isolated by means of its bisulphite compound by working at a low temperature. The bisulphite compound is decomposed by alkaline carbonates in the usual manner, and the small quantity of methyl heptenone, which is generally present, is then separated by fractional distillation. It may be prepared artificially by the usual methods, namely, by oxidation of the corresponding alcohol (*geraniol*), or by distilling a mixture of calcium formate and calcium geraniate. Since geranic acid has been itself synthesized

40 MODERN RESEARCH IN ORGANIC CHEMISTRY

we are in possession of a complete synthesis of citral. The key to the synthesis of the aldehyde was first found by a study of its decomposition products, particularly those of its oxidation with potassium permanganate, whereby it yields lævulinic acid, acetone, and carbon dioxide; and of its hydrolysis with potassium carbonate when it yields acetaldehyde and methyl-heptenone.

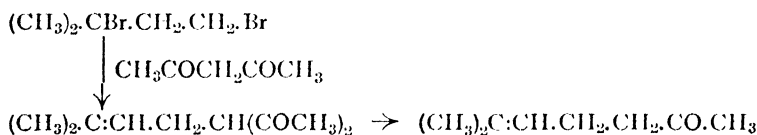


These results show the unsaturated nature of the aldehyde (which is also determined by the formation of addition products) and enable the position of the ethylene linkages to be fixed as shown in the annexed formula

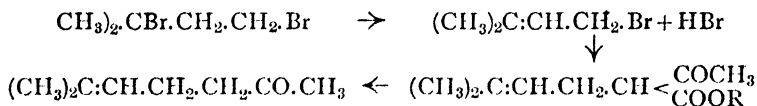


oxidation taking place at *a* and *b*, hydrolysis at *b* alone.

The synthesis of geranic acid took for its starting point methyl-heptenone, which was previously prepared by Barbier and Bouveault by the condensation of *gem*-dimethyltrimethylene bromide with sodium acetylacetone and decomposition of the resulting ketone with concentrated sodium hydroxide solution

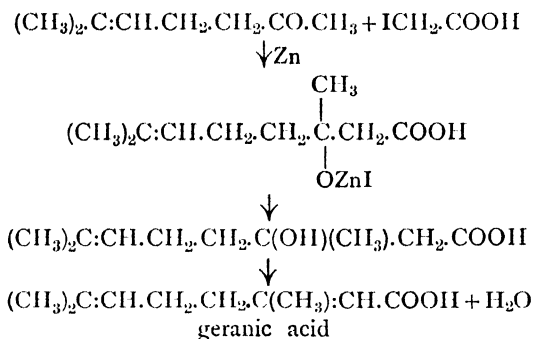


and also by Ipatiew from the same bromo-compound and sodium aceto-acetate the *gem*-dimethylallylacetacetic ester being hydrolyzed by caustic baryta.

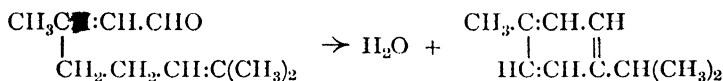


The methyl heptenone thus produced condenses with iodoacetic acid in the presence of metallic zinc to form an addition compound which hydrolyzes in the presence of dilute acids to an

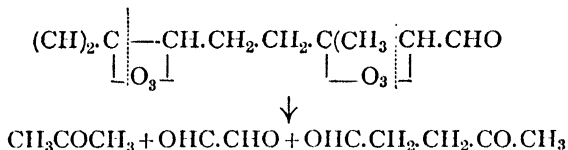
unsaturated hydroxy-acid, and this latter on heating loses a molecule of water and passes into geranic acid.



Citral is converted into cymene by the action of acid condensation agents, the ring closing between the third and eighth carbon atoms of the chain.



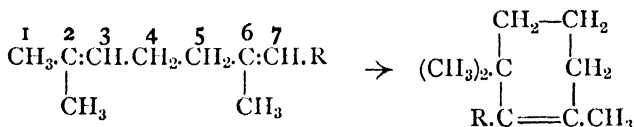
It has been shown that crude citral is a mixture of two isomers, citral-*a* and citral-*b*, since two different semicarbazones may be obtained from the mixture and two different citrylidene-cyanacetic acids. The two are stereoisomers, since Harries in 1907 showed their structural identity by converting them into oxides (by passing ozone into their solution in carbon tetrachloride) and found that the decomposition of these ozonides in each case gave rise to the same products, namely, acetone, glyoxal and lævulinic aldehyde, from which it follows that the two are of a similar structure.



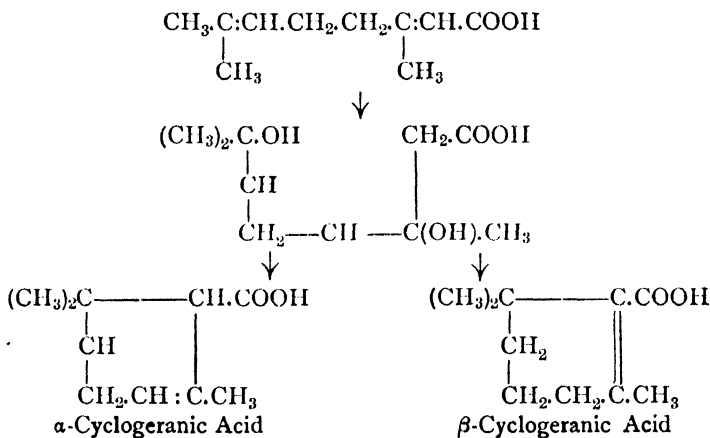
The two isomers exist in very different proportions in the crude oils, the *a* variety occurring to about the extent of 73% and the *b* variety to about 8% in lemon grass oil.

42 MODERN RESEARCH IN ORGANIC CHEMISTRY

It was shown above that citral may be readily converted into cymene by acid reagents, but it is found that if the reactivity of the carbonyl group is reduced by replacement of the carbonyl oxygen, then the condensation undergoes another course, the ring closing between the carbon atoms in positions 2 and 7, yielding cyclic isomers.

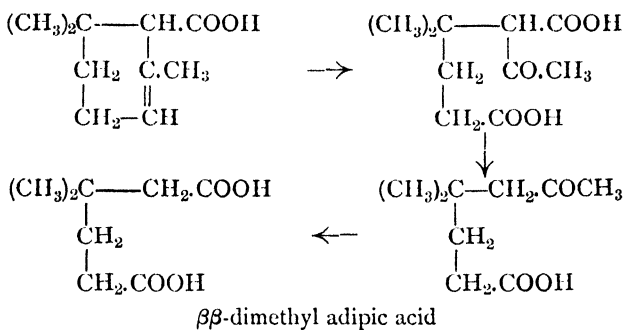


These cyclic isomers may exist in two isomeric forms, the α -series and the β -series, the isomerism being due to the position of the double linkage in the molecule, thus taking geranic acid as an example, two cyclo-geranic acids may be prepared.

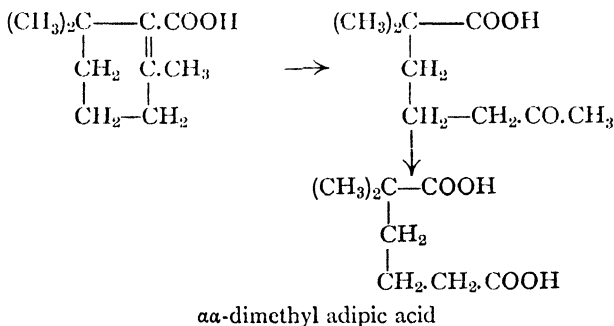


The position of the double linkage in the α -series is shown by the fact that, on oxidation, they yield isogeranic acid, which, on further oxidation, is converted into $\beta\beta$ -dimethyl adipic acid, the β -series in the same way being transformed into geranic acid and $\alpha\alpha$ -dimethyl adipic acid, thus :—

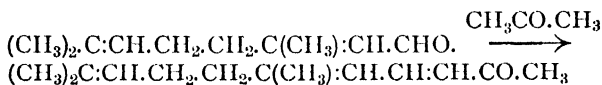
α-Series.



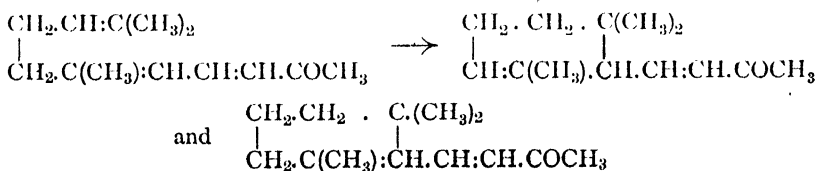
β-Series.



One of the most important derivatives of citral is *ionone*, which, in the form of pseudo-ionone $\text{C}_{13}\text{H}_{20}\text{O}$, is formed by the condensation of citral with acetone.



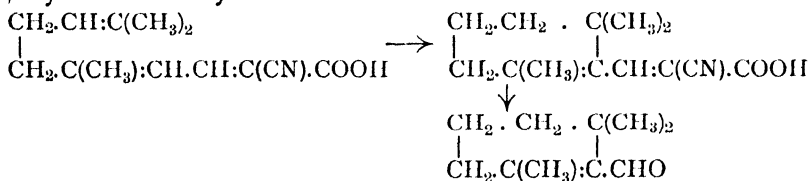
The ψ -ionone, when boiled with dilute sulphuric acid, then passes into α - and β -ionone.



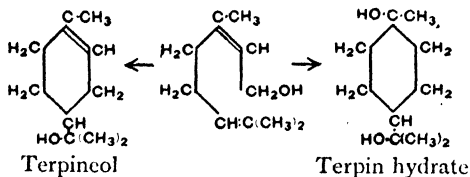
44 MODERN RESEARCH IN ORGANIC CHEMISTRY

These two isomers are oils which possess a remarkable odour of violets, and are employed largely in the manufacture of violet essence. Their constitution is determined by the fact that they yield $\beta\beta$ and $\alpha\alpha$ dimethyl adipic acids respectively.

The two isomeric cyclo-citral are also known, but have to be prepared in an indirect manner, since citral on treatment with acids passes into paracymene, so that for their preparation citral is shaken with cyanoacetic acid in the presence of sodium hydroxide, and the resulting citrylidencyanacetic acid converted into the derivative corresponding to cyclo-citral by the action of acids. On hydrolysis of the cyclic compounds with alkali, the corresponding cyclo-citral are obtained, thus the formation of β -cyclocitral may be shown.

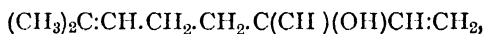


These cyclo-citral readily oxidize to the corresponding cyclo-geranic acid. β -cyclo-citral, alone is known in a state of purity. It condenses directly with acetone to form β -ionone. The reduction of citral by sodium amalgam converts it into *geraniol* $\text{C}_{10}\text{H}_{17}\text{OH}$, an alcohol found in many essential oils, from which it may be isolated by conversion into the characteristic calcium chloride compound $\text{C}_{10}\text{H}_{18}\text{O} \cdot \text{CaCl}_2$. Its constitution follows from its relationship to citral and to geranic acid, into which it readily passes on oxidation. Acetic acid, containing a small quantity of sulphuric acid, converts it into terpineol, whilst if it be shaken with a 5% solution of sulphuric acid alone, it yields terpin hydrate.



When geraniol is heated with potassium bisulphate to 170°C ., it loses water, and yields the hydrocarbon $\text{C}_{10}\text{H}_{16}$ (anhydro-

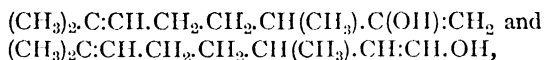
geraniol), which was the first olefine terpene to be prepared. By the action of hydrochloric acid on geraniol a mixture of chlorides is obtained, and these, on digestion with alcoholic potash, yield the inactive modification of another olefine terpene alcohol, known as *linalool*, $C_{10}H_{17}OH$. The *d*-form of this alcohol is found in coriander oil, and the *l*-form in oil of linaloes. It is also formed when a faintly alkaline solution of acid geranyl phthalate is distilled in a current of steam. It is most probable that it corresponds to the structural formula—



which accounts for its optical activity by the presence of an asymmetric carbon atom, and for the extreme readiness with which it passes into methylheptenone on oxidation, a fact necessitating the presence of a grouping

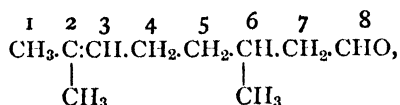


The alternative formulæ proposed by Barbier and Bouveault, namely,



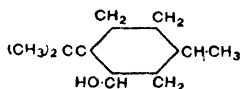
representing the enolic forms of an unsaturated methyl ketone and an aldehyde (citronellal).

Of the other aldehydes of the olefine terpene series which have been described, *citronellal* $C_{10}H_{18}O$, and *rhodinal* $C_{10}H_{18}O$, are the more important. Citronellal was first obtained by F. Dodge from citronella oil. It is a dextro-rotatory liquid and shows the usual aldehydic properties. On reduction it is converted into the corresponding alcohol citronellol. A considerable amount of controversy has taken place as to the structure of this aldehyde and its derivatives, and the matter can hardly be said to be definitely decided at the present time. Tiemann and Schmidt considered, from a study of the decomposition of the aldehyde, that it was a substance of the following structure:—

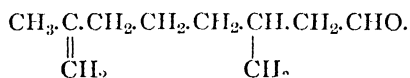


46 MODERN RESEARCH IN ORGANIC CHEMISTRY

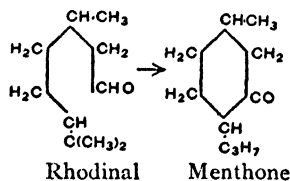
because, on reduction to the alcohol, the latter on oxidation with potassium permanganate, was converted into acetone and β -methyl adipic acid $\text{HOOC}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}(\text{CH}_3)\cdot\text{CH}_2\cdot\text{COOH}$, a result requiring the double linkage to be between the carbon atoms 2 and 3, and a methyl group at 5 or 6. Position 6 was decided upon for the methyl group, because citronellal and acetic anhydride condensed together to form a cyclic alcohol, which was assumed to be isopulegol



showing that the carbonyl group in the aldehyde was in the *meta*-position to the $>\text{CH}\cdot\text{CH}_3$ group. Later work has, however, shown that the above constitutional formula of isopulegol is not quite correct. Barbier and Bouveault, on the other hand, are of the opinion that citronellal is to be represented thus:—

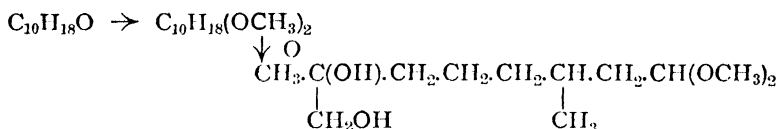


and that Tiemann's formula represents the isomeric rhodinal. As arguments in favour of their view they point out that although the physical properties of rhodinol and citronellol are almost identical, and although drastic oxidation yields acetone and β -methyl adipic acid in the case of both alcohols, a limited oxidation, on the other hand, in the case of rhodinol, yields a mixture of rhodinal and menthone and an acid, rhodinic acid $\text{C}_{10}\text{H}_{18}\text{O}_2$. Again, rhodinal-oxime, on treatment with acetic anhydride, is spontaneously transformed into menthone, whilst the oxime of citronellal yields only the corresponding nitrile. Thus rhodinal would appear to be—



They also pointed out that the derivatives of rhodinal and citronellal possessed different physical constants, an argument

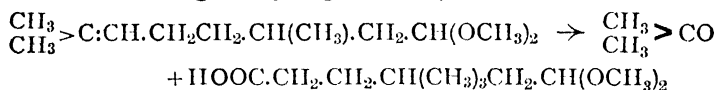
objected to by Tiemann on the grounds that Barbier and Bouveault were working with mixtures and not definite compounds. Further confirmation of Barbier and Bouveault's views was apparently obtained by Harries and Schauwecker, who found that citronellal yielded a dimethylacetal, which, on oxidation with potassium permanganate, was converted into the corresponding glycol derivative.



This was assumed to possess the above constitution, since on further oxidation by chromic acid it yielded a keto-aldehyde.



They also found that the citronellaldimethylacetal could be further oxidized by potassium permanganate in acetone solution to acetone and the acetal of an aldehyde acid, which on hydrolysis was found to be the semi-aldehyde of β -methyl adipic acid, the latter reaction being easily explained by the Tiemann formula.

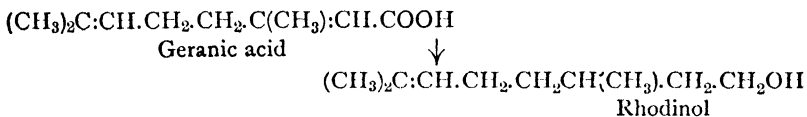


More recently Harries has tried to settle the question definitely by a study of the action of ozone on citronellal and its derivatives. Thus, if the Barbier and Bouveault formula were correct, the ozonide should decompose into formaldehyde and a compound of nine carbon atoms containing a $> \text{CO}$ group at the position of the double bond, but all the ozonides, with the exception of citronellal ozonide, yielded on decomposition with water a mixture of equivalent quantities of acetone peroxide and β -methyl adipic acid. From a consideration of these complex results Harries concludes that the citronellal derivatives are mixtures of the two different types, the portion of the mixture of the citronellal (Barbier) type being the more unstable, as the terminal oxygenated group becomes more acidic in character.

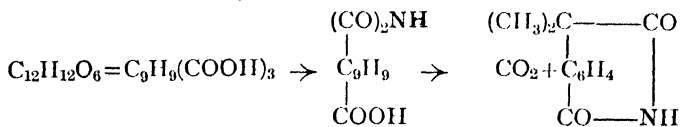
Rhodinol, $\text{C}_{10}\text{H}_{19}\text{OH}$. The *l*-form of this alcohol is found in the essences of geranium and of rose. The inactive variety has

48 MODERN RESEARCH IN ORGANIC CHEMISTRY

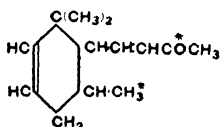
been prepared by Barbier and Bouveault by the reduction of synthetic geranic acid (see p. 41) with alcohol and sodium, or the geranic acid may be reduced by sodium, in amyl alcohol solution to *i*-rhodinic acid, the ester of which, on reduction with sodium and ethyl alcohol, yields *i*-rhodinol



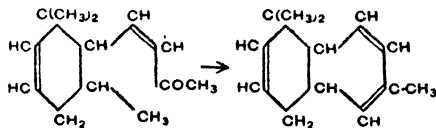
Before passing to the consideration of the cyclic terpenes, mention might be made of an isomer of ionone, namely, *irone* $\text{C}_{13}\text{H}_{20}\text{O}$, the odoriferous principal of the iris root. It is a colourless liquid which boils at 144°C . (16 mm.). The constitution of this cyclic ketone has been determined by Tiemann and Krüger in the following manner. *Irone*, when heated with hydriodic acid and phosphorus, yields the hydrocarbon *irene* C_{13}H_8 , oxidation of the latter compound then yielding a number of degradation products of the empirical formula $\text{C}_{13}\text{H}_{16}\text{O}_3$, $\text{C}_{13}\text{H}_{14}\text{O}_5$, $\text{C}_{13}\text{H}_{12}\text{O}_7$, and $\text{C}_{12}\text{H}_{12}\text{O}_6$, known respectively as trioxydehydroirene, iregenondicarboxylic acid, iregenontricarboxylic acid, and ioniregentricarboxylic acid. The distillation of the ammonium salt of the last-named acid gives rise to an imide acid, the silver salt of which, when heated, is transformed into dimethylhomophthalimide, thus:—



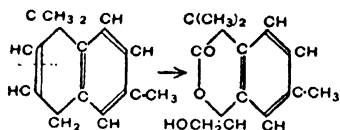
From these results it may be deduced that *irone* is in all probability a trimethyltetrahydrocinnamenyl methyl ketone of the following structure:—



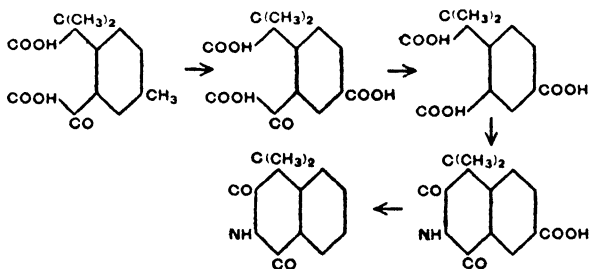
If this be so, the effect of the hydriodic acid is to convert the ketone into a naphthalene derivative by loss of water at *



oxidation then taking place and transforming this hydrocarbon first into a dehydro-irene and then further into an hydroxy-acid. This acid lactonizes readily, so that, instead of the free acid, the lactone $C_{13}H_{16}O_3$ or trioxydehydroirene is obtained.



The subsequent stages of the formation of the dimethylhomophthalimide are shown in the following scheme:—



Cyclic Terpenes—The chief sources of the terpenes, and their naturally occurring derivatives are the essential oils obtained from various plants belonging for the most part to the natural order of the Coniferæ. Many of these oils, *e.g.* turpentine, oil of citron, orange oil, and oil of thyme, consist chiefly of hydrocarbons, whilst others, such as oil of camphor, caraway oil, thuja oil, oil of peppermint, etc., contain oxygen-holding compounds mainly of an alcoholic or ketonic nature. The products obtained as oils from the various plants either by extraction by pressure, by solvents, or by distillation in a current of steam are in the case of the hydrocarbons for the most part substances of the empirical

50 MODERN RESEARCH IN ORGANIC CHEMISTRY

formula $C_{10}H_{16}$, and which have approximately equal boiling-points, ranging from $160-190^{\circ} C$. On this account it is almost impossible to separate the hydrocarbons by fractional distillation, so that in order to prepare individual members of the series it is necessary to obtain a series of crystalline derivatives. These may be separated from one another by taking advantage of their varying physical properties, and the separate members may then be converted into terpenes again.

With the exception of camphene, all the terpenes are liquids at ordinary temperature. They possess a characteristic odour, are fairly stable towards alkalis, but as a rule undergo decomposition when subjected to the action of acids. Many resinify rapidly on exposure to air. They are characterized by the formation of addition compounds with the halogens or halogen halides, and as Tilden has shown, form well-defined compounds with nitrosyl chloride. Baeyer regards these latter compounds not as simple addition products, but considers them to be bimolecular compounds, the nitrosochloride of limonene being represented, for example, as $C_{10}H_{16} (Cl) - N_2O_2 - (Cl)C_{10}H_{16}$.

The terpenes may be sub-divided into two groups, the *monocyclic terpenes* and *camphors*, which may be considered as reduced cymene derivatives, since many of them can be converted into cymene or its derivatives by relatively simple reactions; and the more complex (usually *bi-cyclic*) terpenes.

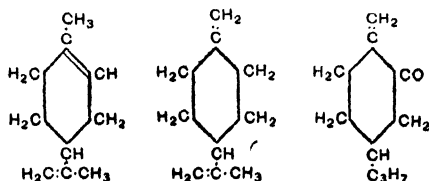
The monocyclic terpenes are shown by their reactions, as mentioned above, to contain a nucleus of six carbon atoms, and as many of them yield terephthalic acid on oxidation, it may be concluded that they possess two side chains, usually in para-positions, these chains consisting generally of a methyl group

and the grouping $- C \begin{array}{l} \diagup C - \\ \diagdown C - \end{array}$. They are also unsaturated, and

contain two double bonds in the molecule, since they form dihydrochlorides, tetrabromides, bisnitrosochlorides, etc. These double bonds may be either both in the nucleus, or one in the side chain and one in the nucleus. Semmler has also shown that a division of the terpenes may also be made into (1) those

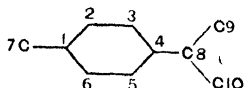
possessing a methyl group in the side chain with a double bond in the nucleus, and (2) those in which a second double bond

connects the group $\begin{array}{c} \diagup \text{C} - \\ \text{C} \\ \diagdown \text{C} - \end{array}$ to the nucleus, or may be contained in this group. The former he designates as *ortho-terpenes*, the latter as *pseudo-terpenes*, thus:—

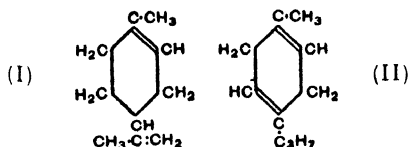


ortho-limonene *pseudo*-limonene *pseudo*-carvone

A convenient system of nomenclature for the monocyclic terpenes has been devised by Wagner, who considers them as all derived from the saturated cyclic hydrocarbon $C_{10}H_{20}$, namely, *p*-methylisopropylhexamethylene, which he designates as *menthane*, the hydrocarbons $C_{10}H_{16}$ thus becoming *menthadienes*. The carbon atoms in the nucleus are then numbered in accordance with the following scheme:—

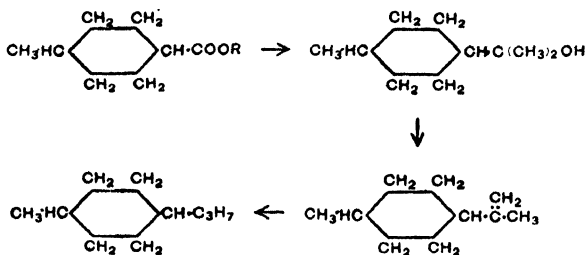


Baeyer, as an alternative, advocates the use of the terms *terpane* and *terpadiene*. The position of the double linkage in the unsaturated members of the series is shown by the use of the symbol Δ followed by a numeral indicating the carbon atom immediately preceding the double bond, the numeral being enclosed in a bracket when the double bond is in the side chain; thus—

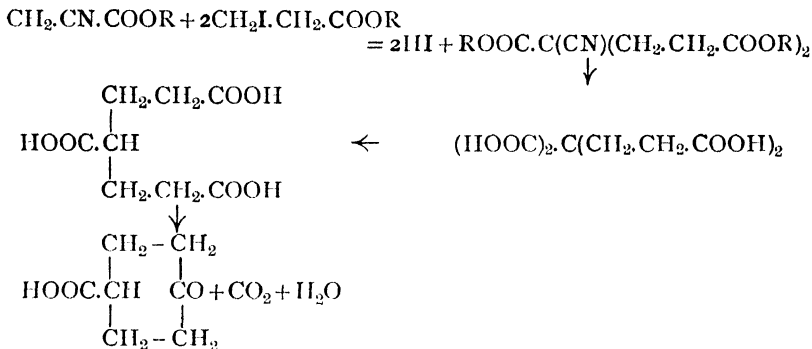


(I) is Δ 1.8(9)-menthadiene, and (II) is Δ 1.4 menthadiene.

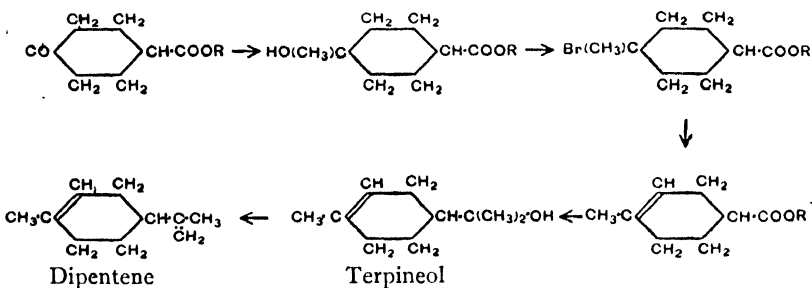
The parent hydrocarbon of the group (hexahydro-*p*-cymene) has been synthesized recently by W. H. Perkin by the application of the Grignard reaction to ethylhexahydro-*p*-toluate, which leads to the formation of *p*-menthanol. The alcohol loses water when subjected to the action of potassium hydrogen sulphate and is converted into Δ .8(9) menthene, from which the hydrobromic acid addition product is then formed, and this on reduction with zinc dust and acetic acid yields *p*-menthane.



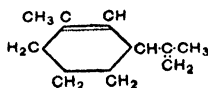
Many attempts have been made from time to time to synthesize the naturally occurring terpenes, but until recent years these were quite unsuccessful; now, however, owing to the ingenuity of W. H. Perkin and his collaborators, and others, particularly Wallach, Semmler, and Harries, several members of the series have been prepared. As examples of Perkin's method the syntheses of dipentene and carvestrene may be described. In the former case, it was found that cyanacetic ester readily condensed with β -iodopropionic ester to form γ -cyanopentane tricarboxylic ester, which on hydrolysis with hydrochloric acid was converted into pentane- $\alpha\gamma\epsilon$ -tricarboxylic acid. By digestion of this acid with acetic anhydride and subsequent distillation, ring formation takes place, and δ -ketohexahydrobenzoic acid is formed.



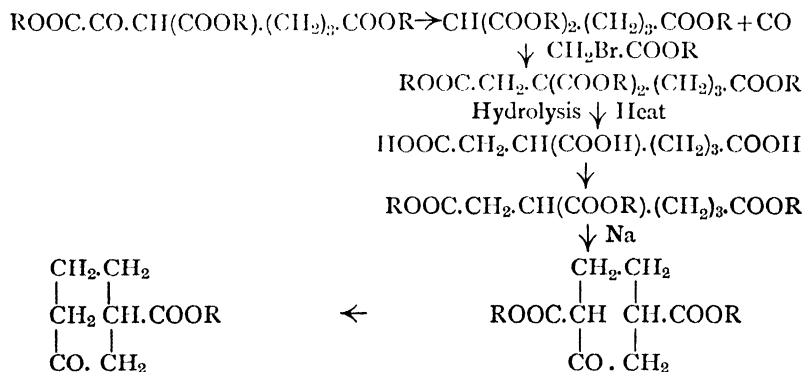
The ester of this acid on treatment with the Grignard reagent is then converted into δ -hydroxyhexahydro-*p*-toluic acid, and this acid on treatment with fuming hydrobromic acid yields the corresponding bromo-derivative. On digestion of this bromo-compound with pyridine, hydrobromic acid is removed and Δ .3-tetrahydro-*p*-toluic acid is formed, the ester of which on treatment with an excess of an ether solution of the Grignard reagent and then with dilute hydrochloric acid yields terpineol. Terpineol, when treated with potassium hydrogen sulphate, is converted into dipentene.



For the preparation of carvestrene the starting-point was *m*-hydroxybenzoic acid, which was reduced to cyclohexanol-3-carboxylic acid, and the latter then oxidized to the corresponding cyclohexanone carboxylic acid, and the process as shown from δ -keto-hexahydrobenzoic acid above was repeated, giving finally the hydrocarbon required.



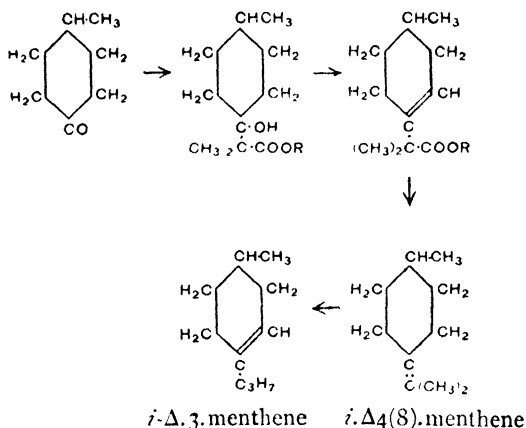
The yield of the cyclohexanone carboxylic acid obtained was unsatisfactory, and Perkin in 1909 tried to improve it by adopting the following method, but again without very satisfactory results. Ethyl oxaladipate, when distilled, yields butane- $\alpha\delta\delta$ -tricarboxylic ester, the sodium derivative of which may be condensed with ethyl bromo-acetate to form pentane- $\alpha\delta\delta\epsilon$ -tetracarboxylate. This ester was then hydrolyzed, and the free acid heated until evolution of carbon dioxide ceased, when pentane- $\alpha\delta\epsilon$ -tricarboxylic acid was formed. Esterification of the acid and subsequent heating with sodium transformed it into ethyl cyclohexanone-3,6-dicarboxylate, from which by hydrolysis and elimination of carbon dioxide, cyclohexanone-3-carboxylic acid was ultimately obtained.



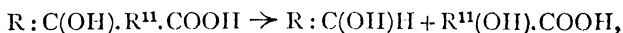
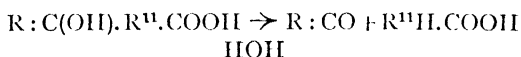
By a similar process a series of menthenols, menthadienes, menthanols, and menthanes have been obtained, starting from partially reduced toluic acids.

Various hydrocarbons of the monocyclic terpene series have been synthesized by other processes from open chain and other compounds, a resumé of some of the more important methods being here given. Thus Wallach has shown that 1,4-methylcyclohexanone, which can be prepared from α -hydroxyhexahydro-*p*-

toluic acid, condenses with ethyl- α -bromoisobutyrate in the presence of zinc to form a cyclic hydroxy-ester, and this latter compound on hydrolysis, and subsequent heating loses carbon dioxide and passes into *i*. Δ .4(8)-menthene. The hydrocarbon so obtained, when boiled with dilute sulphuric acid, isomerizes to Δ .3-menthene.



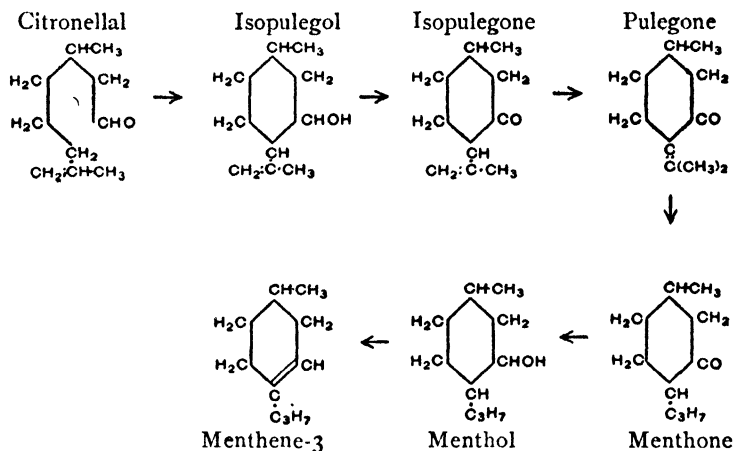
It was found that the hydroxy-esters, such as those mentioned above, are only hydrolyzed with difficulty by caustic alkali, decomposition taking place with the formation of compounds of the type shown as under :—



but the esters formed by unsaturated acids are more easily hydrolyzed.

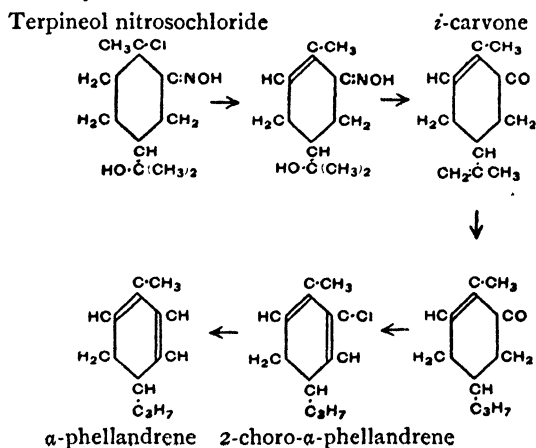
Δ .3-menthene may also be prepared by the xanthogenic ester process from menthol, and since this alcohol may be obtained from citronellal, a complete terpene synthesis is obtained from an open chain compound. In this process citronellal is converted into isopulegol by the action of acetic anhydride, and the alcohol oxidised to isopulegone, which is then transformed into pulegone by baryta water. The reduction of pulegone hydrobromide yields menthone, further reduction by sodium and alcohol leading to the formation of menthol.

56 MODERN RESEARCH IN ORGANIC CHEMISTRY

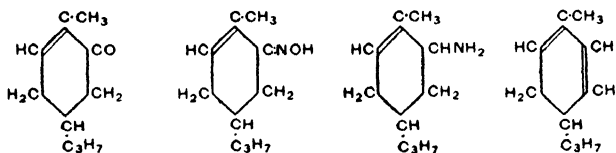


As menthone has been synthetically prepared in various other ways (see p. 71), one has numerous syntheses of mentene-3.

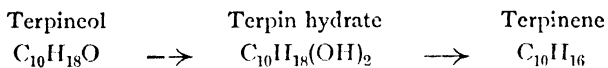
α -Phellandrene can now be considered as a synthetic hydrocarbon, since terpineol, which was artificially prepared by Perkin, yields a nitrosochloride, and this, by the action of sodium ethoxide, is converted into hydroxydihydrocarboxime. The oxime on hydrolysis yielded *i*-carvone. Carvone hydrobromide was reduced to Δ -6.menthenone-2, and Harries showed that phosphorus pentachloride converted the latter ketone into 2-chloro- α -phellandrene, from which α -phellandrene was obtained by boiling with zinc dust and methyl alcohol.



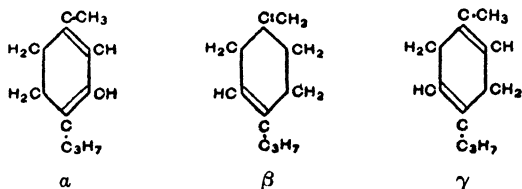
Better results are obtained in this latter case if Δ -6-menthenone-2 is converted into its oxime, the oxime reduced to the amine, and the amine distilled under reduced pressure with phosphoric acid.



Synthetic terpineol, in presence of 5 per cent. sulphuric acid, passes into terpin hydrate, and terpin hydrate, when boiled with a diluted sulphuric acid (2 : 1), loses water and gives rise to several products, among which is found the hydrocarbon terpinene.

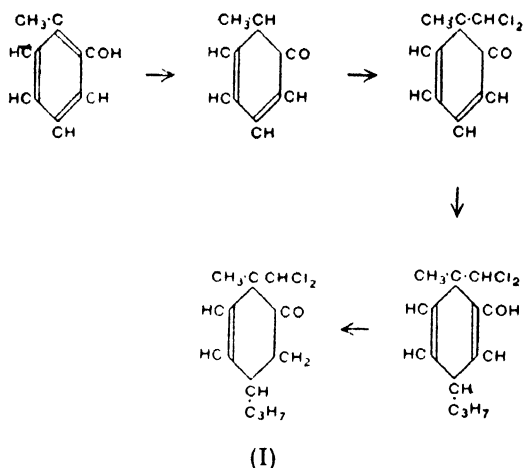


This hydrocarbon terpinene may exist in three isomeric forms, known as the α , β , and γ -terpinenes, which possess the following structures :—

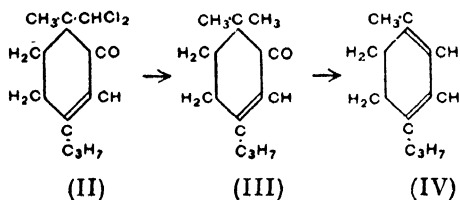


and a hydrocarbon practically identical with the α -form has been recently synthesized by Auwers and Hessenland in the following manner. Chloroform and *o*-cresol condense in the presence of caustic alkali to form 2-methyl-2-dichloromethyl-1-ketodihydrobenzene, which reacts with magnesium isopropyl iodide to form a ketone of the structure shown in (I).

58 MODERN RESEARCH IN ORGANIC CHEMISTRY

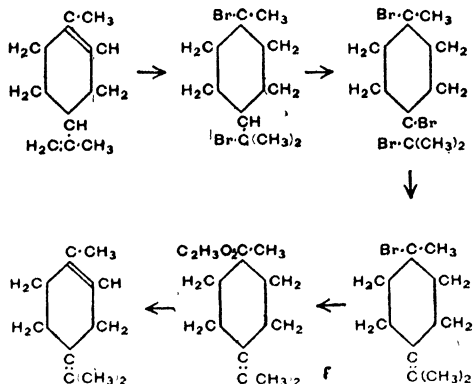


This ketone in contact with sulphuric acid isomerizes to one of the structure shown in (II), and is then reduced to the cyclohexenone (III) by zinc and acetic acid.

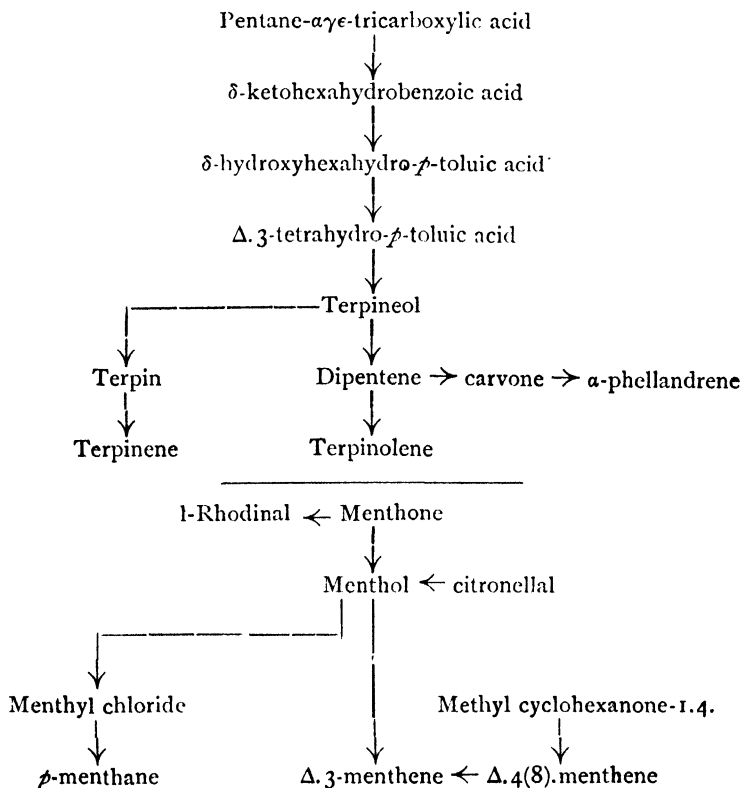


Finally, the cyclohexenone, under the influence of hot alcoholic potash, passes into the hydrocarbon (IV) identical in almost all respects with α -terpinene.

Terpinolene may also be included among the synthetic terpenes, since it can be obtained from dipentene, the dihydrobromide of which by bromination is converted into tribromo-1.4.8-menthane. The latter, on reduction with zinc and glacial acetic acid, yields the acetate of Δ .4(8)-menthenol, and by boiling this with quinoline Baeyer obtained terpinolene.

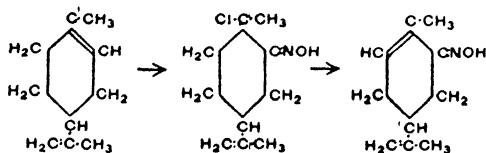


The relationships of these terpenes may be illustrated by means of the following chart :—



60 MODERN RESEARCH IN ORGANIC CHEMISTRY

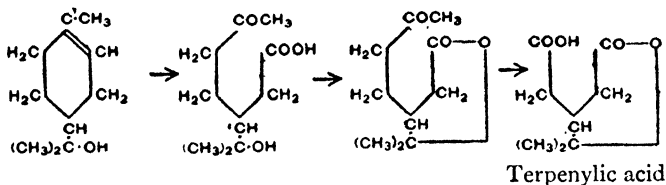
To consider these hydrocarbons in slightly more detail it may be observed that *dipentene* is the optically inactive form of *limonene*. It is found in many essential oils and is a product of the action of high temperatures on many terpenes (pinene, camphene, etc.). It is also formed when linalool is heated with formic acid. The dipentene obtained by these methods is more or less impure, and Wallach has shown that, in order to obtain the pure hydrocarbon it is best to heat the dihydrochloride with anhydrous sodium acetate and glacial acetic acid and distil the product in a current of steam, the oily distillate being further heated with potassium hydroxide, redistilled in steam, and finally fractionated. The active *d*-limonene is best prepared from oil of orange rind, or from caraway oil, by fractionation; the *l*-variety from oil of fir-cones, or synthetically by the xanthogenic ester method from dihydrocarveol (p. 76). Dry hydrochloric acid converts both forms into the active limonene hydrochlorides, but in the presence of water both forms give the inactive dipentene dihydrochloride. The nitroso chlorides exist in four optically active modifications, two corresponding to each form of limonene, and known respectively as the α and β -forms. These isomers may in each case be separated by digestion with cold chloroform, the β -form being insoluble in the solvent. When heated with alcoholic potash they pass by loss of hydrochloric acid into the corresponding *d* and *l*-carvoximes.



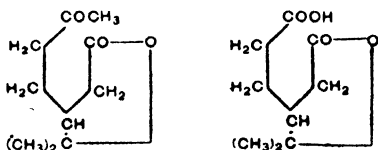
Again these nitrosochlorides condense readily with organic bases to yield nitrolamines of the type $C_{10}H_{15}(:NOH).NHR$.

The constitution of dipentene (and of limonene) has been definitely settled by the synthesis of the hydrocarbon by Perkin's method, although Wallach had earlier arrived at a similar conclusion by a study of the oxidation products of terpineol. Thus it was found that terpineol, on oxidation with chromic acid, gave

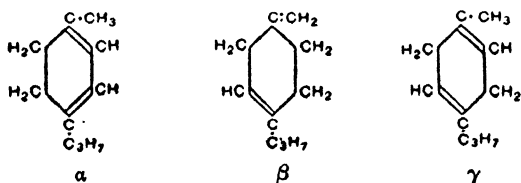
rise to a keto-lactone $C_{10}H_{16}O_3$, which on further oxidation was decomposed into terpenylic acid (a lactonic acid) and acetic acid, a result which precludes the hydroxyl group in terpineol from being in any other position than in the side chain, thus:—



Further support for this terpineol formula was also given by Tiemann and Semmler, who showed that on oxidation with chromic acid the above keto-lactone was converted into homo-terpenylic acid,

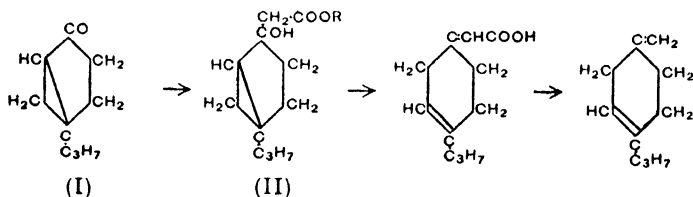


the presence of the $CH_3.CO-$ group being shown by the formation of bromoform or carbon tetrabromide when the keto-lactone was treated with bromine and sodium hydroxide. Thus, knowing the constitution of terpineol, that of limonene and dipentene follows by elimination of water from positions 8 and 10. *Terpinene* is found in cardamom oil and in oil of margarom, and is formed by the action of alcoholic sulphuric acid on many terpenes or terpene derivatives. Since it may be prepared by the action of concentrated sulphuric acid on terpineol and is inactive, three possibilities arise, and the hydrocarbon may be represented as



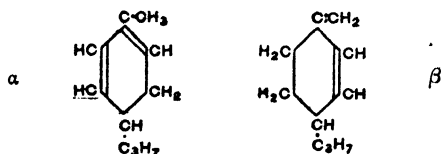
62 MODERN RESEARCH IN ORGANIC CHEMISTRY

β -terpinene has been synthesized by Wallach by the condensation of sabina-ketone (I) with bromoacetic ester in the presence of zinc. The sabinol acetic ester (II) is heated with acetic anhydride and the product hydrolyzed when an unsaturated acid is produced, from which by elimination of carbon dioxide a hydrocarbon identical with β -terpinene is obtained.



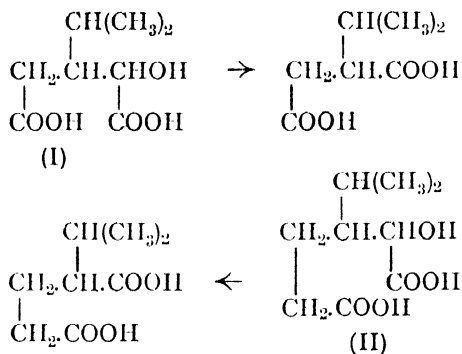
On oxidation this hydrocarbon does not give rise to any of the known products of oxidation of ordinary terpinene, so that β -terpinene cannot be considered as a constituent of ordinary terpinene. The α -terpinene obtained by Auwers (p. 58) yields a nitrosite which melts at the same temperature as that of Wallach's α -terpinene. Crude terpinene on oxidation yields an acid identical with $\alpha\alpha$ -dihydroxy- α -methyl- α^1 -isopropyl adipic acid, and Auwers' hydrocarbon yields the inactive form of this acid. The crude terpinene is thus probably a mixture of the α and γ forms, but the matter cannot as yet be considered as definitely decided.

Phellandrene—The naturally occurring phellandrene is a mixture of two isomers, viz. α -phellandrene ($\Delta_{1.5}$ -menthadiene) and $\Delta_{2:1(7)}$ menthadiene or β -phellandrene.



as was shown by Semmler, who found that crude phellandrene on oxidation with potassium permanganate was converted into a

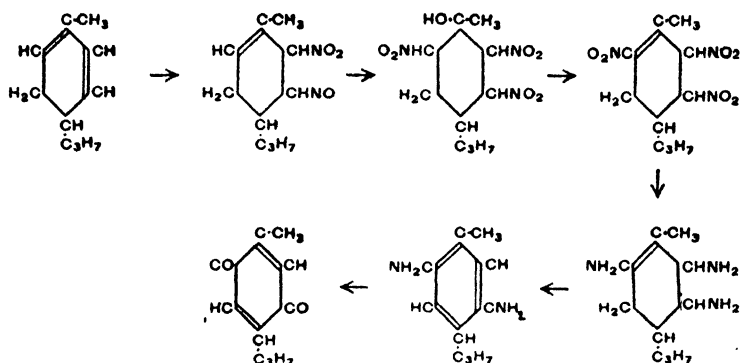
mixture of two hydroxy-acids, which on further oxidation with lead peroxide yielded respectively *L*-isopropyl succinic acid and *L*- α -isopropyl glutaric acid thus :—



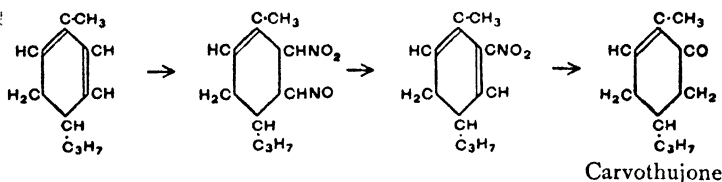
and since it was also shown that the hydroxy-acid (II) could not be oxidized to (I) by potassium permanganate, it follows that the simultaneous production of the two acids in the oxidation of phellandrene must arise from the occurrence of two isomeric hydrocarbons in the crude terpene. The formation of the hydroxy-acid shows that a double bond necessitating the grouping $-\text{CH}:\text{CH}-$ must exist in the molecule, and since the molecular refraction indicates a second double bond, this can only be of necessity between positions 1 and 6, or 1 and 7, in order to allow of the formation of the above acids. Further observations of Wallach have led to the conclusions that the phellandrene of elemi and fennel is a δ - α -phellandrene, the one obtained from Australian eucalyptus, being the corresponding *L*-compound, whilst water-fennel yields δ - β -phellandrene.

The oxidation of α -phellandrene by nitric acid gives a compound $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_6$, which on reduction yields an unstable diaminocymene, and since the hydrochloride of this base is oxidized by ferric chloride to thymo-quinone, it must be a *p*-diaminocymene. These reactions may be explained in the following manner :—

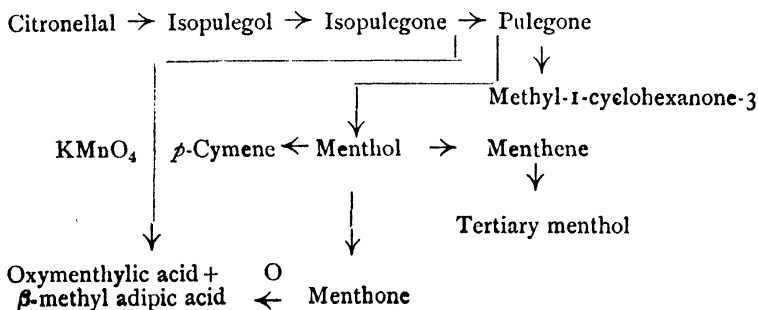
64 MODERN RESEARCH IN ORGANIC CHEMISTRY

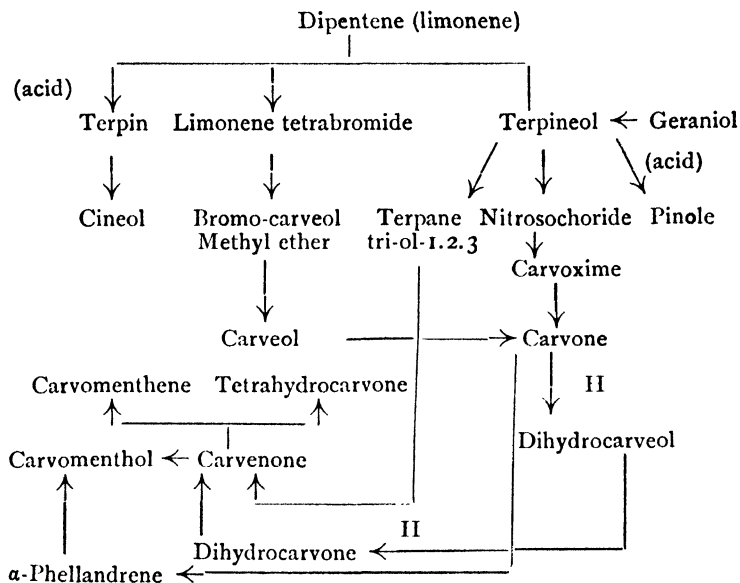


The position of one double bond in α -phellandrene is also shown by its conversion into carvothujone (or carvotanacetone), of which the constitution is known. This conversion is brought about by the transformation of phellandrene nitrosite into α -nitrophellandrene by the action of alcoholic potash, reduction of the nitro compound with zinc dust and acetic acid, then giving the ketone, thus:—

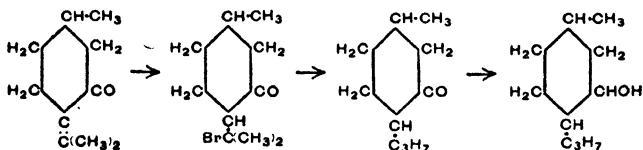


Oxygen Derivatives of Monocyclic Terpenes—The genetic relationships and chief decomposition products of these compounds are illustrated in the following diagrams:—





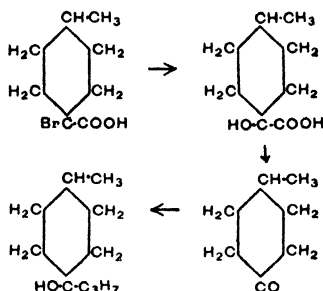
Among the alcohols of this series, *p*-menthol, terpin, and terpineol may be considered as the more important. Ordinary menthol is a secondary alcohol, the *l*-variety being the chief constituent of oil of peppermint. This form has been obtained synthetically from pulegone, by converting the hydrobromide into menthone, the reduction of which by sodium and alcohol yields *l*-menthol.



By the reduction of ordinary menthone, a mixture is obtained from which on benzoylation a liquid *d*-menthol benzoate may be separated, and this on hydrolysis yields *d*-menthol. This variety has $[\alpha]_D = +2.03$, whilst Kondakow, by reduction of the *l*-menthone of Bucco leaves with sodium and methyl alcohol, has obtained a *d*-menthol with $[\alpha]_D = +32^\circ.37'$. On oxidation with

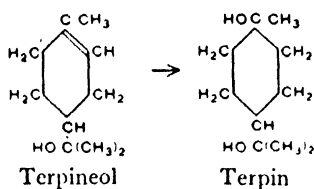
66 MODERN RESEARCH IN ORGANIC CHEMISTRY

chromic acid, menthol is converted into the ketone, menthone, whilst if potassium permanganate be used, oxymenthyl acid, $C_{10}H_{18}O_3$, β -methyl adipic acid, $C_7H_{12}O_4$, carbon dioxide, and other fatty acids are formed. Hydriodic acid at high temperatures reduces menthol to *p*-cymene. The constitution of menthol is determined from that of menthone (*q.v.*). A *tertiary-p-menthol* (*p*-menthanol-4) has been synthesized by Perkin by the following process. α -Bromohexahydro-*p*-toluic acid is converted by the action of sodium carbonate into Δ .1-tetrahydro-*p*-toluic acid and α -hydroxyhexahydro-*p*-toluic acid, the latter acid, on treatment with sulphuric acid, yielding methyl-1-cyclohexanone-4, from which by treatment with magnesium isopropyl iodide and subsequent hydrolysis, tertiary-*p*-menthol is obtained.

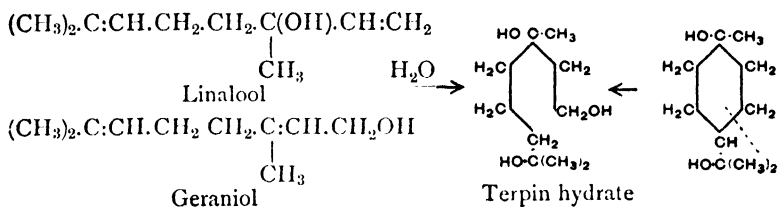


This menthol when heated with potassium bisulphate loses water and passes into *i*-menthene

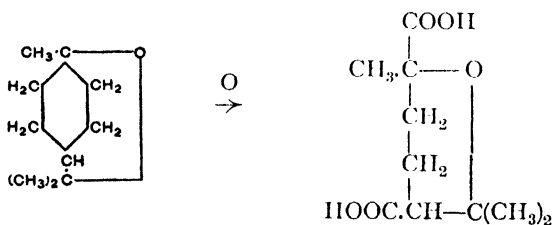
Terpin, $C_{10}H_{18}(OH)_2$, is a *p*-menthane-diol-1.8. Two stereoisomeric forms of this alcohol are known, viz., *cis*-terpin and *trans*-terpin. The latter modification is anhydrous and is formed by the addition of silver acetate to a glacial acetic acid solution of dipentene dihydrochloride. The precipitated silver halide is filtered off, the acid solution neutralized and extracted with ether, and the acetyl derivative so obtained, then hydrolysed, with caustic alkali. It melts at $156^\circ C$. The *cis*-compound, melting at $104^\circ C$., is obtained by heating terpin hydrate, the synthesis of which was accomplished by Perkin by the action of dilute sulphuric acid on synthetic terpineol (see p. 53), a reaction proving the alcohol to be a menthane di-ol.



Terpin hydrate is also obtained synthetically by the action of formic acid on linalool and on geraniol; a reaction which points to it being an alcohol of the fatty series. This result is in direct accordance with the formation of the hydrate from terpin itself, if it be considered that the hexamethylene ring is broken between the carbon atoms 3 and 4 and the elements of water then added.



By the action of dilute sulphuric acid on terpin hydrate numerous decomposition products are obtained, such as terpineol, cineol, terpinene, terpinolene, etc. Cineol is a constituent of many essential oils, and is to be considered as an inner anhydride of terpin,



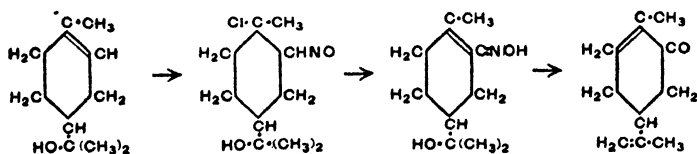
since its oxygen atom does not seem to possess either alcoholic, ketonic, aldehydic, or acidic properties. Potassium permanganate oxidizes it to the dibasic cineolic acid, which on dry distillation

68 MODERN RESEARCH IN ORGANIC CHEMISTRY

decomposes into carbon monoxide and dioxide and methyl heptenone $(\text{CH}_3)_2\text{C}:\text{CH}.\text{CH}_2.\text{CH}_2.\text{CO}.\text{CH}_3$.

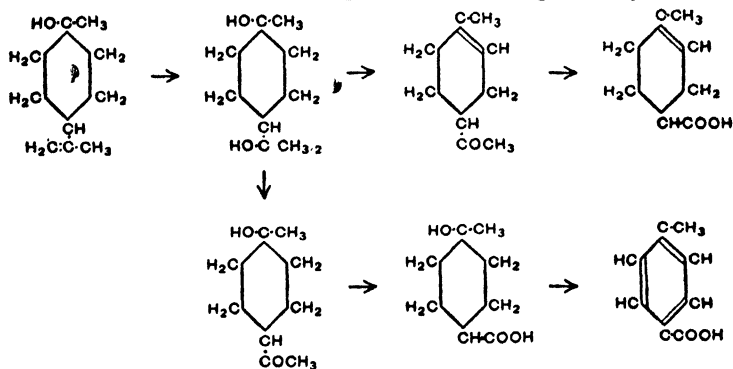
The oxidation products obtained from terpin vary with the oxidant used; thus nitric acid gives terebic acid, $\text{C}_7\text{H}_{10}\text{O}_4$, chromic acid gives a keto-lactone, $\text{C}_{10}\text{H}_{16}\text{O}_3$, which oxidizes further to acetic acid and terpenylic acid, $\text{C}_8\text{H}_{12}\text{O}_4$ (see dipentene, p. 61), whilst potassium permanganate gives acetic and oxalic acids.

Under the name of *terpineol* various products have been described which are now known to consist of mixtures of isomeric alcohols. Restricting the term to the tertiary alcohols, three isomers are known, α -terpineol (Δ .1-menthenol-8) m.p. 35° ; β -terpineol (Δ 8(9)-menthenol-1) m.p. 32° , and γ -terpineol (Δ 4(8)-menthenol-1) m.p. 69° C. The ordinary (α) terpineol is prepared synthetically from pentane- $\alpha\gamma\epsilon$ -tricarboxylic acid (see p. 53), this series of reactions giving rise to the inactive form, a similar result arising from the action of formic acid on geraniol. The active d -terpineol was obtained by Semmler from limonene hydrochloride by replacement of the halogen by the hydroxyl group. The constitution of terpineol follows from its synthesis as mentioned above. Since it is an unsaturated compound it readily forms a nitrosochloride, from which by elimination of hydrochloric acid a hydroxy-oxime is obtained, and this oxime on hydrolysis is converted into *i*-carvone, a series of reactions determining the structure of the latter ketone.



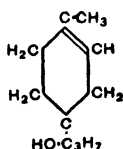
The β -terpineol is obtained by the fractionation of commercial terpineol, of which it constitutes the portion boiling between 212 and 215° C. Its constitution as a Δ 8(9) derivative is shown by the fact that on oxidation with potassium permanganate it is converted into menthane-triol-1.8.9 (as was shown by Stephan and Helle), and the latter alcohol on further oxidation with chromic acid yields *p*-methyltetrahydroacetophenone and *p*-methyl-*p*-hydroxy-

hexahydroacetophenone, which can be still further oxidized to tetrahydro-*p*-toluic acid and to *p*-toluic acid respectively.



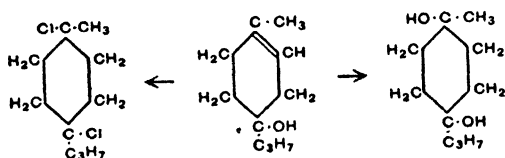
The γ -terpineol was obtained by Baeyer from dipentene dihydrobromide by converting the latter into 1.4.8-tribromomenthane, and reducing the latter with zinc dust and acetic acid to acetyl- $\Delta_4(8)$ menthenol-1, which on hydrolysis with alcoholic potash yields the required terpineol (see p. 58). This terpineol on oxidation with potassium permanganate is converted into menthane tri-ol-1.4.8. Its constitution follows from the fact that it furnishes dipentene dihydrobromide by the action of hydrobromic acid dissolved in glacial acetic acid.

Wallach, in examining the Ceylon oil of cardamoms, isolated a terpineol different from the known forms. This terpineol has also been found in oil of marjoram, and is identical with the one formed by the action of aqueous alkali on terpinene dihydrochloride, or when sabinene is shaken with sulphuric acid. To distinguish it from the other terpineols, and to indicate its relationship to terpinene, it is called *terpinenol*. It is represented by the structural formula—



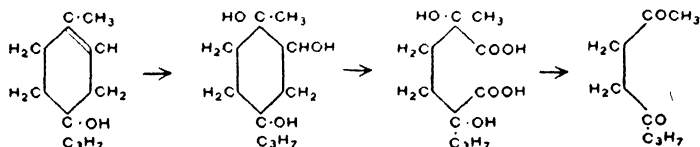
which readily accounts for its transformation into terpinene dihydrochloride by the action of hydrochloric acid, and for the

formation of the terpin of terpinene (m.p. 137° C.) by the action of dilute sulphuric acid—



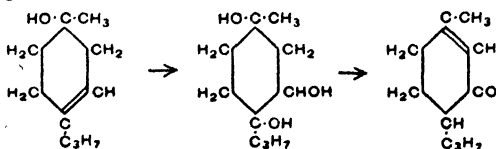
Terpinene dihydrochloride Terpinenol Terpin of terpinenol

On oxidation with potassium permanganate it yields a trihydroxy-1.2.4-menthane (which, when heated with acid, is transformed into carvenone and cymene), a more drastic oxidation of the latter leading to the formation of $\alpha\alpha$ -dihydroxy- α -methyl- α -1-isopropyl adipic acid by the disruption of the ring between the second and third carbon atoms. This acid exists in two forms, one active and one inactive, and on further oxidation with acid potassium permanganate, yields a diketone which has been recognized as ω -dimethylacetylacetone. This series of reactions may be thus illustrated—



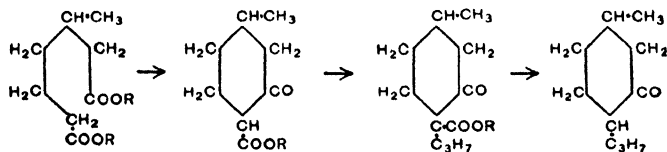
The inactive form of the above dibasic acid has been synthesized from dimethylacetylacetone by condensing it with hydrocyanic acid, and hydrolyzing the nitrile thus obtained.

By the fractionation of ordinary commercial terpinol, an isomeric terpinenol is obtained which has the structure of a Δ_3 -terpinenol, since on oxidation with potassium permanganate it yields a trihydroxy-1.3.4-menthane, capable of further oxidation to the same substituted adipic acid as the above terpinenol, but if heated with mineral acid does not yield carvenone but Δ_1 -menthenone-3.



Confirmation of the above structure is given by the fact that this terpinenol may be obtained synthetically from the action of magnesium methyl iodide on Δ .3-isopropylcyclohexenone.

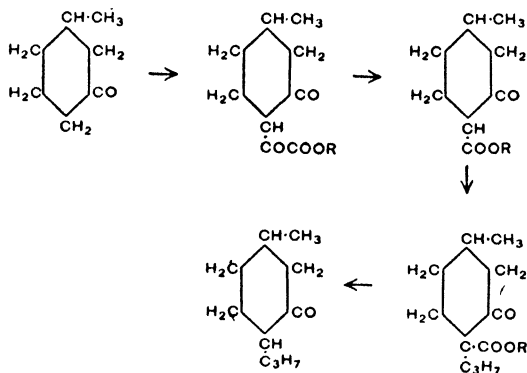
Among the ketones of this group, menthone, pulegone, and carvone are the most important. Ordinary menthone (*p*-menthanone-3), $C_{10}H_{18}O$, is found in oil of peppermint, and is prepared artificially by the oxidation of menthol with chromic acid. If this oxidation be carried out at $135^{\circ}C$. a *d*-menthone is obtained. The *l*-form is best obtained, according to Beckmann, by the oxidation of *l*-menthol, if the action of excess of acid be avoided as much as possible, as menthone is readily inverted by acid. This inversion gives rise to what Beckmann describes as *d*-menthone, but which should in all probability be described as *d*-isomenthone, since it does not seem to be a chemical individual but a mixture of *l*-menthone, and the, as yet, unisolated *d*-isomenthone. The reduction of pulegone hydrobromide also gives rise to menthone, but this menthone was shown by Martine to be not quite identical with ordinary *l*-menthone, and is designated by him as *P*-menthone. Several syntheses of menthone have been performed, the simplest being that of Barbier and Bouveault, by the action of acetic anhydride on *l*-rhodinal oxime (see p. 46). Einhorn and Klages have prepared an inactive menthone from β -methyl pimelic ester, which is transformed by the action of sodium ethoxide into methyl-1-cyclohexanone-3-carboxylic ester-4, the isopropyl group then being introduced into position 4 by the action of isopropyl iodide and sodium ethoxide. The resulting ester is then hydrolyzed and carbon dioxide eliminated from the carboxyl group, when *i*-menthone is produced.



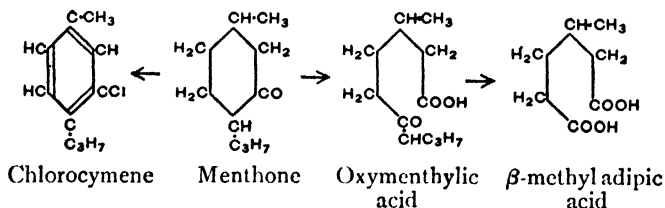
Haller and Martine have synthesized active menthone by the action of isopropyl iodide on the sodium derivative of methyl-1-cyclohexanone-3 (the sodium derivative of the ketone being

72 MODERN RESEARCH IN ORGANIC CHEMISTRY

obtained by the use of sodamide), whilst Koetz and Hesse by condensation of the same ketone with ethyl oxalate and subsequent hydrolysis obtain methyl cyclohexanone carboxylic acid, the isopropyl derivative of which on heating with potassium hydroxide dissolved in methyl alcohol yields *d*-menthone.

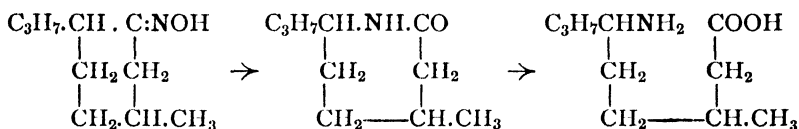


The constitution of this ketone follows from the various syntheses given above, and from the consideration of the various products which it yields on oxidation and decomposition with various reagents. The fact that phosphorus pentachloride converts it into a compound which by successive treatment with bromine and quinoline yields *m*-chlorocymene, indicates the presence of a six-membered ring with the methyl and isopropyl groups in the para position to each other; and since oxidation with potassium permanganate yields oxymenthylic acid, $C_{10}H_{18}O_3$, and finally β -methyl adipic acid, $C_7H_{12}O_4$, the existence of the reduced benzene ring with the keto group in the ortho position to the isopropyl group may be considered as definitely established.

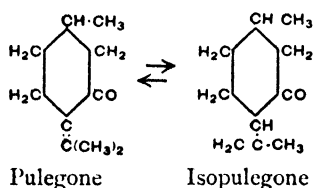


Menthone shows most of the characteristic properties of ketones,

but does not combine with acid sodium sulphite. As already mentioned under *Polymethylenes*, the oxime is converted by the action of phosphorus pentoxide into an iso-oxime. This iso-oxime, in the case of menthone, is converted on hydrolysis into the ϵ -amino-decylic acid.



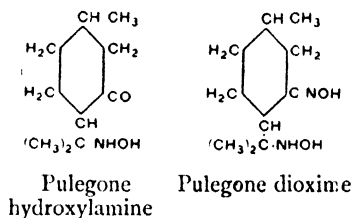
Pulegone ($\Delta.4(8)$ -menthenone-3) is an unsaturated ketone found in oil of pennyroyal. It is a dextro-rotatory liquid boiling at 221°C . The synthesis of pulegone from citronellal has already been mentioned (p. 55), and the fact that the carbonyl group is in position 3 is shown by the conversion of pulegone into menthone. In the above-mentioned synthesis the formation of pulegone is brought about by the rearrangement of isopulegone under the influence of baryta water, and Harries and Roeder have shown that pulegone can be reconverted into isopulegone by heating pulegone hydrobromide with basic lead nitrate, the resulting isopulegone being a laevo-rotatory liquid.



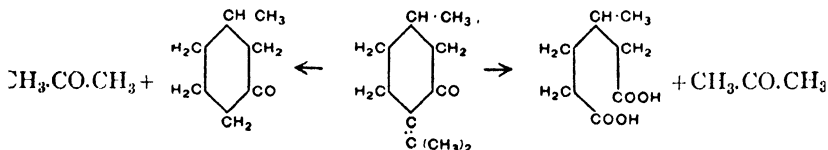
This reaction shows that the two ketones differ only in the position of the double bond, and possess consequently the same skeletal structure. This result is confirmed by the fact that pulegone on treatment with hydroxylamine yields an oxamino-ketone, a reaction characteristic of unsaturated ketones containing the group $>\text{C}:\text{C}-\text{CO}$, whilst in isopulegone the double bond would be in the $\beta\gamma$ position, and would pass into the $\alpha\beta$

74 MODERN RESEARCH IN ORGANIC CHEMISTRY

position under the influence of alkalis, which is in accordance with the formation of a true oxime from isopulegone. A pulegone dioxime has also been obtained, the two compounds produced by the action of hydroxylamine under different conditions being represented as—

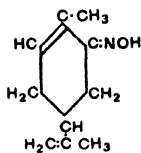
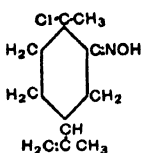


The position of the double bond in the 4(8) position is shown by the fact that pulegone on oxidation with potassium permanganate yields acetone and β -methyl adipic acid, confirmation of which is given by Wallach's observation that hydrolysis of pulegone by water at 250° C. leads to the formation of acetone and methyl-1-cyclohexanone-3.

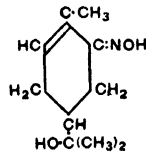
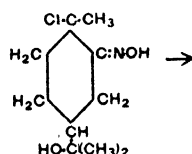
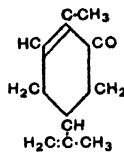


Carvone ($\Delta 6.8(9)$ menthadiene-one-2), $\text{C}_{10}\text{H}_{14}\text{O}$, is found widely distributed in nature. The *d*-form is the chief constituent of oil of caraway, and the *l*-form is found in oil of spearmint. Synthetically it may be prepared from limonene by the action of alcoholic potash on the nitroso-chloride of this hydrocarbon, *l*-carvoxime being obtained. Hydrolysis of this oxime with sulphuric acid yields *l*-carvone. Similarly, terpineol nitroso-chloride, in the presence of sodium ethoxide, is converted into hydroxymenthenone-oxime, the hydrolysis of which by acids yields *i*-carvone. Thus this latter method leads to a complete synthesis of carvone since that of terpineol has been effected.

Limone nitrosochloride

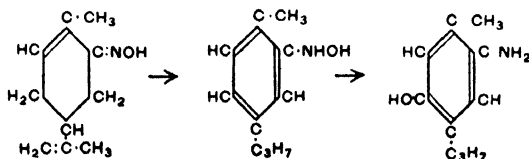


Carvone



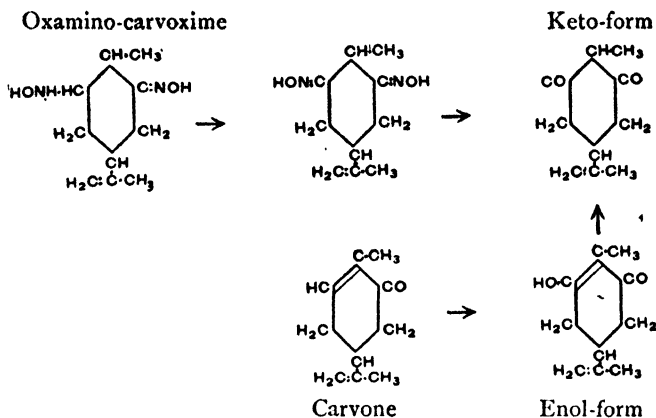
Terpineol nitrosochloride

Carvone does not yield a normal condensation product with acid sodium sulphite, but when boiled with this reagent is converted into sodium carvonedihydrodisulphonate, $C_{10}H_{16}O(NaSO_3)_2$, which is unaffected by alkali. The oxime, on treatment with concentrated sulphuric acid, passes into (*p*)aminothymol, cymylhydroxylamine probably being formed as an intermediate stage in the transformation—

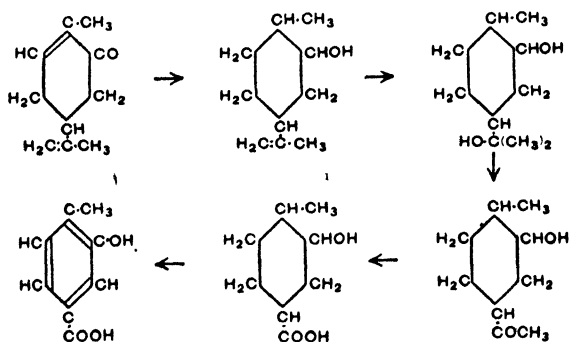


whilst if alcoholic sulphuric acid be used carvacrylamine is formed. When shaken with air in the presence of baryta, carvone undergoes autoxidation, barium peroxide being formed, together with methyl-1-propenyl-4-dihydroresorcin, identical with the ketone obtained (in the form of its dioxime) by the oxidation of oxaminocarvoxime—

76 MODERN RESEARCH IN ORGANIC CHEMISTRY

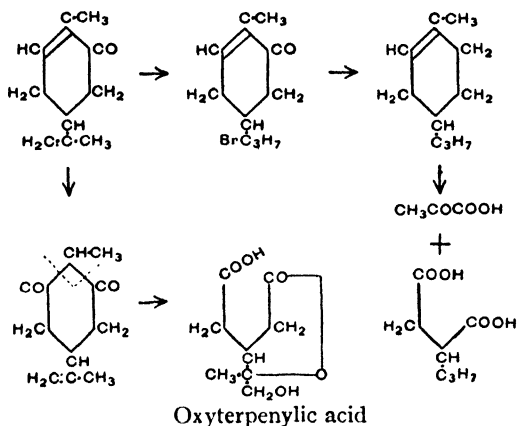


The constitution of carvone is determined by its synthesis from terpineol, and from its relationship to dihydrocarvone and dihydrocarveol into which it passes on reduction. This reaction determines the situation of one double bond in the 8(9) position, since the oxidation of dihydrocarveol leads to a menthane-triol-2.8.9, capable, as Tiemann showed, of further oxidation by chromic acid to a ketone alcohol, from which, by the action of sodium hypobromite, a hydroxy-acid was obtained. This acid must be a methyl cyclohexanol-carboxylic acid, since on heating with bromine to 190° C. it is converted into *m*-hydroxy-*p*-toluic acid.

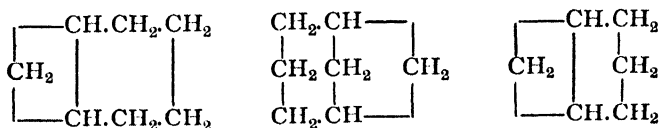


The position of the second double bond is shown by the oxidation of carvone by potassium permanganate to oxyterpenylic acid, and by the reduction of its hydrobromide to carvotan-

acetone. The latter, on oxidation with potassium permanganate, yields pyruvic acid and isopropyl succinic acid, a series of reactions showing that the double bond must be at position 6 in the nucleus.



Bi-Cyclic Terpenes.—The members of this group contain two carbocyclic rings united with each other by two or three carbon atoms in common. A convenient system of nomenclature for the members of this group is due to Baeyer, who observed that each saturated hydrocarbon of the group contains two tertiary carbon atoms which are combined with each other three times, either directly or by means of intervening carbon atoms, the whole system forming a series of “bridges.” To distinguish the bridges, the symbol \circ is used to describe the direct union of the tertiary carbon atoms, and the numerals 1, 2, 3, etc., to describe the number of carbon atoms that are present in the bridges between the tertiary carbon atoms. The hydrocarbons of the series, containing five carbon atoms, are described as bi-cyclopentanes, those with six carbon atoms as bi-cyclo-hexanes, and so on. Thus hydrocarbons of the following structure—



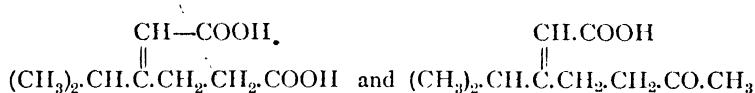
would be described as bi-cyclo (\circ .1.4) heptane, bi-cyclo (1.1.3)

78 MODERN RESEARCH IN ORGANIC CHEMISTRY

heptane, and bi-cyclo (0.1.3) hexane, indicating, for example, in the first case that the tertiary carbon atoms were directly united, and also that they were united by two other bridges, containing respectively one and four carbon atoms.

In the bi-cyclo (0.1.3) hexane series the most important compounds are the hydrocarbon thujene, $C_{10}H_{16}$, and its derivatives, and the isomeric sabinene, $C_{10}H_{16}$, and its derivatives. The chief naturally occurring compound of the series is the ketone *thujone* (tanacetone), $C_{10}H_{16}O$, which is found in many essential oils. It has been questioned for some time whether the thujones obtained from different sources were identical or not, and Wallach has shown that even if they be considered as identical chemical individuals, they differ markedly in their physical aspects. He concludes that certainly two, if not three forms exist; thus oil of thuja contains chiefly α -thujone, which is a laevorotatory liquid, boiling at 200° - 210° C., and forming two semicarbazones, melting respectively at 187° C. and 110° C., whilst oil of absinthe contains principally β -thujone, which is dextro-rotatory, and yields a semicarbazone, which is dimorphous, and melts at 175° C. or 170 - 172° C. The isomeric thujones may be separated by the fractional crystallization of their semicarbazones from methyl alcohol. When warmed with alcoholic potash, the β -variety is partially converted into the α -form. Thujone shows the usual properties of a ketone, it combines with sodium bisulphite and forms semicarbazones and oximes. The α -form on reduction gives thujyl alcohol, $C_{10}H_{17}OH$, which, on re-oxidation, yields β -thujone. Both varieties of the ketone, when oxidized with cold potassium permanganate, yield the isomeric monobasic ketonic acids, $C_{10}H_{16}O_3$, known as thujaketonic acids (α and β). The constitution of thujone has been determined by Semmler from a study of its oxidation products. The thuja-ketonic acids contain the grouping $-CO.CH_3$, since in the presence of bromine and an alkaline hydroxide they are further converted into two dibasic acids of composition $C_9H_{14}O_4$, with simultaneous formation of bromoform. α -Thujaketonic acid is a saturated acid, and on heating to 150° C. passes into the β -acid, which is unsaturated, so that the former probably contains a cyclic complex,

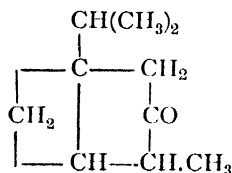
whilst in its transformation to the β -form, ring fission occurs, and the β -acid results as an open chain compound. The acids $C_9H_{14}O_4$ were called respectively α and β -tanacetogen dicarboxylic acids, and the β -acid, on oxidation with potassium permanganate, is transformed into ω (or δ)-dimethyl laevulinic acid $(CH_3)_2.CH.CO.CH_2.CH_2.COOH$, which had been earlier obtained by Fittig from $\beta\gamma$ -dibromo-isoheptane acid, and also by Conrad from the ester $(CH_3O_2C)_2CH.CH_2.CO.C(CH_3)_2.CO_2CH_3$ (formed by the action of γ -bromodimethyl aceto-acetic acid dimethyl ester and sodio-malonic acid methyl ester), by heating it with sulphuric acid. Again, β -thujaketonic acid, on oxidation by potassium permanganate, yields a diketone, $C_8H_{14}O_2$, and this, when heated with alcoholic ammonia, passes into α -methyl- α^1 -isopropyl pyrrol, a reaction showing the presence of the isopropyl group in the diketone, and also that it is a γ -diketone, since only such diketones yield pyrrol derivatives. Thus the diketone seems to be ω -dimethyl acetyl-acetone $(CH_3)_2CH.CO.CH_2.CH_2.CO.CH_3$, and it would appear most probable, from these reactions, to regard β -tanacetogen dicarboxylic and β -thujaketonic acids as—



whilst the corresponding α -acids may be looked upon as possessed of the following structures:—

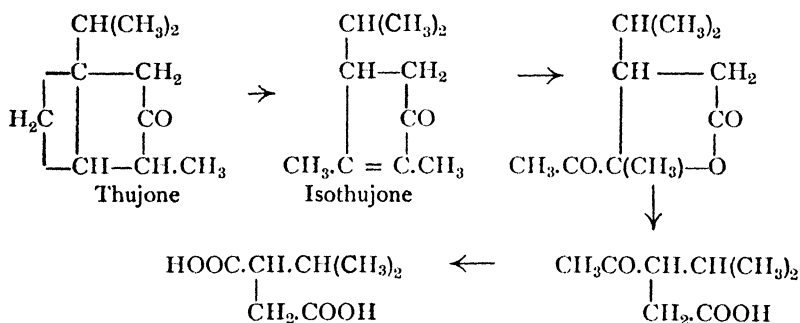


and thujone itself as—



80 MODERN RESEARCH IN ORGANIC CHEMISTRY

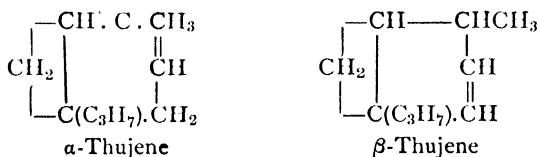
Thujone is converted into carvacrol when boiled with ferric chloride, and when heated alone to 280° C., passes into the isomeric carvotanacetone, a Δ .6-menthenone-2, since this ketone on reduction passes into tetrahydrocarvone, and also on oxidation yields pyruvic acid and isopropylsuccinic acid (p. 77). When heated with dilute sulphuric acid, thujone is transformed into isothujone, a ketone of the cyclopentane series, formed by the fission of the cyclopropane ring of the original thujone. The constitution of this isothujone was determined by Semmler, who found that on oxidation with potassium permanganate it yielded a keto-lactone, $C_{10}H_{16}O_3$, from which, by further oxidation, a ketonic acid, $C_8H_{14}O_3$, is produced. This acid is β -isopropyl-laevulinic acid, since on further oxidation by bromine in alkaline solution it gives isopropyl succinic acid.



The above reactions are thus explained on the assumption of isothujone as a cyclopentene-one, and also favour the configuration of thujone as a bi-cyclo compound. As an alternative to the above formula of isothujone, one might be given in which the positions of the $>\text{CH} \cdot \text{CH}(\text{CH}_3)_2$ and the $>\text{CH}_2$ groups were interchanged, leading to the formation of a keto-lactone and of α -isopropyl-laevulinic acid on oxidation, but this structure is negated by the fact that isothujone gives rise to a benzylidene derivative when acted upon by benzaldehyde in the presence of sodium ethoxide, a fact necessitating the presence of the $-\text{CH}_2 \cdot \text{CO}-$ grouping.

The reduction of thujone oxime leads to the formation of thujylamine, $C_{10}H_{17}NH_2$; and Semmler, by distillation of the hydro-

chloride of this base, obtained a hydrocarbon $C_{10}H_{16}$, which he called *thujene*. Somewhat later, however, Tschugaeff, by the distillation of the methyl xanthogenate of thujyl alcohol, obtained a hydrocarbon differing from that of Semmler, the hydrocarbon of the latter investigator apparently being a monocyclic compound, and containing two double bonds. Consequently, Tschugaeff considers that it is derived from isothujone by the group $-CH_2-CO-$ becoming $-CH=CH-$, and so designates it as isothujene. The thujene obtained by the xanthogenic reaction is called α -thujene to distinguish it from the isomeric β -thujene obtained by the distillation of trimethyl-thujyl ammonium hydroxide, the two hydrocarbons differing merely in the position of the double bond.

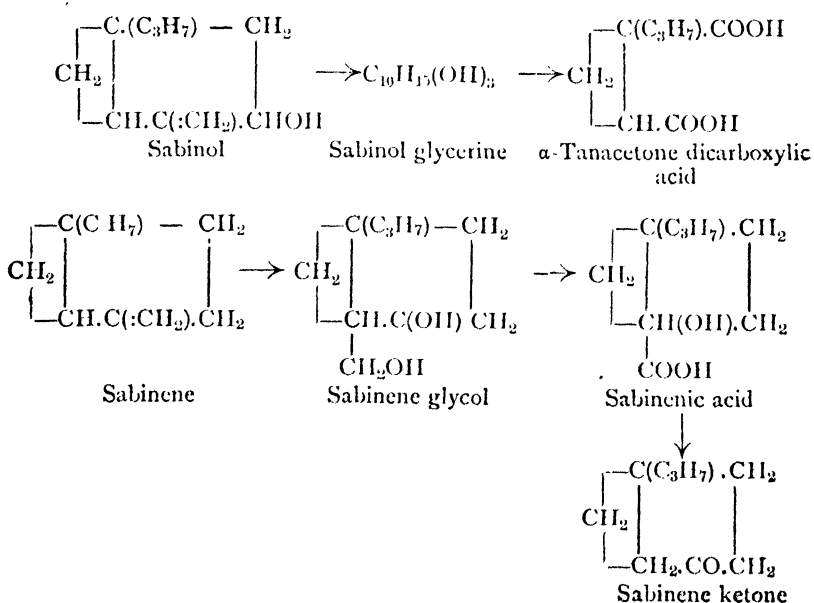


α -Thujene does not form either a crystalline nitrosochloride or a crystalline bromo-additive compound. It instantaneously decolourizes potassium permanganate solution, and rapidly resinifies on exposure. Its molecular refraction is 44.21, the calculated value for a bi-cyclic terpene being 43.54. β -thujene differs from the α -form by its much greater rotatory power, and it seems probable that thujone on reduction to thujyl alcohol yields two stereo-isomeric thujyl alcohols, the elimination of water from which can take place in two directions, giving rise to the two different hydrocarbons, since β -thujene is obtained by the xanthogenic process also.

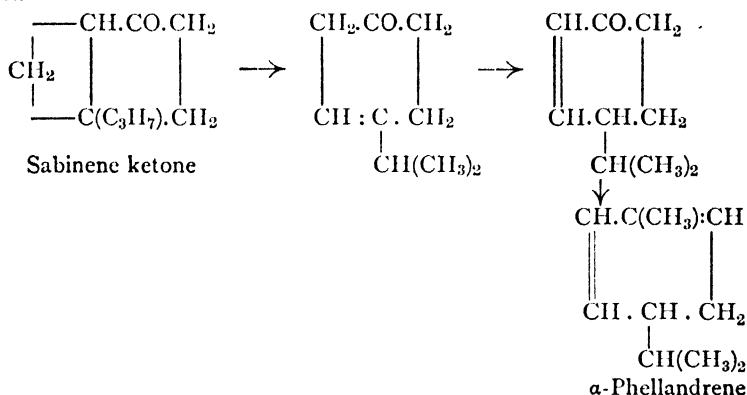
Sabinene, $C_{10}H_{16}$, is a hydrocarbon obtained from oil of savine by fractional distillation. It is a dextro-rotatory liquid of molecular refraction 44.9, the calculated value derived from its refractive index (1.466) for a bi-cyclic hydrocarbon with one double bond being 44.4. On oxidation with potassium permanganate it yields sabinene glycol $C_{10}H_{18}O_2$, and a hydroxy-acid sabinenic acid $C_{10}H_{16}O_3$, whilst if lead peroxide be used as oxidant,

82 MODERN RESEARCH IN ORGANIC CHEMISTRY

sabinene ketone $C_9H_{14}O$ is formed. Sabinene ketone when boiled with dilute acids is converted into dihydro-cuminic alcohol, which on oxidation with chromic acid yields cuminic alcohol (*p*-isopropyl benzyl alcohol) $C_3H_7.C_6H_4.CH_2OH$; whilst sabinenic acid on distillation in vacuo passes into cuminic acid (*p*-isopropyl benzoic acid) $C_3H_7.C_6H_4.COOH$. The constitution of sabinene is partially derived from that of *sabinol* $C_{10}H_{15}OH$, an unsaturated alcohol which constitutes the chief portion of oil of savine. This alcohol on oxidation with a dilute solution of potassium permanganate is converted into sabinol glycerine $C_{10}H_{15}(OH)_3$, a reaction indicating the presence of the $-C=C-$ grouping, the glycerine passing into cuminic alcohol $C_3H_7(1).C_6H_4.CH_2OH(4)$ in the presence of traces of mineral acid. Again, by further oxidation, sabinol glycerine yields α -tanacetone dicarboxylic acid, a reaction pointing to the double bond in sabinol being outside the ring system, as otherwise the formation of the group $-CH_2OH$ in the cuminic derivatives would be impossible. Thus the above compounds may be formulated—



A certain amount of confirmation of the above formulæ is given by the observations of Wallach that sabinene ketone is converted into isopropyl-1-cyclohexene-2-one-4 by the action of mineral acids, and that this ketone, on treatment with the Grignard re-agent, passes into α -phellandrene, of which the structure is known.

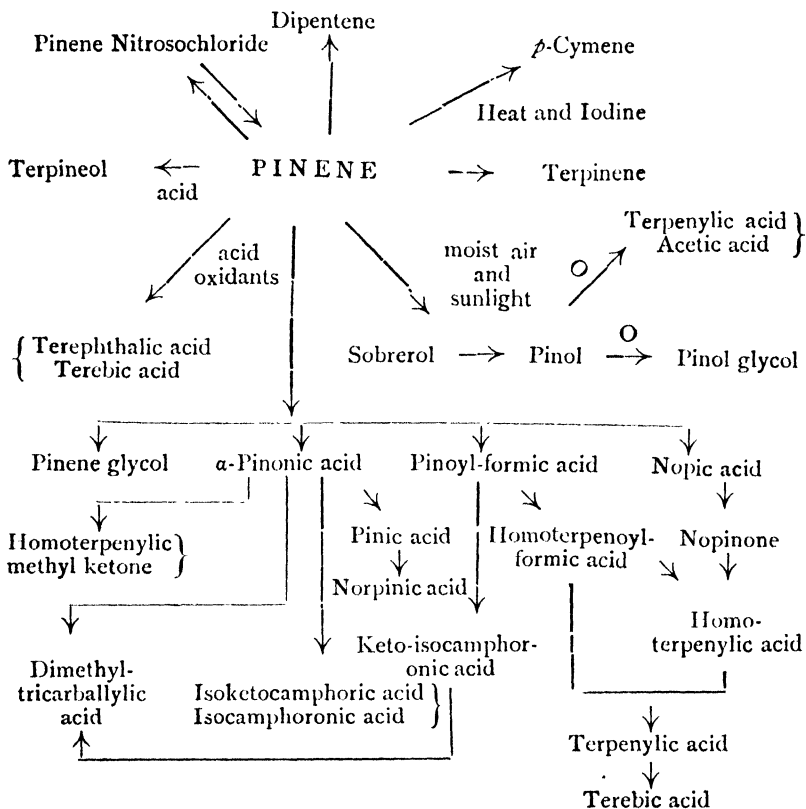


The more important bi-cyclo-terpenes and their derivatives are those of the bi-cyclo (1.1.3)-heptane group, comprising as its chief member pinene, and those of the corresponding (1.2.2) group, which includes as its more important derivatives bornylene, camphene, and fenchene, and the corresponding alcohol and ketone derivatives.

Pinene, $\text{C}_{10}\text{H}_{16}$, is the chief constituent of oil of turpentine, the *l*-form being found in the French oils, whilst the *d*-form is found in the Swedish, Russian, and American oils of turpentine. It absorbs oxygen from the air, with formation of resinous products. When heated with iodine it yields cymene. Dilute nitric acid oxidizes it to terephthalic acid and other acids, chiefly of the aliphatic series. It behaves as an unsaturated compound, forming a nitrosochloride and a dibromide. Its hydrochloride is a colourless solid known as "artificial camphor." This hydrochloride is identical with bornyl chloride, and on removal of hydrogen chloride by a weak alkali, passes into camphene. Nitric acid in aqueous alcohol solution converts pinene into terpin hydrate, whilst in the presence of organic acids it is converted into esters

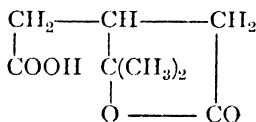
84 MODERN RESEARCH IN ORGANIC CHEMISTRY

of terpineol. The determination of the constitution of pinene has been a long and complicated process, the earlier experimental work being in the main incorrect, and it is chiefly to the investigations of Wagner and of Baeyer at the end of the last century that we owe our present knowledge of the structure of this hydrocarbon. The chief decompositions of pinene, together with its products of oxidation, are shown in the following chart:—

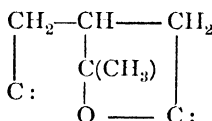


The constitution of pinene is derived in the following manner. The oxidation of the hydrocarbon with one per cent. potassium permanganate yields pinene glycol $C_{10}H_{16}(OH)_2$, which, on treatment with very dilute hydrochloric acid, passes into pinol $C_{10}H_{16}O$, and this latter compound, on oxidation with more

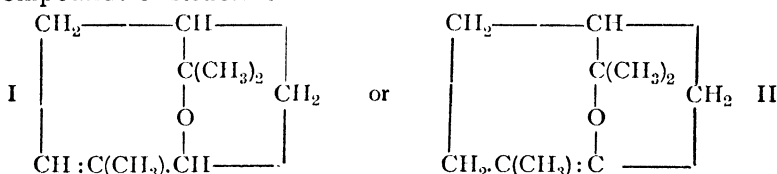
potassium permanganate, is converted into terpenylic acid. Since terpenylic acid possesses the structure¹



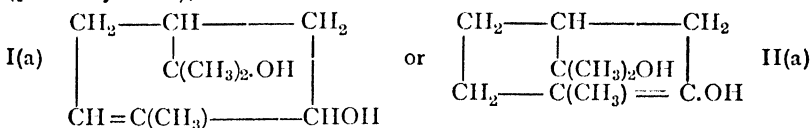
it follows that pinol contains the skeleton system



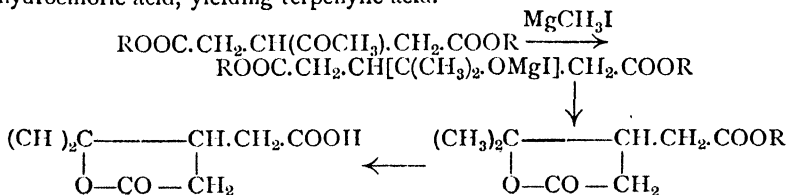
to which must be now attached a hydrogen atom and the group (CH₃.C), the latter group being necessary to account for the transformation of the pinene molecule into paracymene derivatives. The addition may take place in two ways, giving rise to compounds of structure



and since pinol, by the addition of a molecule of water (a reaction carried out by the decomposition of its hydrobromic acid addition compound with sodium hydroxide), passes into sobrerol (pinol hydrate), the latter must be either

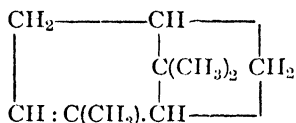


¹ This structural formula for the acid has now been definitely established by the synthesis of the acid by Simonsen from ethyl β-acetyl glutarate and magnesium methyl iodide, the resulting lactonic ester, on hydrolysis with hydrochloric acid, yielding terpenylic acid.



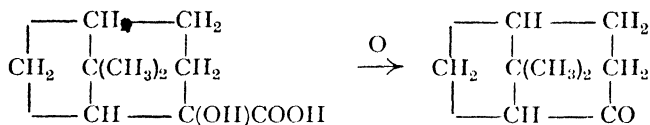
86 MODERN RESEARCH IN ORGANIC CHEMISTRY

but now, as the oxidation of *sobrerol* leads to the production of *sobrerithrite*, which is a tetrahydric alcohol, it follows that *sobrerol* must be of the structure I(a), because a compound of structure II(a) would give rise to an oxy-ketone on oxidation. Consequently, *pinol* must be represented by formula I, which leads to the following representation of *pinene* :—

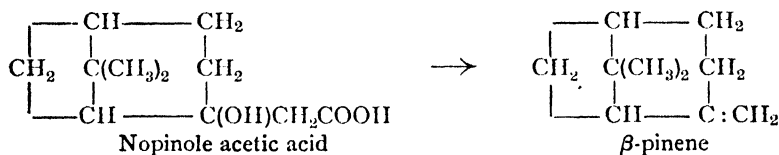


Confirmation of this is given by Baeyer's oxidation of *pinene* to α -*pinonic acid*, *pinic acid*, and other products (see Cap. I. p. 13).

A substance closely related to *pinene* is the ketone *nopinone*, a substance formed by the action of potassium permanganate and concentrated sulphuric acid on sodium *nopate*.



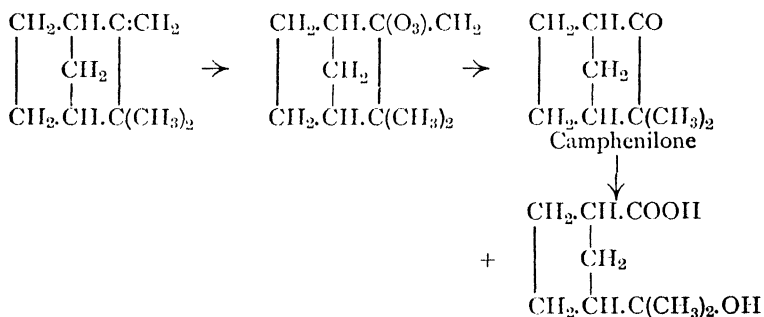
The ketone condenses readily with bromo-acetic ester in the presence of zinc to form *nopinole acetic ester*, from which the free *nopinole acetic acid* is obtained in small yields on hydrolysis. When this acid is heated with acetic anhydride it yields a mixture of two unsaturated acids, one of which is very unstable, and during the reaction loses carbon dioxide and passes into β -*pinene* (the semi-cyclic isomer of ordinary *pinene*).



Camphene, $\text{C}_{10}\text{H}_{16}$, is found as a constituent of oil of *citronella*, oil of *camphor*, oil of *rosemary*, and also of French and American oils of *turpentine*. It may be obtained by heating *pinene* with sulphuric acid, but, according to Konowalow, is best prepared by

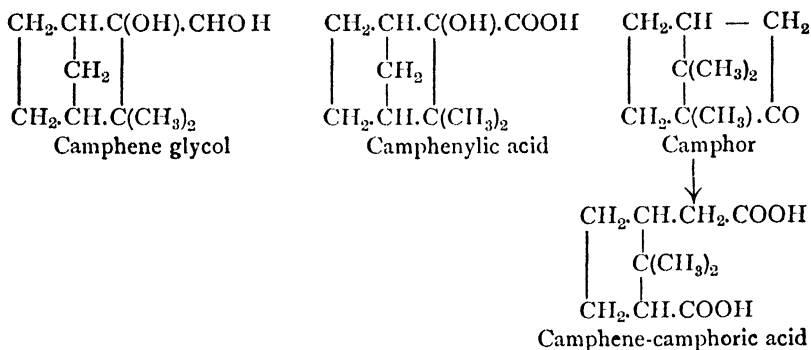
heating borneol with dilute sulphuric acid (1 : 2) for several hours at 60-100° C., with continual shaking. It is known in the *d*-, *l*-, and racemic forms. Numerous oxidation products are obtained from the hydrocarbon by the use of different oxidizing agents. Thus, with chromic acid it yields camphor; with chromyl chloride, camphenylanic aldehyde C₁₀H₁₆O; with dilute nitric acid, carboxyapocamphoric acid C₇H₁₁(COOH)₃; and with dilute potassium permanganate solution, camphenilone C₉H₁₄O, camphene glycol C₁₀H₁₆(OH)₂, camphenylic acid C₁₀H₁₆O₃, and camphene-camphoric acid C₁₀H₁₆O₄. A large number of investigations have been undertaken with the object of deciding the constitution of camphene, and the concensus of opinion is now in favour of the semi-cyclic structure of the hydrocarbon.

Confirmation of this structure has been sought by Semmler in the action of ozone on camphene, the ozonide obtained decomposing in two ways, either with the production of camphenilone and *δ*-oxycamphenilonic acid, or by loss of water into two acids C₉H₁₄O₂, of which the structure has not yet been determined. The former decomposition may be illustrated as follows :—

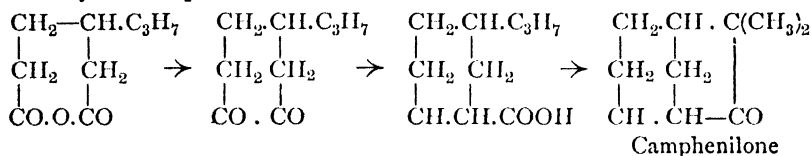


These reactions show that camphene could not possess an unsaturated nucleus, for if that were the case then the ozonide should yield a di-aldehyde on decomposition, and further, the splitting off of a carbon atom in the formation of the decomposition products of the ozonide confirms its semi-cyclic constitution. The various oxidation products of camphene can consequently be represented as

88 MODERN RESEARCH IN ORGANIC CHEMISTRY

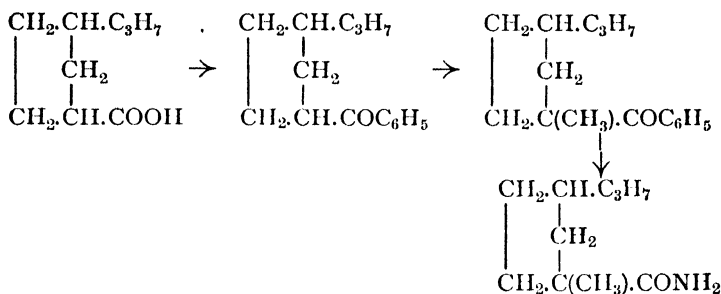


Still further confirmatory evidence is given by the fact that camphenilone when heated with sodamide yielded the amide of dihydrocampholenic acid, a compound synthesized by Bouveault from β -isopropyladipic anhydride in the following manner. The anhydride when heated yielded 3-isopropylcyclopentanone, which was then reduced to the corresponding alcohol. This alcohol was converted into its bromo-derivative, the ether solution of which on treatment with magnesium and carbon dioxide gave a carboxylic acid, the amide of this acid being identical with that of dihydrocampholenic acid.

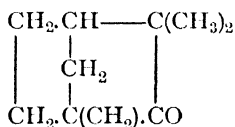


Fenchene, $\text{C}_{10}\text{H}_{16}$, is not found in any naturally occurring products, but may be prepared by the elimination of the elements of water from fenchyl alcohol, the reduction product of fenchone. Agreement has not yet been reached regarding the constitution of fenchone, and consequently that of fenchene cannot be settled, the only derivative of the series which may be considered as absolutely fixed being dihydrofencholenamide, the substance obtained by the inter-action of fenchone and sodamide. This substance has been synthesized by Bouveault and Levallois from dihydrocampholenic acid (see above). The acid was converted into its chloride, which by the Friedel and Crafts reaction was then transformed into its phenyl ketone. Sodamide reacts

with the ketone to yield a sodium derivative, in which the sodium atom is readily replaced by the methyl group, and the resulting ketone then undergoes the normal decomposition with sodamide, which leads to the formation of benzene and dihydrofencholenamide.



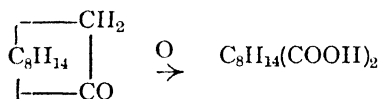
This reaction would seem to point to fenchone as most probably being possessed of the following structure:—



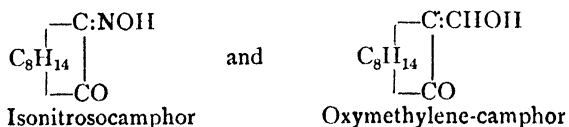
Of the ketones of the bi-cycloterpenes the most important is *camphor* $\text{C}_{10}\text{H}_{16}\text{O}$, the *d*-form of which is found in the camphor tree (*Laurus camphora*), whilst the *l*-variety occurs in the oil of *Matricaria parthenium*. The ordinary camphor of commerce is obtained, together with oil of camphor, by the distillation of the wood of the camphor tree with steam, and is finally purified by sublimation, generally with quicklime and charcoal. It crystallizes in prisms, and is readily soluble in the ordinary organic solvents. It sublimes readily, and boils at 209°C . The *d*-form has been obtained synthetically by Haller, by the distillation of calcium homocamphorate. A vast amount of experimental investigation has been carried out in order to settle the constitution of camphor, and the earlier experimenters were led to incorrect conclusions owing to the ease with which the ketone is transformed into benzenoid derivatives, such, for example, as the production of *p*-cymene and carvacrol when the ketone is heated with phosphorus pentoxide, of *m*-cymene and tetramethyl-

benzene when phosphorus pentasulphide is used, and of carvacrol, *a*-ethyl orthoxylene and *a*-tetramethylbenzene when camphor is heated with iodine, these results being explained in the light of modern knowledge by the occurrence of intra-molecular change in the molecule. Numerous oxidation products of camphor have been obtained by working under different conditions, thus with nitric acid it yields the dibasic camphoric acid $C_8H_{14}(COOH)_2$, camphoronic acid $C_6H_{11}(COOH)_3$ and other products; with potassium permanganate or chromic acid, camphoric acid is obtained, whilst if Caro's acid be used as oxidant campholid $C_{10}H_{10}O_2$ and a compound $C_{10}H_{16}O_4$ result.

The structural formula which at present is given to camphor rests on Bredt's investigations on camphoronic acid and also on the following facts. Camphor is a ketone since it yields an oxime, a hydrazone, and a semicarbazone, whilst on reduction it passes into a secondary alcohol (borneol) from which camphor can again be regenerated by ordinary oxidation processes. It is also a saturated ketone, and may consequently be regarded as containing two closed carbon rings attached to a $-CO$ group. The carbonyl group is attached to the $-CH_2-$ group since oxidation of camphor gives the saturated dicarboxylic camphoric acid $C_8H_{14}(COOH)_2$ which can only be explained on the assumption

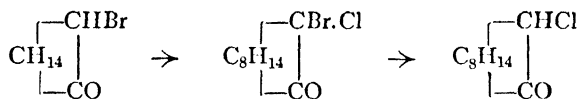


and further evidence of this structure is given by the fact that camphor combines with aldehydes in the presence of sodium ethoxide to form alkylidene compounds, and it also yields an isonitroso- and an oxymethylene derivative, reactions only shown by ketones containing the grouping $-CH_2.CO-$,

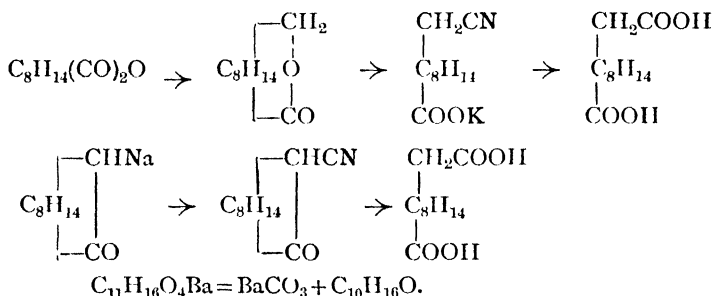


As still further arguments in favour of this grouping may be mentioned the facts that it yields only mono- and disubstitution

derivatives, and that with aliphatic saturated ketones the position of substitution is at the carbon atom adjacent to the -CO group. Again, the α -bromo-camphor has been shown by Lowry to yield a mixture of two stereoisomeric bromo-chloro-camphors on chlorination, and these are transformed into the same α -chlorocamphor on treatment with alkali, consequently both halogen atoms must be attached to the same carbon atom.



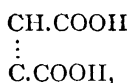
The relationship existing between camphor and camphoric acid has also been shown in the following manner by Haller. Camphoric anhydride on reduction by sodium amalgam yields campholide, which, on treatment with potassium cyanide and subsequent hydrolysis, passes into homocamphoric acid, from which camphor may be regenerated by distillation of the barium or calcium salt ; or cyanogen gas if brought into contact with freshly prepared sodium camphor yields cyancamphor, which may be directly hydrolyzed to homocamphoric acid.



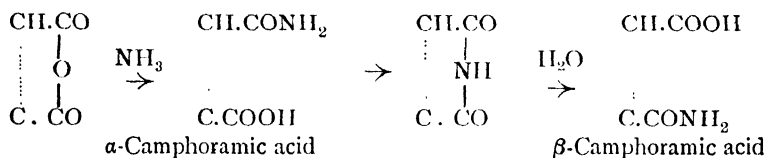
Since camphoric acid readily yields an anhydride when left in contact with acetyl chloride even in the cold, it follows that it must be a derivative of succinic acid or of glutaric acid, and a choice can be made between the two alternatives by the following considerations. In the first place, camphoric acid contains only one hydrogen atom in the α -position with regard to a carboxyl group, for on bromination it yields a monobromo-camphoric acid, and in the case of acids generally, it is known that it is only

92 MODERN RESEARCH IN ORGANIC CHEMISTRY

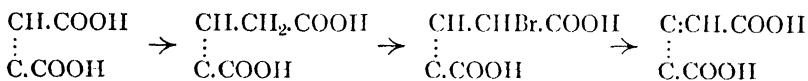
possible to introduce as many bromine atoms into the molecule, as there are hydrogen atoms in the α -position. Again, camphoric anhydride in alcoholic solution, on treatment with ammonia, passes into α -camphoramic acid almost exclusively, the distillation of this acid then yielding camphorimide, which on hydrolysis by alkali hydroxides passes into β -camphoramic acid. These reactions show that there is a great difference in the reactivity of the carboxyl groups in camphoric acid, which may be accounted for by the fact that camphoric acid contains the grouping—



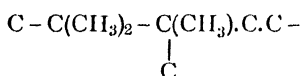
since the reactivity of carboxyl groups in aliphatic acids appears to be great or small accordingly as the adjacent carbon atom is hydrogenized or not.



Still further evidence of the existence of the one hydrogen atom in the α -position is furnished by the fact that the bromination of homocamphoric acid yields an α -bromohomocamphoric acid from which, by heating the diethyl ester with quinoline, a dehydrohomocamphoric acid is obtained, the formation of this acid necessitating a hydrogen atom in the β -position in homocamphoric acid, and hence in the α -position in camphoric acid.

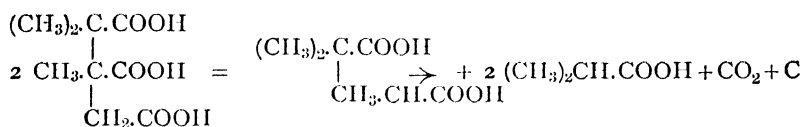


Camphor must also contain the grouping—

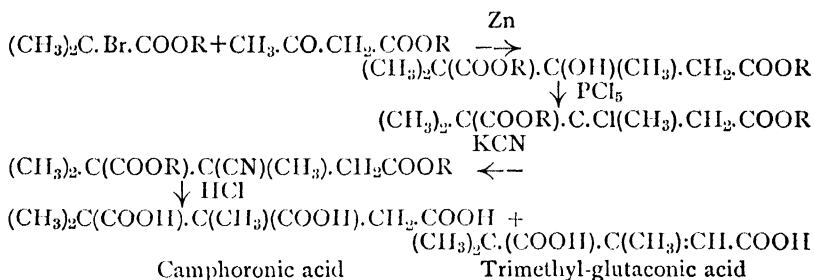


for on oxidation with nitric acid it yields camphoronic acid, $\text{C}_9\text{H}_{14}\text{O}_8$, which according to Bredt is an $\alpha\alpha\beta$ -trimethylcarballylic acid, since

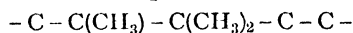
on dry distillation it is decomposed into isobutyric and trimethylsuccinic acids, carbon dioxide, and carbon.



This structure for the acid was confirmed later by its synthesis by Perkin and Thorpe from aceto-acetic ester and α -bromoisobutyric ester, which condense in the presence of zinc to form ethyl- β -hydroxytrimethyl-glutarate. The hydroxyl group is successively replaced by chlorine and cyanogen, and the cyano-acid hydrolyzed by means of hydrochloric acid when camphoronic and trimethylglutaconic acids are simultaneously produced, the latter acid separating directly from the solution.



Again, it may be shown that the configuration of an α -methyl- $\beta\beta$ -dimethyl-glutaric acid exists in the camphor molecule, because camphoric acid, when oxidized with potassium permanganate, is converted into an acid, $\text{C}_8\text{H}_{12}\text{O}_5$ (Balbiano's acid), a dibasic acid in which the fifth oxygen atom does not function as ketonic, since only addition compounds are obtained on treatment with hydroxylamine and hydrazines. This acid may be reduced by hydriodic acid to another acid of composition $\text{C}_8\text{H}_{14}\text{O}_4$, from which, by oxidation, $\alpha\beta\beta$ -trimethyl glutaric acid is obtained, a result which indicates that camphoric acid contains the grouping—

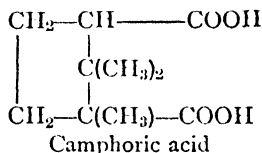
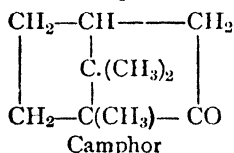


The fact that camphoric acid contains the cyclopentane ring is shown by the investigations of Lapworth (see p. 21), and also

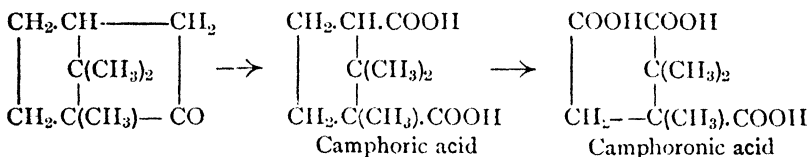
94 MODERN RESEARCH IN ORGANIC CHEMISTRY

by the conversion of bornyl chloride, on oxidation with nitric acid, into camphoric acid and apocamphoric acid, the latter acid being undoubtedly a cyclopentane derivative, as is shown by its synthesis by Komppa (see p. 19).

Chiefly from the study of the decomposition products of camphoric acid, Bredt was led in 1893 to assign the following formulæ to camphor and camphoric acid :—

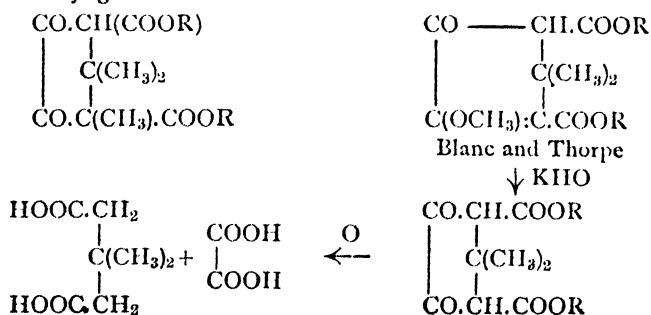


and these formulæ are largely justified by the facts noted in the preceding pages. Thus the oxidation of camphor may be illustrated—



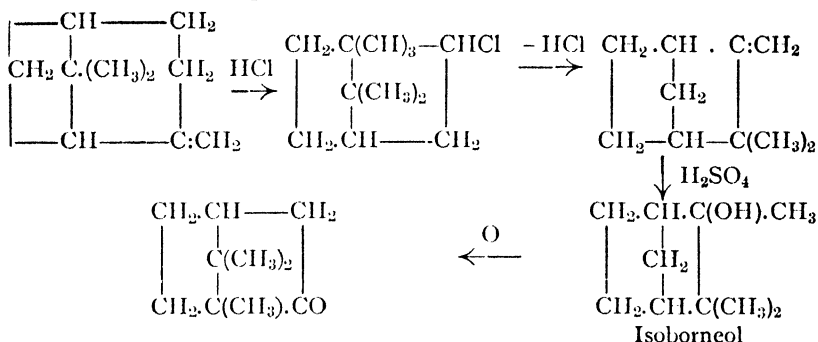
Further confirmation of the Bredt formula is given by the synthesis of racemic camphoric acid¹ by Komppa (see p. 22),

¹ Since the above was written, doubt seems to be cast on Komppa's work by the investigations of Blanc and Thorpe, who consider that the methyl diketocamphorate of Komppa is not, as he supposed, a C-methyl derivative, but is really an *O*-methyl ether, for on treatment with a large excess of aqueous alkaline hydroxide it yields methyl diketoapocamphoric acid, as is shown by the oxidation of this latter compound with potassium permanganate to $\beta\beta$ -dimethyl glutaric acid.

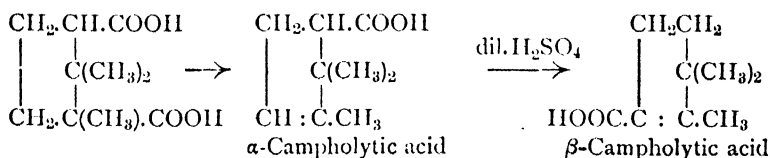


which renders that of camphor an accomplished fact, since camphoric anhydride may be converted into homocamphoric acid, and the distillation of the barium salt of this acid yields camphor (see above).

A further synthesis of camphor has been carried out by Wallach, who finds that nopinene (β -pinene), on saturation with a current of hydrogen chloride, yields a mixture of dipentene dihydrochloride and bornyl chloride. The bornyl chloride is then converted into camphene, which in its turn can be transformed into isoborneol and camphor.



Objections may be raised to the above formula for camphor, since such a compound should apparently give thymol, $\text{C}_6\text{H}_3(\text{C}_3\text{H}_7)(\text{OH})(\text{CH}_3)[1.2.4]$, whereas one actually gets carvacrol, $\text{C}_6\text{H}_3(\text{C}_3\text{H}_7)(\text{OH})(\text{CH}_3)[1.3.4]$; again, it does not explain the conversion of α -campholytic acid into β -campholytic acid (isolauronic acid)—

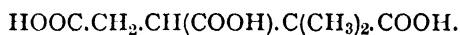


the structure of the β -acid having been confirmed by its synthesis

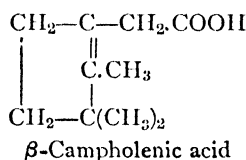
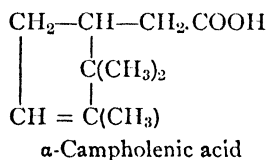
Komppa has, however, repeated his work (*Jour. Chem. Soc.* 1911, 99, 29), and insists that his views are correct, at the same time pointing out that Blanc and Thorpe's interpretation of the above ester as an *O*-methyl ester cannot hold, since the methyl group is not removed when the ester is boiled with hydriodic acid.

96 MODERN RESEARCH IN ORGANIC CHEMISTRY

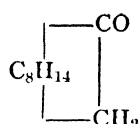
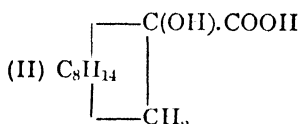
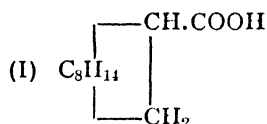
(p. 25), and that of the α -acid following from its oxidation to $\alpha\alpha$ -dimethyltricarballic acid,



A similar case is seen in the α - and β -campholenic acids, which result as nitriles from camphor-oxime by the action of dilute sulphuric acid and hydriodic acids respectively.



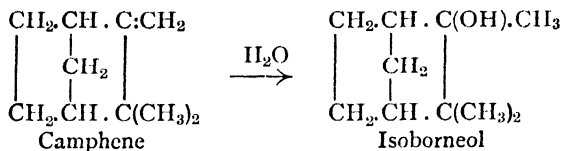
Perkin has recently (1911) obtained an isomer of camphor which he designates as *epicamphor*. This ketone is produced when camphane carboxylic acid (I) is brominated, the bromine replaced by the hydroxyl group, and the resulting hydroxy-acid (II), oxidized by lead peroxide.



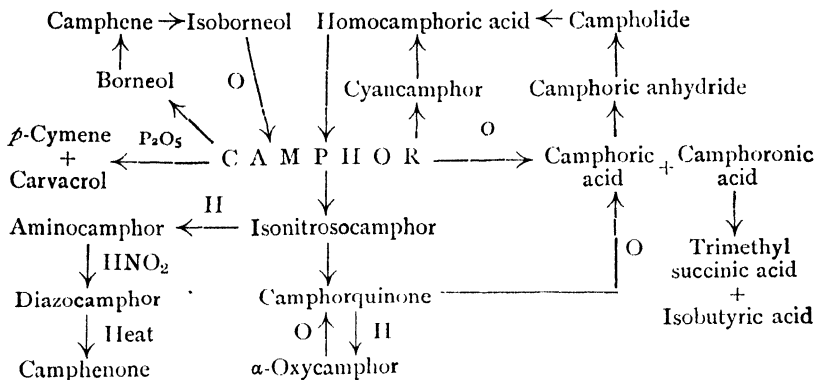
Epicamphor is really volatile in steam and has the same odour as camphor. It melts at about 165°C . and closely resembles camphor in its properties.

By the reduction of camphor in alcoholic solution with sodium Wallach obtained the secondary alcohol borneol, which, however, was found to be mixed with more or less isoborneol. Tschugaeff showed that the mixture could be separated by the xanthogenic ester process, as only a small quantity of the ester of isoborneol is obtained, and may be removed by distillation in a current of steam, the main portion of the isoborneol not entering into reaction.

Since camphene may be converted into isoborneol by dissolving the hydrocarbon in glacial acetic acid, and heating the mixture with dilute sulphuric acid, there must evidently be a close relationship between the two compounds. Thus isoborneol appears to be a tertiary alcohol—



The genetic relations of camphor and its most important derivatives are shown in the following chart :—



BIBLIOGRAPHY

Only the most important papers dealing with the various compounds mentioned in the text are referred to, and cross-references may be obtained in most cases from these. For fuller details, Heusler's "Terpenes," Wallach's "Die Terpene," Semmler's "Die Aetherische Oele," and Aschan's "Chemie d. Alicyclischen Verbindungen," should be consulted.

Olefine Terpenes :—

- Oilral** Tiemann, *Ber.* 1898, **31**, 3278, 3324; 1899, **32**, 107; 1900, **33**, 559, 877, 3703, 3710, 3713, 3719, 3726; *Bull. Soc.* 1899, (iii), **21**, 212.
Barbier and Bouveault, *C.R.* 1896, **122**, 393 1422.
Ipatiew, *Ber.* 1901, **34**, 594.
Harries, *Ber.* 1904, **37**, 2823.
- Ionone** Tiemann, *Ber.* 1893, **26**, 2691; 1898, **31**, 806, 867, 1736, 2313; 1899, **32**, 827; 1900, **33**, 3703.

98 MODERN RESEARCH IN ORGANIC CHEMISTRY

- Citronellal** Dodge, *Amer. Chem. Jour.* 1889, **11**, 456.
 Tiemann, *Ber.* 1896, **29**, 913; 1897, **30**, 22.
 Barbier and Bouveault, *C.R.* 1897, **124**, 1308.
 Harries, *Ber.* 1900, **33**, 857; 1901, **34**, 1498,
 2981; 1908, **41**, 2187.
- Irene** Tiemann, *Ber.* 1893, **26**, 2675; 1895, **28**, 1754;
 1898, **31**, 808.

Cyclic Terpenes :—

- (a) **Monocyclic** **General** :— Semmler, *Ber.* 1900, **33**, 1455.
 Wagner, *Ber.* 1894, **27**, 1636 (Ann.).
 Bayer, *Ber.* 1894, **27**, 436.
- Syntheses** :—W. H. Perkin, *Jour. Chem. Soc.*
 1904, **85**, 654; 1905, **87**, 639,
 1083; 1906, **89**, 832; 1907, **91**,
 480; 1908, **93**, 1871, 1876; 1909,
95, 2010.
 Wallach, *Ann.* 1901, **314**, 147; 1906,
350, 141; 1908, **362**, 285.
 Tschugaeff, *Ber.* 1899, **32**, 3332.
 Harries and Johnson, *Ber.* 1905, **38**,
 1832.
 Auwers and Hessenland, *Ber.* 1908,
41, 1790.
 Bayer, *Ber.* 1894, **27**, 448.
- Dipentene** Wallach, *Ann.* 1887, **239**, 3; *Ber.* 1895, **28**,
 1776.
 Tiemann and Semmler, *Ber.* 1895, **28**, 1781,
 2141.
 Goldschmidt and Zürrer, *Ber.* 1885, **18**, 2220.
- Terpinene** Wallach, *Ann.* 1908, **362**, 285.
- Phellandrene** Harries, *Ber.* 1901, **34**, 1924.
 Semmler, *Ber.* 1903, **36**, 1749.
 Wallach, *Ann.* 1904, **336**, 9, 30.
- Menthol** Beckmann and Pleissner, *Ann.* 1891, **262**, 21
 Kondakow, *Jour. prak. Chem.* 1901, (ii), **63**, 49.
 Manasse and Rupe, *Ber.* 1894, **27**, 1820.
 Perkin, *Proc. Chem. Soc.* 1905, **21**, 255.
- Terpin** Perkin, *Jour. Chem. Soc.* 1904, **85**, 654.
 Bertram and Walbaum, *Jour. prak. Chem.* 1892,
 (ii), **45**, 601.
 Wallach and Gildemeister, *Ann.* 1888, **246**, 268.
- Terpineol** Perkin, *loc. cit.*
 Semmler, *Ber.* 1895, **28**, 2190.

- Wallach, *Ber.* 1895, **28**, 1773.
 Stephen and Helle, *Ber.* 1902, **35**, 2147.
 Baeyer, *Ber.* 1894, **27**, 443, 815.
- Terpinenol** . . . Wallach, *Ann.* 1908, **362**, 261; *Ber.* 1907, **40**, 596.
- Menthone** . . . Beckmann, *Ann.* 1889, **250**, 325; 1891, **262**, 21; 1896, **289**, 362.
 Barbier and Bouveault, *C.R.* 1896, **122**, 737.
 Einhorn and Klages, *Ber.* 1901, **34**, 3793.
 Haller and Martine, *C.R.* 1905, **140**, 130.
 Koetz and Hesse, *Ann.* 1905, **342**, 306.
 Wallach, *Ann.* 1900, **312**, 171.
- Pulegone** . . . Harries and Roeder, *Ber.* 1899, **32**, 3357.
 Wallach, *Ann.* 1896, **289**, 337.
- Carvone** . . . Goldschmidt, *Ber.* 1884, **17**, 1577; 1885, **18**, 1729.
 Wallach, *Ann.* 1888, **245**, 256, 268; 1888, **246**, 226; 1892, **270**, 171; 1894, **279**, 369; *Ber.* 1894, **27**, 1495.
 Harries, *Ber.* 1901, **34**, 1924, 2105.
 Tiemann and Semmler, *Ber.* 1895, **28**, 2141.
- (b) **Bi-cyclo** . . . Baeyer, *Ber.* 1900, **33**, 3771.
- Thujene and Thujone** . Wallach, *Ann.* 1893, **275**, 164, 179; 1894, **279**, 383; 1895, **286**, 90, 109; 1904, **336**, 247; 1906, **350**, 162.
 Semmler, *Ber.* 1892, **25**, 3347; 1900, **33**, 275, 2459; 1903, **36**, 4367.
 Fromm, *Ber.* 1900, **33**, 1191.
 Tschugaeff, *Ber.* 1900, **33**, 3118; 1901, **34**, 2279; 1904, **37**, 1481.
- Sabinene** . . . Semmler, *Ber.* 1900, **33**, 1459; 1902, **35**, 2045; 1906, **39**, 4416.
 Wallach, *Ber.* 1907, **40**, 577, 592; *Ann.* 1906, **350**, 162.
- Pinene** . . . Wagner, *Ber.* 1891, **24**, 2187; 1894, **27**, 1644, 2270; 1896, **29**, 883, 886; 1899, **32**, 2064, 2302.
 Baeyer, *Ber.* 1896, **29**, 3, 13, 20, 326, 529, 1907, 1927; 1895, **28**, 648.
 Tiemann and Semmler, *Ber.* 1895, **28**, 1079, 1344.
 Simonsen, *Jour. Chem. Soc.* 1907, **91**, 184
 Wallach, *Ann.* 1907, **356**, 227.
- Camphene** . . . Konowalow, *Jour. Russ. phys. chem. G.* 1900, **82**, 76.

100 MODERN RESEARCH IN ORGANIC CHEMISTRY

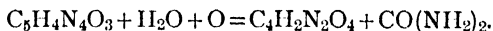
- Wagner, *Ber.* 1890, **23**, 2311; *Jour. Russ. phys. chem. G.* 1897, **29**, 124; 1899, **31**, 680.
- Semmler, *Ber.* 1909, **42**, 246.
- Fenchene** Bouveault and Levallois, *C.R.* 1908, **146**, 180.
- Camphor** Bredt, *Ann.* 1885, **229**, 1.
- Lapworth, *B. A. Rep.* 1902.
- Claisen, *Ann.* 1893, **274**, 79; 1895, **284**, 314.
- Lowry, *Jour. Chem. Soc.* 1898, **73**, 569.
- Haller, *Dissert.* (Nancy), 1897; *C.R.* 1900, **130**, 376.
- Perkin and Thorpe, *Jour. Chem. Soc.* 1899, **75**, 61; 1906, **89**, 795.
- Balbiano, *Ber.* 1895, **28**, 16.
- Komppa, *Ber.* 1901, **34**, 2472; 1903, **36**, 4332; *Ann.* 1909, **370**, 209.
- Thorpe and Blanc, *Jour. Chem. Soc.* 1910, **97**, 836.
- Borneol** Wallach, *Ann.* 1885, **230**, 225.
- Tschugaeff, *Jour. Russ. phys. chem. G.* 1904, **36**, 988.
- Bertram and Walbaum, *Jour. prak. Chem.* 1894, (ii), **49**, 1.
- Montgolfier, *C.R.* 1876, **83**, 341.
- Haller, *C.R.* 1889, **109**, 187.
- Epicamphor** Perkin, *Proc. Chem. Soc.* 1911, **27**, 166.

CHAPTER III

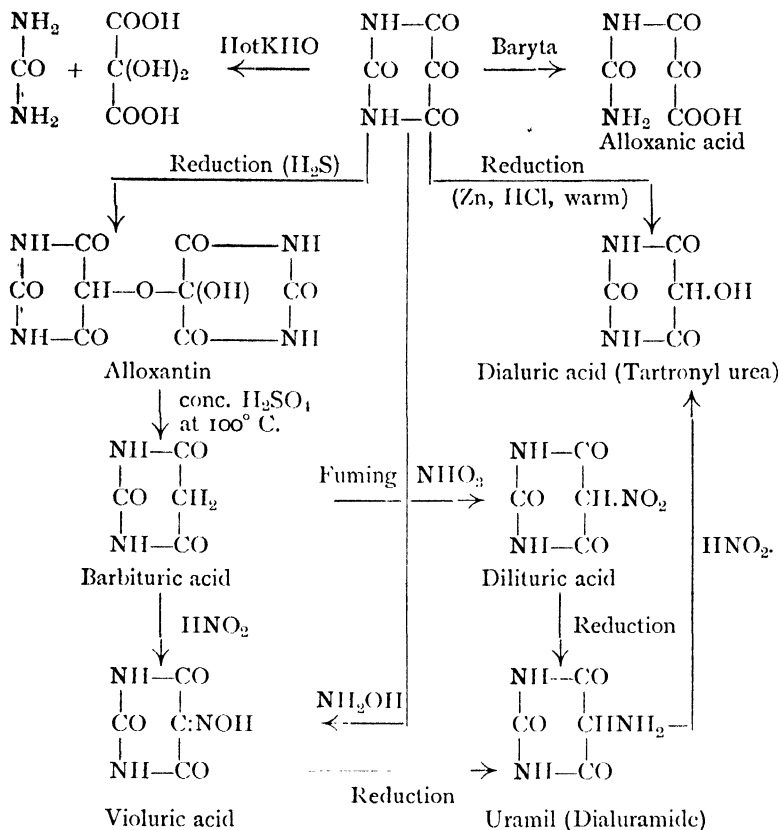
THE URIC ACID OR PURINE GROUP

THE study of the members of this group of compounds has always been a fascinating one for chemists on account of the fact that many individual members are obtained as the products of animal and vegetable metabolism, and it has always seemed probable that a detailed investigation of the various substances under consideration might lead to a knowledge of the way in which the living organism was able to synthesize complicated derivatives from comparatively simple compounds.

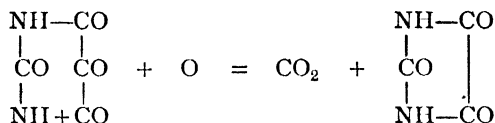
One of the earliest researches on uric acid was that of Liebig and Wöhler in 1838, in which it was shown that the acid and its derivatives may be considered as derived from barbituric acid, $C_4H_4O_3N_2$, the ureide of malonic acid. These ureides may be considered as the acyl derivatives of urea, and many of them are obtained in the decomposition of uric acid and its derivatives, more particularly those which may be considered as derived from the condensation of one molecule of urea with one molecule of a dibasic acid, giving rise to cyclic ureides. Of these cyclic ureides one of the most important is *alloxan*, or mesoxalyl urea, obtained by the oxidation of uric acid with cold nitric acid



Alloxan is of considerable importance on account of its ready transformation into other ureides, some of which have been used in the synthetic production of uric acid and its derivatives. A synopsis of its more important decompositions is given in the chart below.



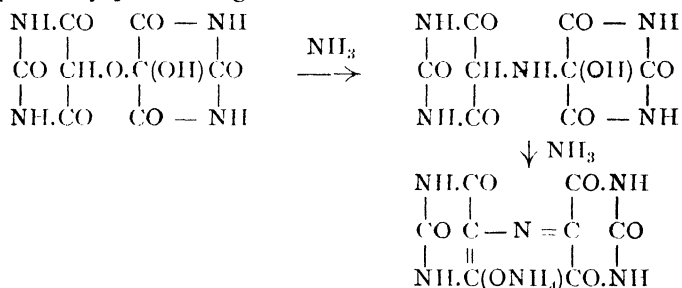
Alloxan on oxidation with warm dilute nitric acid passes into parabanic acid (oxalyl urea) $\text{C}_3\text{H}_2\text{O}_3\text{N}_2$



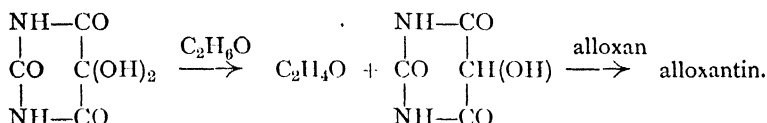
The ureides readily hydrolyze, yielding, according to conditions, either a ureido-acid (see alloxanic acid above), or urea and a dibasic acid. The majority are more or less strong acids, in which, since they do not contain a carbonyl group, one must assume that the acid character depends upon the presence of

replaceable hydrogen in the imino-groups, the acidic nature of which is determined by the adjacent carbonyl groups.

Alloxan combines directly with dialuric acid to form alloxantin, $C_8H_4O_7N_4 \cdot 3H_2O$, a compound in which one of the water molecules is probably to be considered as constitutional. This substance crystallizes in small prisms, which turn red on exposure to air containing ammonia, owing to their conversion into murexide (ammonium purpurate), $C_8H_4(NH_4)N_5O_6$, a substance also formed when uric acid is evaporated to dryness with dilute nitric acid and the residue moistened with ammonia, this reaction being known as the "*murexide*" test for uric acid. Murexide has recently been investigated by Hartley, who has obtained it by the action of ammonia on alloxantin at $100^\circ C.$, the decomposition probably proceeding thus:—

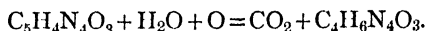


and also by the action of alcoholic ammonia at $73^\circ C.$ on alloxan, the first steps in the reaction probably leading to the oxidation of the alcohol to aldehyde and the consequent reduction of some of the alloxan to tartronyl urea, which then unites with the unaltered alloxan to yield alloxantin, when the reaction proceeds as above.

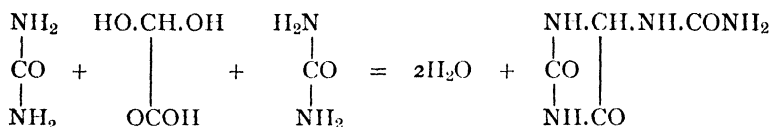


Among other ureides which are obtained by the decomposition of uric acid and its derivatives may be mentioned dimethyl alloxan, $C_4(CH_3)_2O_4N_2$, obtained by the oxidation of caffeine with nitric acid, tetramethyl alloxantin (amalic acid), $C_8(CH_3)_4O_7N_4$, formed when caffeine is oxidized with potassium chlorate and

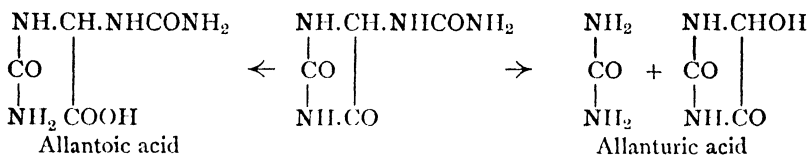
hydrochloric acid, parabanic acid (oxalyl urea), $C_3H_2O_3N_2$, formed in the alkaline oxidation of uric acid, dimethyl parabanic acid, $C_3(CH_3)_2O_3N_2$, a product of the oxidation of caffeine with chlorine water, and allantoin, $C_4H_6O_3N_4$, obtained when uric acid is oxidized by lead peroxide, manganese dioxide, etc.



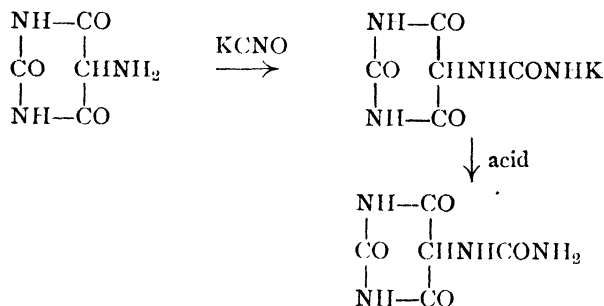
Allantoin is the di-ureide of glyoxylic acid, its constitution being determined by its synthetical formation when glyoxylic acid and urea are heated together for some hours at $100^\circ C$.



On standing with concentrated caustic potash it yields allantoinic acid, whilst if heated for some time with water it yields urea and allanturic acid.

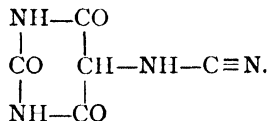


In the course of his investigations on the ureides, Baeyer found that uramil or aminobarbituric acid combined with potassium cyanate to form a salt of an acid, which he called *pseudo-uric acid*.



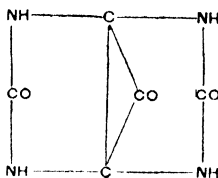
This acid differs from uric acid in containing the elements of one molecule of water more than uric acid (*i.e.* $C_5H_6N_4O_4$ as against

$C_5H_4N_4O_3$), and Baeyer considered that if the pseudo-uric acid could be made to lose one molecule of water it would pass into uric acid, and from the resulting analogy between urea and cyanamide he gave as the formula for uric acid.

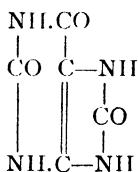


He was, however, not successful in his attempts to synthesize uric acid in this way, and his formula was not generally accepted.

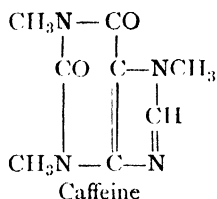
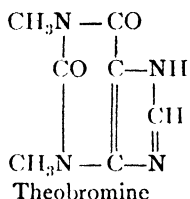
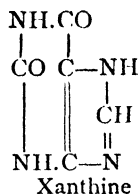
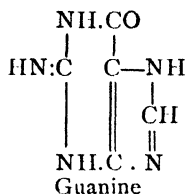
Very little work was done on the group in the few succeeding years, although Fittig in his "Traité d. Chem. organique" proposed the following formula for uric acid :—



whilst Medicus in 1875 gave as an alternative :—



advancing as reasons that uric acid on hydrolysis with mineral acids yields amino-acetic acid, ammonia and carbon dioxide, whilst on oxidation with nitric acid it yields alloxan and urea, and with alkaline potassium permanganate solution it yields allantoin, which readily hydrolyzes to urea and glyoxylic acid. Making use also of earlier observations of Strecker and other investigators, who showed that nitrous acid converted guanine into xanthine, and that the methylation of theobromine yielded caffeine, Medicus proposed the following formulæ for these substances :—



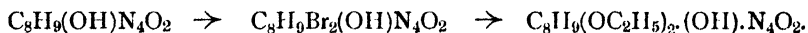
Here the matter rested for several years until in 1882 Emil Fischer published an elaborate investigation on caffeine, which may be said to have given the first insight into the true nature of the grouping in these substances. Earlier investigators had shown that oxidation of caffeine, under varying conditions, had given rise to dimethyl parabanic acid, and to tetramethyl alloxantin, whilst hydrolysis with baryta water had yielded *caffeidine*, $\text{C}_7\text{H}_{12}\text{ON}_4$, which could be further broken down into ammonia, carbon dioxide, methylamine and sarcosine



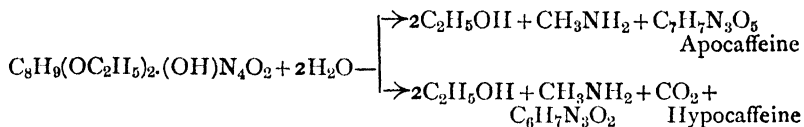
These observations were confirmed by Fischer, who further found that the oxidation of caffeine with chlorine water yielded monomethyl urea and dimethyl alloxan, thus showing that there are three methyl groups present in the caffeine molecule. Again, caffeine may be brominated and the bromo-compound on treatment with alcoholic potash yields ethoxy-caffeine, which on hydrolysis with dilute hydrochloric acid is converted into hydroxy-caffeine.



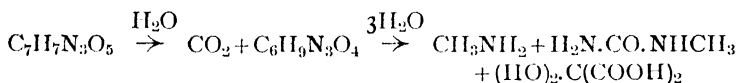
This hydroxy-caffeine behaves as an unsaturated compound combining directly with one molecule of bromine to form a product which by the action of alcoholic potash exchanges its bromine for ethoxy-groups, and is transformed into diethoxy-hydroxy-caffeine.



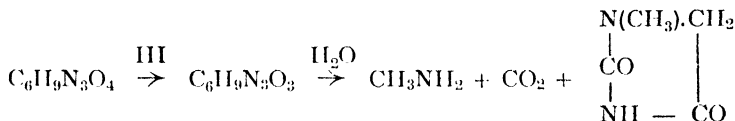
Now on hydrolysis with concentrated hydrochloric acid, this substance decomposes, the action proceeding in two directions,



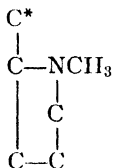
and it is from the products of fission of these two substances that one arrives at an idea of the structure of the caffeine molecule. Apocaffeine when boiled with water passes into caffuric acid, $C_6H_9N_3O_4$, and this on hydrolysis with basic lead acetate yields methylamine, monomethyl urea, and mesoxalic acid.



On reduction with hydriodic acid, caffuric acid yields hydrocaffuric acid, $C_6H_9N_3O_3$, which, on hydrolysis with caustic baryta, decomposes into methylamine, carbon dioxide, and methylhydantoin.

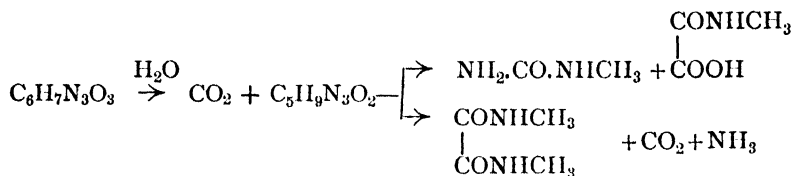


Thus it will be recognized that hydrocaffuric and caffuric acids, apocaffeine and caffeine must contain the grouping



in order to account for these various decomposition products, C^* representing the carbon atom which is eliminated as carbon dioxide. The decomposition of hypocaffeine throws further light on the subject. This substance, when boiled with water, loses carbon dioxide, and yields caffolin, $C_5H_9N_3O_2$, the latter substance, on oxidation with potassium ferricyanide, being converted into monomethyl urea and methyloxamic acid, whilst if potassium

permanganate be used as oxidant, it is transformed into dimethyl oxamide, carbon dioxide, and ammonia.

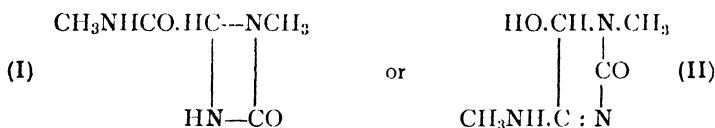


Thus caffolin contains the grouping :—

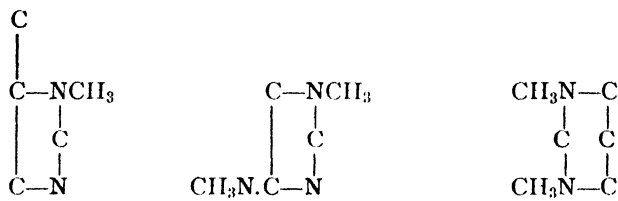


the dotted lines showing the different courses of the oxidation.

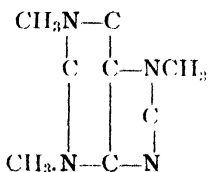
Consequently, caffolin must be either



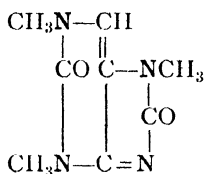
the former being excluded on account of the relation of caffolin to hydrocaffuric acid, which, as shown above, must contain the grouping (II). Thus, since caffeine yields dimethyl alloxan and monomethyl urea, beside the above products, one has the following groupings to connect together :—



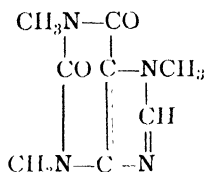
and the caffeine skeleton must consequently be



and Fischer first gave as the structural formula for caffeine, the following :—

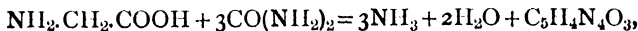


a view which he afterwards modified in 1897, when he prepared trimethylpseudo-uric acid, which he found on dehydration passed into hydroxycaffeine. This reaction shows that uric acid and caffeine contain the same carbon chain, which would not be the case if the above structure were correct. The corrected formula for caffeine is

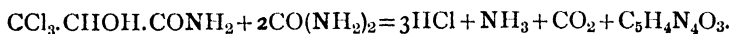


(see synthesis later). The earlier formula shown above was chiefly given on account of the fact that the direct methylation of the silver salt of hydroxycaffeine did not give a compound identical with tetramethyl uric acid.

From a chronological point of view the next synthetic work in this group was the synthesis of uric acid by Horbaczewski on heating amino-acetic acid for some time to 250° C. with a large excess of urea,

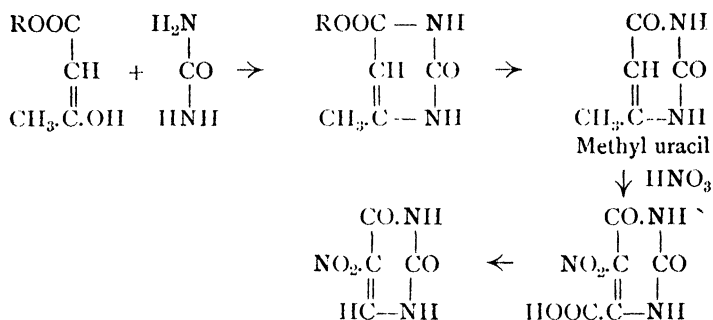


and also by heating urea with β -trichlorolactamide.

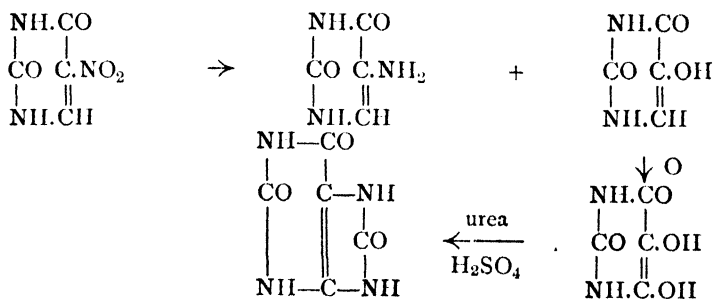


These two methods are both unsatisfactory, very small quantities of uric acid being obtained. A much more elegant but somewhat involved synthesis was, however, worked out somewhat later (1885) by Behrend, who showed that on leaving aceto-acetic ester in contact with urea in vacuo, over sulphuric acid, a β -uramido-crotonic ester is obtained, which, if its alkaline solution

be saturated with carbon dioxide, is converted into methyl uracil. This methyl uracil in contact with concentrated nitric acid undergoes simultaneous oxidation and nitration, yielding a nitro-uracil carboxylic acid which, when boiled with water, loses carbon dioxide, and is transformed into nitro-uracil.



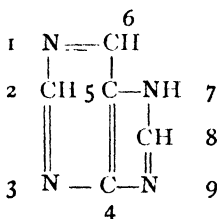
Nitro-uracil on reduction with tin and hydrochloric acid is converted into amido-uracil, the reaction proceeding somewhat further, the amino group being replaced by a hydroxyl group, and a hydroxy-uracil being simultaneously formed. This hydroxy-uracil (or isobarbituric acid) on further oxidation with bromine water yields a dihydroxy-uracil (isodialuric acid) which condenses readily with urea, in the presence of concentrated sulphuric acid, to form the desired uric acid.



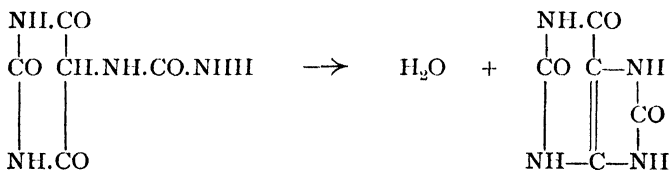
This synthesis of uric acid, of course, points to the validity of the Medicus formula as against that of the Fittig formula, and further confirmation of the former is given by an examination of the mono-methyl uric acids. The formula of Fittig (p. 105) is

symmetrical, and would allow of only one mono-methyl uric acid, whilst that of Medicus would allow of four isomers. Hill in 1876 obtained a mono-methyl uric acid, which on oxidation yielded mono-methyl alloxan and urea, whilst Fischer in 1884 prepared a methyl uric acid, which on oxidation yielded alloxan and mono-methyl urea, showing that in this latter case methylation has taken place outside the alloxan ring. This latter result would be impossible in the case of the Fittig formula, and hence the Fittig formula is incorrect and the Medicus formula is shown to be correct, both from the synthetic formation of uric acid, either by Behrend's method or Fischer's method (see below), and also from the fact that the four isomeric mono-methyl uric acids are all known.

The next great steps in the investigation of the compounds of the uric acid group were the classical researches of Emil Fischer, extending over a period from 1895 to 1900, in which he showed how these substances were inter-related and might be synthesized. To indicate the relationship of all the compounds of the group, Fischer calls the parent substance *Purine*, and assigns to it the following structural formula :—

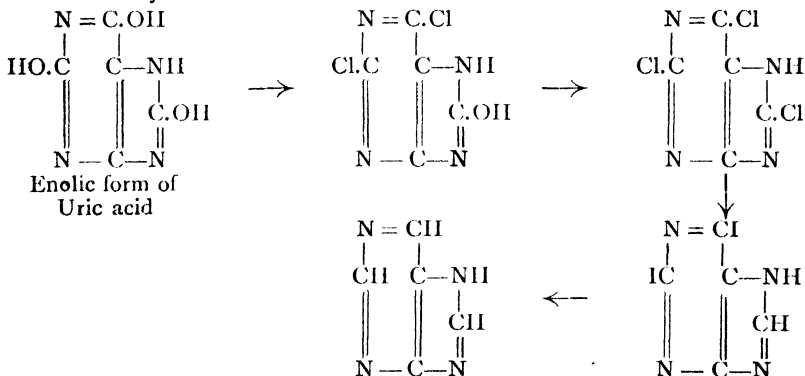


the ring being numbered as shown, to indicate the position of substituents. The first synthesis effected by Fischer was that of uric acid itself, from the pseudo-uric acid of Baeyer (p. 104). This may be dehydrated by heating to about 185° C. with anhydrous oxalic acid, or as was shown later (1897) by boiling it with about five hundred times its weight of 20 per cent. hydrochloric acid for about a quarter of an hour, and concentrating the liquid to a small bulk, when the uric acid crystallizes out.



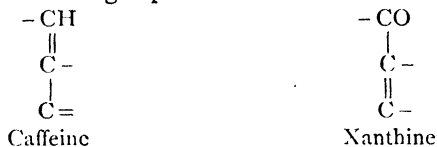
Thus uric acid appears as the keto-form of 2.6.8-trihydroxypurine, the keto-enolic form of tautomerism being characteristic of this series of compounds containing the -NH - CO - grouping, since they behave in some reactions as ketonic derivatives, and in others as hydroxylic compounds.

Purine itself was isolated a little later, in the following manner. Potassium urate, on being heated for some time with phosphorus oxychloride, yields at first 2.6-dichloro-8-oxypurine, which is finally converted into 2.6.8-trichloropurine. Hydriodic acid partially reduces this and at the same time replaces the chlorine atoms at 2 and 6, the resulting 2.6-di-iodopurine, on treatment with zinc dust and water, forming a zinc double salt, which is broken up by sulphuretted hydrogen with precipitation of zinc sulphide, whilst the purine goes into solution, and may be recovered by concentration of the solution. Thus we have

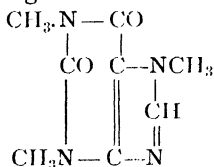


Since xanthine possesses the empirical formula $\text{C}_5\text{H}_4\text{N}_4\text{O}_2$, and uric acid is $\text{C}_5\text{H}_4\text{N}_4\text{O}_3$, it seemed probable that by reduction of the latter one might arrive at xanthine. Numerous attempts were made to carry out this reduction, but none of them were successful, the ultimate synthesis of xanthine from uric acid being due to Fischer in 1897.

But it is necessary here to make a slight digression. Caffeine is a trimethyl xanthine, and Fischer, as the result of his earlier work on caffeine, had come to the conclusion that it (and consequently xanthine) possessed a different carbon chain to that of uric acid, the two being represented thus—

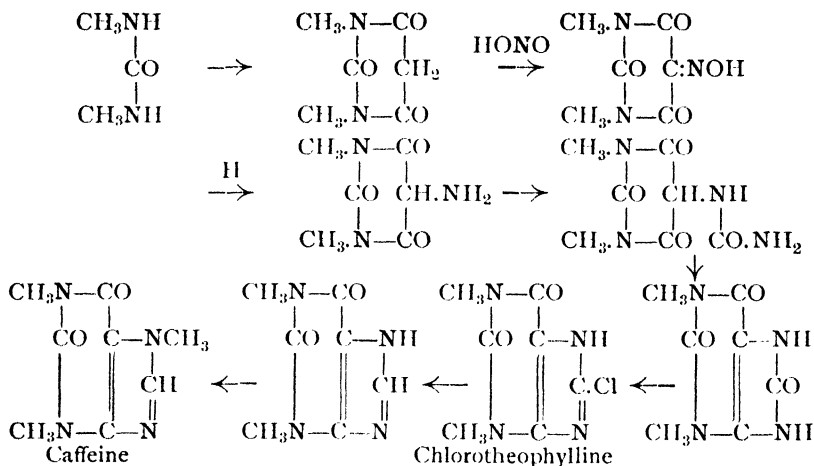


In an examination, however, of 1.3.-7-trimethyl pseudo-uric acid, he found that on dehydration it yielded a compound identical with hydroxy-caffeine, consequently hydroxy-caffeine is a trimethyl-uric acid, and hence caffeine and also xanthine must possess the same skeletal structure as that observed in uric acid. A further proof of this is given by the fact that the methylation of an aqueous alkaline solution of hydroxycaffeine yields tetramethyl-uric acid identical with that obtained by the direct methylation of uric acid itself. This result, of course, led Fischer to modify his original views as to the structure of caffeine, and as a result he assigned to it the following constitution :—

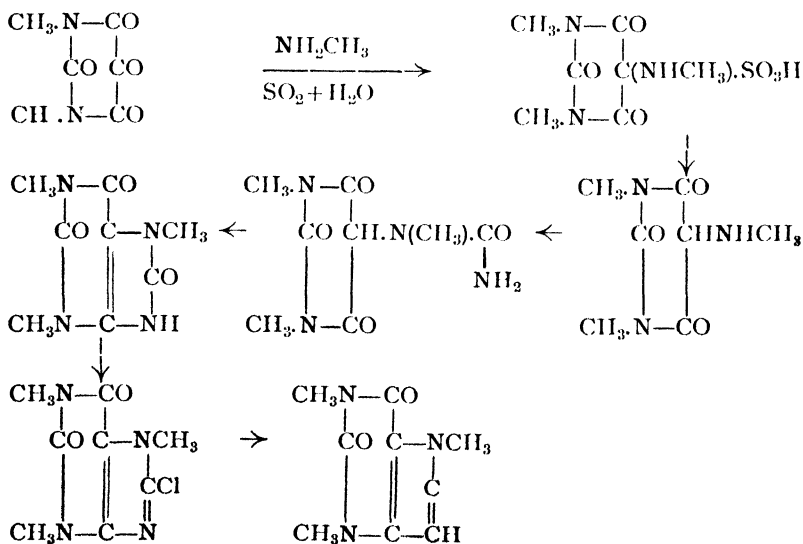


the correctness of which was shown by its synthesis from chlorotheophylline and from dimethyl alloxan. In the first method, dimethyl urea on condensation with malonic acid yields dimethylbarbituric acid, which reacts with nitrous acid to form dimethylvioluric acid, reduction of the latter yielding dimethyluramil. This readily combines with potassium cyanate to form dimethyl pseudo-uric acid, which on dehydration is converted into 1.3(δ)-dimethyl uric acid. This acid, on treatment with phosphorus pentachloride, is converted into chlorotheophylline, and the chloro-compound, on reduction with hydriodic acid and phosphonium iodide, passes into theophylline, which on methylation is transformed into caffeine.

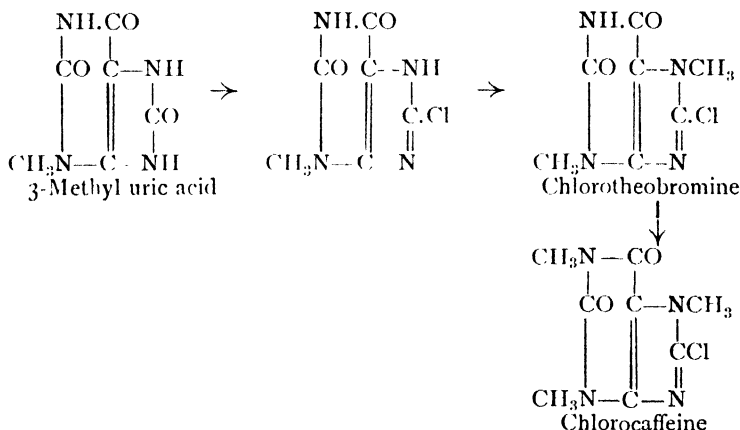
114 MODERN RESEARCH IN ORGANIC CHEMISTRY



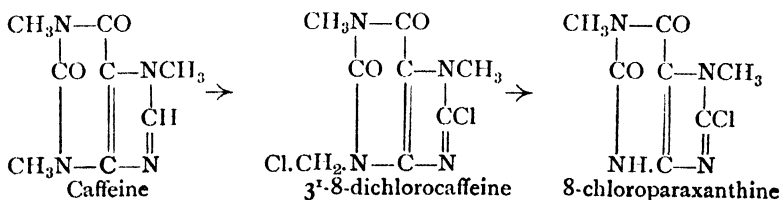
In the second method, dimethyl alloxan was left in contact with methylamine and an aqueous solution of sulphur dioxide, a trimethyl thionuric acid being formed, which on hydrolysis was converted into 1,3,7-trimethyl uramil. This uramil on treatment with potassium cyanate and dehydration in the usual manner yielded hydroxycaffeine (1,3,7)-trimethyl-uric acid. Chlorination and subsequent reduction of the latter compound then gave caffeine.



A year later saw yet another synthesis of caffeine, as follows. Hill's methyl uric acid, obtained by the action of methyl iodide on acid lead urate at 150° C., is 3-methyl uric acid, since Fischer showed that on treatment with phosphorus oxychloride and pentachloride it yielded 3-methyl-chloroxanthine. Further methylation of the latter substance in alkaline solution gave chloro-theobromine, and finally chloro-caffeine, from which caffeine is obtained by reduction.

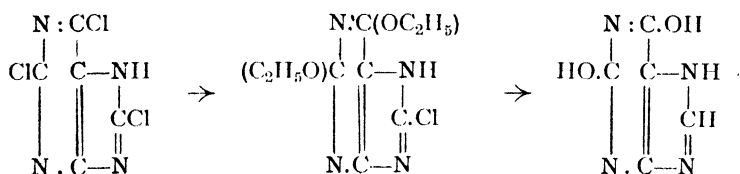


Somewhat recently Fischer and Ash have shown that caffeine may be transformed in paraxanthine, theophylline, and xanthine by preliminary treatment with phosphorus pentachloride. This leads to the formation of a small quantity of 7-methyl-2.6.8-trichloropurine and an amorphous compound. By slightly altering the experimental details the amorphous mass can be obtained as a 3¹-8-dichloro caffeine, which on hydrolysis by hydrochloric acid is converted into 8-chloro-paraxanthine. The latter on reduction yields paraxanthine.



The same 3¹-8-dichlorocaffeine is obtained by chlorination at 160° C., but at 100° C., 7¹-8-dichloro caffeine results, and on hydrolysis yields 8-chlorotheophylline, which passes into theophylline by reduction. When caffeine is chlorinated at 160° C. by means of a solution of chlorine in phosphorus oxychloride, a tetrachloro caffeine (1¹,3¹,7¹,8) is formed, and on hydrolysis yields chloroxanthine. This, of course, passes into xanthine by reduction. In the hydrolysis of these compounds, the chlorinated methyl group is eliminated as formaldehyde and hydrochloric acid.

The synthetic production of xanthine was ultimately accomplished in a quite simple manner. It was found that treatment of 2,6,8-trichloro-purine with sodium ethoxide at ordinary temperature led to the replacement of the chlorine in position 6 by the ethoxyl group, but with excess of sodium ethoxide at 100° C. the two chlorine atoms at 2 and 6 were replaced by ethoxyl groups. The resulting compound was converted into xanthine by the action of hydriodic acid. Xanthine thus appears to be 2,6-dihydroxy-purine.

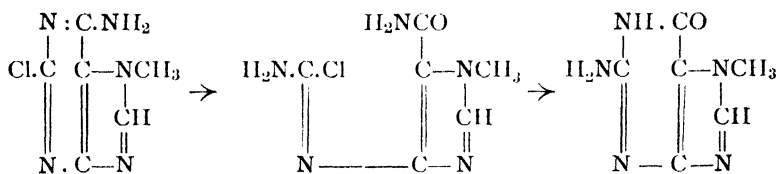


It is also formed, as Strecker had originally showed, by the action of nitrous acid on guanine (2-amino-6-hydroxy-purine).

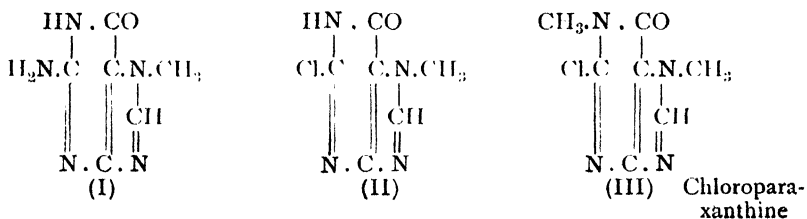
The latter compound may be prepared from 2,6,8-trichloro-purine, which, by the action of caustic potash, is converted into 6-hydroxy-2,8-dichloro-purine. The chlorine atom in position 2 is replaced by the amino group when this substance is heated with alcoholic ammonia, and the resulting 2-amino-6-hydroxy-8-chloro-purine on reduction yields guanine.

A word might be said here as to a curious formation of 7-methyl guanine. This is obtained in a direct manner by the action of ammonia on 7-methyl-6-hydroxy-2-chloro-purine, itself formed by successive treatment of theobromine with phosphorus

oxychloride and caustic soda, the first product obtained being 7-methyl-2,6-dichloro-purine. If this compound be subjected to the action of ammonia, 7-methyl-6-amino-2-chloro-purine results, and by hydrolysis with caustic alkalis it would be expected that a 7-methyl-6-amino-2-hydroxy-purine would be obtained, and not the isomeric 7-methyl guanine. Since, however, 7-methyl guanine is formed the explanation of the reaction seems to be in the fission of the ring between positions 1 and 6, followed by elimination of the elements of hydrochloric acid from the chlorine in position 2 and the amino-group in position 6, with consequent formation of the ring system again.

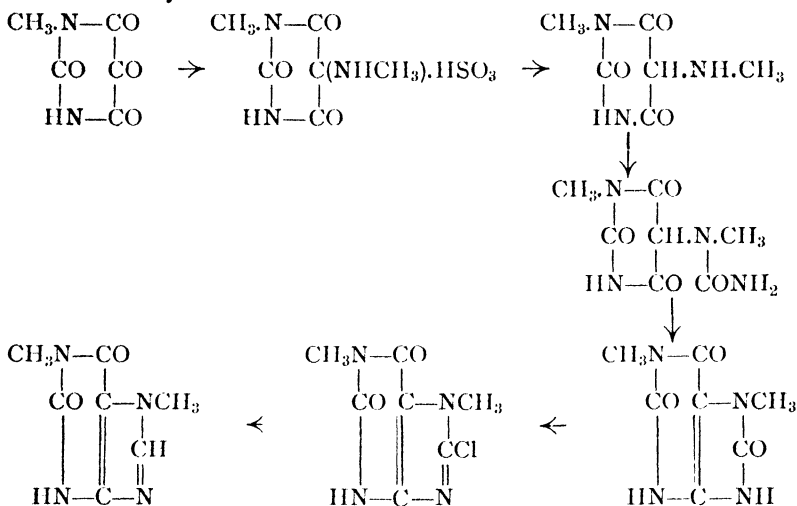


Three dimethyl-xanthines occur naturally, viz., the 1,7-dimethyl-xanthine, or paraxanthine; the 1,3-dimethyl-xanthine or theophylline, and the 3,7-dimethyl-xanthine or theobromine, all of which have been synthesized. Paraxanthine is shown to be the 1,7-dimethyl-xanthine in the following manner. 7-methyl-2,6-dichloro-purine by successive treatment with alkali and ammonia yields a 7-methylamino-hydroxy-purine, which on oxidation with chlorine yields guanidine, and consequently must possess the structural formula (I), so that the 7-methyl-hydroxy-chloro-purine must be (II). Now (II) on methylation gives a dimethyl compound which can only possess the structure shown in (III), and since this, on heating with hydrochloric acid, yields paraxanthine, the methyl groups must consequently occupy positions 1 and 7.

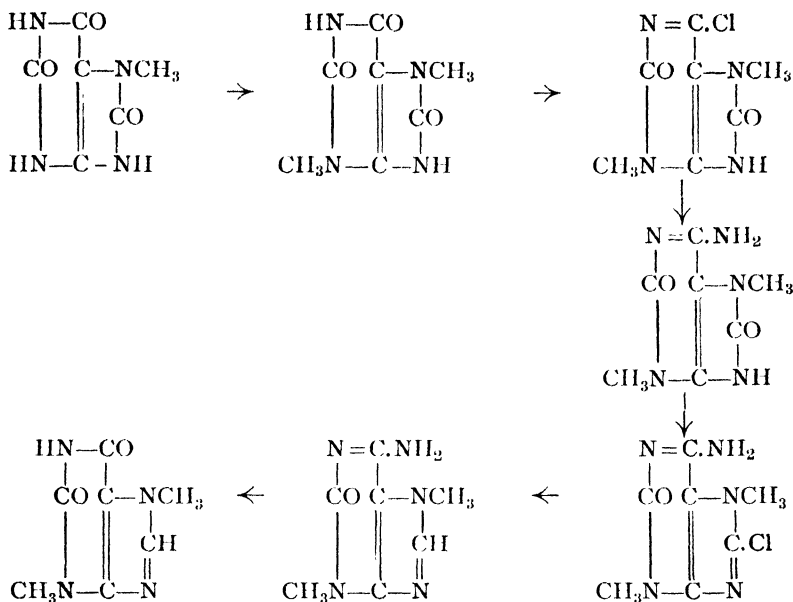


118 MODERN RESEARCH IN ORGANIC CHEMISTRY

A second synthesis took as its starting-point 1,7-dimethyl uric acid prepared from monomethyl alloxan, methylamine, and sulphurous acid, the resulting 1,7-dimethyl uramil on treatment with potassium cyanate yielding the corresponding 1,7-dimethyl pseudo-uric acid, which on dehydration was converted into 1,7-dimethyl uric acid. This acid when heated with phosphorus oxychloride yields chloroparaxanthine, from which paraxanthine is obtained by reduction.



The synthetical preparation of theophylline has been given above (p. 114), while that of theobromine is carried out as follows. Alloxan, methylamine, and sulphurous acid may be condensed together to give methyl uramil as shown in the examples above, and from this 7-methyl uric acid may be obtained in the usual way. The lead salt of this acid is then methylated, and 3,7-dimethyl uric acid is formed, which on treatment with phosphorus oxychloride is converted into 3,7-dimethyl-6-chloro-2,8 dihydroxy-purine. By the action of ammonia on this substance the amino-group is introduced in position 6, and the hydroxyl group in position 8 is then replaced by chlorine through the agency of phosphorus oxychloride. Reduction of this chloro-compound gives 3,7-dimethyl-6-amino-2-hydroxy-purine, which by nitrous acid is converted into theobromine.

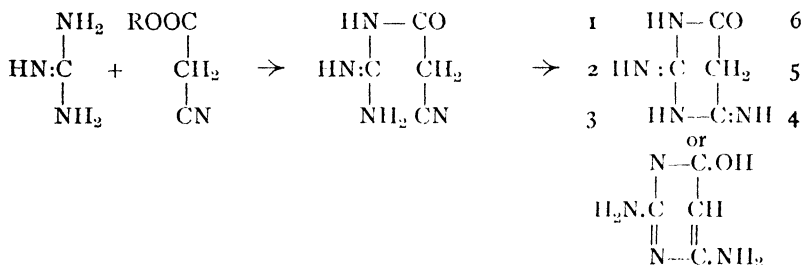


Of the other members of the series, the most important, perhaps, is sarcine (hypoxanthine) or 6-hydroxy-purine. This is obtained directly from 2.6.8-trichloro-purine, by heating it with a dilute solution of caustic potash when 6-hydroxy-2.8-dichloropurine or dichlorohypoxanthine is produced. Direct reduction converts this into sarcine. Another naturally occurring product, adenine (6-amino-purine), a decomposition product of nucleins, has also been obtained from 2.6.8-trichloropurine, which by the action of ammonia is converted into 6-amino-2.8-dichloropurine, reduction of this latter compound furnishing adenine.

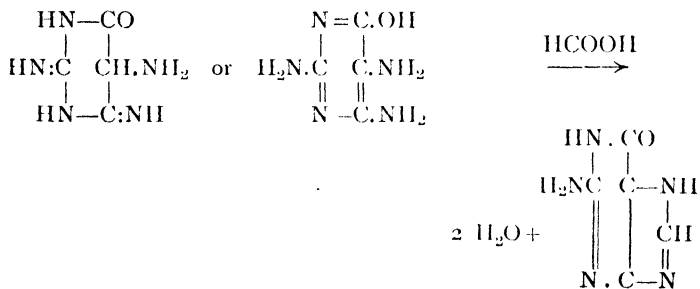
Numerous other derivatives of the previously mentioned compounds have also been synthesized by Fischer and his pupils, for the details of which the original papers should be consulted, a complete summary containing references to the earlier papers appearing in the *Berichte*, 1899, **32**, p. 435.

Thus the vexed question of the constitution of uric acid and its related compounds was solved, and apparently little more work appeared to be required in connection with these compounds when, in 1900, Traube published a complete new series

of synthetical preparations of the chief members of the group. The first paper issued, dealt only with the formation of guanine, the starting-point for which was the condensation of guanidine with cyanacetic ester, the resulting cyanacetyl guanidine on treatment with caustic soda solution undergoing ring closing, with formation of 2,4.-diamino-6-hydroxy pyrimidine.

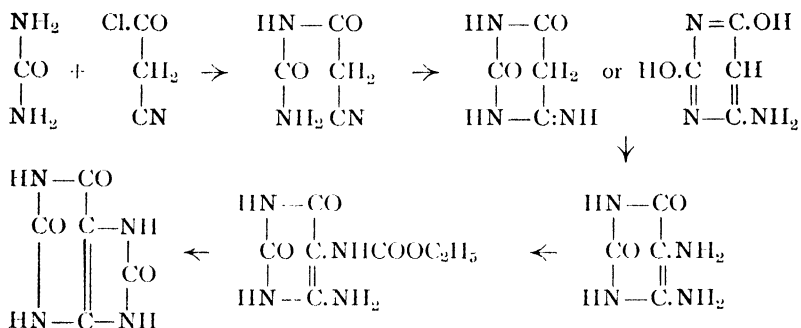


This base readily forms an isonitroso-derivative which, on reduction by ammonium sulphide, passes into 2,4,5-triamino-6-hydroxypyrimidine, and this latter on boiling with formic acid is converted into guanine, a reaction resembling the formation of the anhydro-bases, which are obtained when an orthodiamine is heated with a fatty acid.

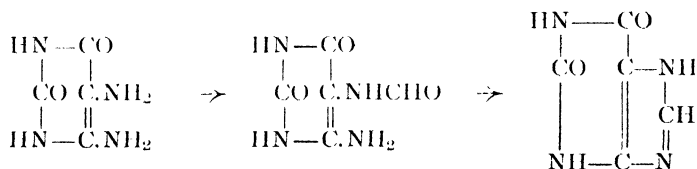


In the second paper in the same year the synthesis of uric acid, xanthine, theobromine, theophylline, and caffeine were described, the method employed being, in the first stages, substantially that given above. The starting-point in these preparations was cyanacetyl urea, which was formed by the condensation of urea and cyanacetic ester in the presence of phosphorus oxychloride. This urea derivative passes into the isomeric 4-amino-2,6-

dihydroxy pyrimidine on treatment with a forty per cent. solution of caustic soda, and from this by conversion into the isonitroso-compound and subsequent reduction with ammonium sulphide, 4,5-diamino-2,6-dihydroxypyrimidine is obtained. For the preparation of uric acid the sulphate of the base is dissolved in an excess of dilute caustic soda solution, and chlorocarbonic ester is added, the resulting urethane derivative on heating to 180-190° C. passing into uric acid by loss of the elements of alcohol.

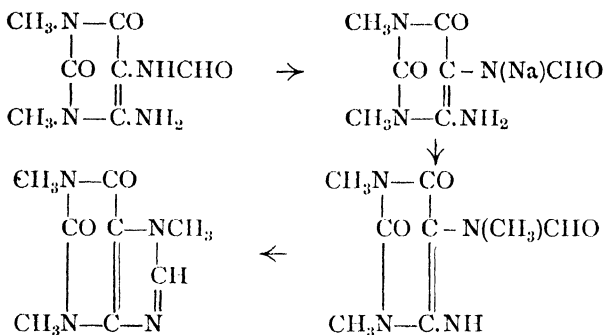


If xanthine be required, the diamino-hydroxy-pyrimidine is converted into its formyl derivative, the sodium salt of which on heating to 220° C. loses one molecule of water and passes into sodium xanthine.

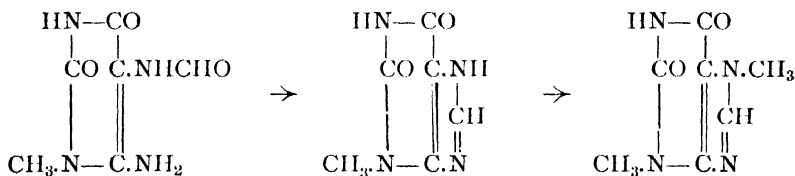


Theophylline is obtained in a precisely similar manner, starting out from symmetrical dimethyl urea and cyanacetyl chloride; the scheme of operations being identical with that used in the synthesis of xanthine. For the preparation of caffeine the method is again similar as far as the formation of the formyl derivative of 1,3 dimethyl-4,5-diamino-2,6-dioxypyrimidine, and here an

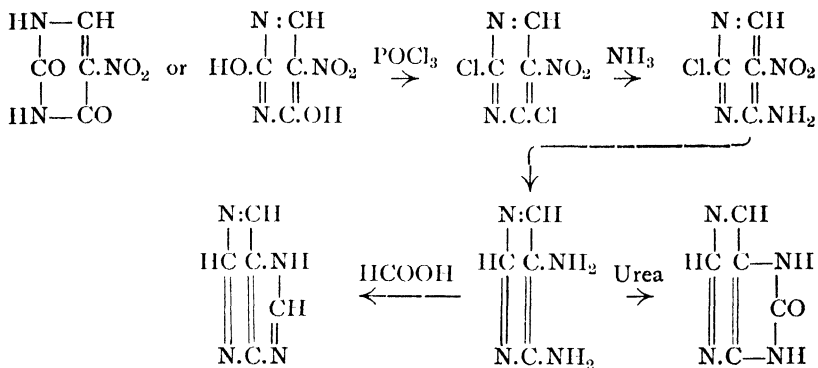
ingenious method is used for introducing the third methyl group. The group $\begin{array}{c} \diagup \\ \text{C.NH.CHO} \\ \diagdown \end{array}$ on, heating with an alcoholic solution of sodium ethoxide, passes into $\begin{array}{c} \diagup \\ \text{C.N.Na.CHO} \\ \diagdown \end{array}$, and this resulting sodium salt when heated with methyl iodide yields caffeine.



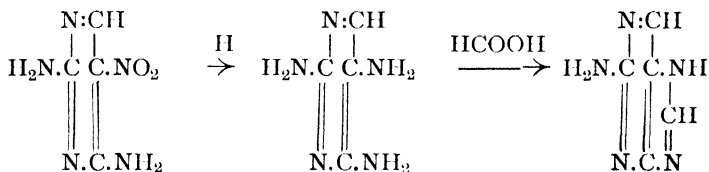
Theobromine is prepared in a similar way from 3-methyl-4,5-diamino-2,6-dioxypyrimidine, the starting out materials for which are monomethyl urea and cyanacetyl chloride. The formyl derivative of the pyrimidine, on heating to 220°C ., is transformed into 3-methyl xanthine, methylation of which in slightly alkaline solution, at 80°C ., yields theobromine—



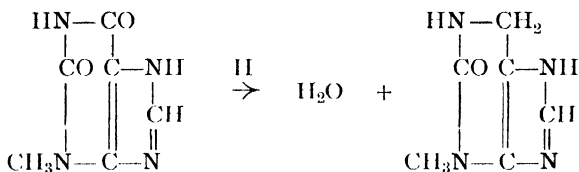
As a further contribution to the synthetical preparations in the group, Oskar Isay has recently (1906) shown how various purine derivatives may be obtained from nitro-uracils. 5-nitro-uracil, on treatment with phosphorus oxychloride, is converted into 2,4-dichloro-5-nitropyrimidine, which, in contact with *cold* ammonia, passes into 2-chloro-4-amino-5-nitropyrimidine, and from this by reduction 4,5-diamino pyrimidine is obtained. This base when heated with formic acid yields purine itself: if acetic acid be employed an 8-methyl purine results, and if it be heated with urea, 8-oxypurine is formed.



If, however, the dichloro-nitropyrimidine be brought into contact with warm ammonia, both the chlorine atoms are replaced by amino groups, and the dinitro-amino pyrimidine may then be reduced to a triamino-pyrimidine, which readily condenses with formic acid to yield 2-amino purine or iso-adenine.



The electrolytic reduction of purine derivatives has been studied by Tafel and his pupils, who find that if the reduction be carried out in sulphuric acid solution, xanthine and its homologues unite with four atoms of hydrogen, eliminating water and yielding desoxy-compounds of basic character; thus from 3-methyl xanthine, 3-methyl desoxyxanthine is obtained.



Uric acid, however, requires six atoms of hydrogen per molecule of acid, and gives purone, $\text{C}_5\text{H}_8\text{N}_2\text{O}_4$, as a product; and it was shown that it must be the $>\text{CO}$ group in position 6 which has

been reduced to a $>CH_2$ group with simultaneous addition of a hydrogen atom at 4 and 5, because on hydrolysis with caustic baryta one molecule of purone gives rise to two molecules of urea in the form of its decomposition products, carbon dioxide and ammonia, which can only be the case if the $>CO$ groups in positions 2 and 8 are unattacked.

It is found necessary in the above reduction processes to employ cathodes of very pure lead (those actually used not containing more than 0.015 per cent. of foreign metals) since impurities in the electrodes diminish the yield of reduction product, the cause being that hydrogen is only evolved by the passage of the electric current through sulphuric acid when the potential difference between the electrodes reaches a certain value. This value is a minimum for platinum electrodes, but is much greater for lead electrodes, that is, a supertension is necessary before the hydrogen is evolved when lead electrodes are used, and as the difference of potential affects the energy with which the discharged ions can react, it is found that reduction processes which cannot be carried out by other methods are possible where such a supertension exists.

BIBLIOGRAPHY

- E. Fischer. A complete summary of Fischer's work is given in *Ber.*, 1899, **32**, 435, whilst all the original papers have been gathered together and published in book form under the title "Untersuchungen in die Puringruppe."
- Liebig and Wöhler, *Ann.* 1838, **26**, 241.
- Hartley, *Journ. Chem. Soc.* 1905, **87**, 1794.
- Fittig, *Traite d. Chim. organique*, p. 324.
- Medicus, *Ann.* 1875, **175**, 230.
- Horbaczewski, *Monats.* 1882, **3**, 796 ; 1885, **6**, 356.
- Behrend and Roosen, *Ann.* 1889, **251**, 235.
- Traube, *Ber.* 1900, **33**, 1371, 3035.
- Tafel, *Ber.* 1900, **33**, 2209 ; 1901, **34**, 144, 258, 279, 1165, 1170 ; 1907, **40**, 3743, 3752.

CHAPTER IV

THE ALKALOIDS

THE term alkaloid, in its widest sense, was first applied to all nitrogenous basic compounds present in plants, or which were derived from plant tissues by various extraction operations, and thus such diverse substances as methylamine, asparagine, caffeine, morphine, etc., were included in the one main group. But with the development of synthetic organic chemistry a more restricted use of the term was adopted, and in 1880 Königs suggested that it should be reserved for those particular members which were derived from pyridine. However, with the increasing knowledge of the constitution of these substances, which has been largely extended in recent years, it has been shown that Königs' classification is not comprehensive enough, and the term is now more generally extended to include those nitrogenous basic constituents of plants which may be considered as derived from pyridine, quinoline, and isoquinoline, together with those of unknown constitution.

The alkaloids are found widely distributed in the vegetable kingdom, practically all being found in dicotyledonous plants, many being found to a large extent in certain particular plant families, such as the Solanaceæ and Papaveraceæ, whilst other families, such as the Labiateæ and Rosaceæ, have not as yet been found to contain any alkaloids. They do not as a rule exist in the free state, but are generally found as salts of various organic acids, such, for example, as malic acid, citric acid, tannic acid, quinic acid (which usually accompanies the cinchona alkaloids), meconic acid (usually found with the opium alkaloids), and aconitic acid. Most alkaloids are solids containing carbon, hydrogen, nitrogen, and oxygen, and are crystalline and non-volatile; coniine, nicotine, and sparteine, on the other hand,

contain carbon, hydrogen, and nitrogen only, and are volatile liquids. Almost all are optically active and lævo-rotatory. They have an alkaline reaction in the majority of cases, and a bitter taste. Most alkaloids are insoluble, or only very slightly soluble, in water, but are readily soluble in alcohol, and less readily in ether and chloroform. Primary bases have not been met with among the alkaloids (using the term in its restricted sense) and only a few secondary bases are known (the most important being coniine). The majority are tertiary bases, the nitrogen atom being bound very tightly in the molecule, since it forms part of a ring system and is not a constituent of an open chain. The only amines yet obtained in the decomposition of alkaloids are the methylamines, so that apparently the methyl group is the only alkyl group which is known to be attached to the nitrogen atom in various alkaloids.

Some substances precipitate many of the alkaloids from their aqueous or acid solutions, the more important of such general alkaloid reagents being

Sonnenschein's reagent (sodium phosphomolybdate), which in the presence of nitric acid gives a yellowish-white flocculent precipitate, from which the alkaloid may be recovered by heating with barium carbonate and water. Scheibler recommends phosphotungstic acid similarly.

Mayer's solution of potassium mercuric iodide, which gives yellowish-white precipitates with most alkaloids, the precipitates being insoluble in acids and in dilute alkalies. The alkaloid may be recovered from the precipitate by digestion with stannous chloride and caustic soda.

Potassium bismuthous iodide, which gives precipitates of the general type $3NR_1I_2BiI_3$, and is generally used in the presence of dilute sulphuric acid or of hydriodic acid.

Picric acid precipitates many. *Iodine* (in potassium iodide solution) in some cases gives brown precipitates of periodides, preferably in acid solution. *Tannic acid* precipitates most alkaloids. The chlorides of gold and platinum also yield precipitates with the alkaloids.

In extracting alkaloids from plants, these are lixiviated by

means of acidified water in a percolator, the solution rendered alkaline, and volatile alkaloids distilled over in a current of steam. The fixed alkaloids which are precipitated on the addition of alkali can be extracted from other substances present by the use of various solvents. Or the infusion of the alkaloid may be treated successively with lead acetate, basic lead acetate, and ammonia, the excess of lead removed by sulphuretted hydrogen, and the alkaloid precipitated by one of the special reagents mentioned above. The free base may then be recovered by a suitable decomposition of the precipitate so obtained.

The alkaloids considered in the following pages may be approximately classified as follows:—

Pyridine derivatives:—Arecaidine, trigonelline, piperine, coniine, nicotine.

Quinoline derivatives:—Strychnine, brucine, cinchonine, and quinine.

Isoquinoline derivatives:—Berberine, hydrastine, laudanose, narcotine, papaverine, codeine, morphine, thebaine, and corydaline.

Pyrrolidine derivatives:—Atropine, cocaine.

In investigations on the constitution of the alkaloids, certain main principles are usually followed out; thus hydroxylic groups are recognized by conversion into acetyl or benzoyl derivatives, and if in addition the group be phenolic, it is shown by the fact that the compound in question is readily soluble in caustic alkali, and will also yield alkyl ethers.

Methoxyl groups are readily recognized by the Zeisel reaction, in which the substance is heated with fuming hydriodic acid to about 140° C., and the methyl group is eliminated as methyl iodide.

Oxygen again, in the form of a carboxyl group, may be identified by the readiness with which the compound will esterify, and if present as an ester may be detected by hydrolysis of the parent substance into acid and alcohol. The determination of the conditions under which nitrogen is present in the molecule is, as a rule, a matter of more difficulty, distillation with caustic

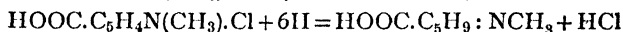
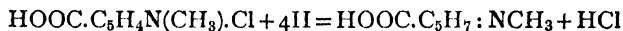
alkali yielding in some cases the various methylamines, and so pointing to the presence of nitrogen combined with one or more methyl groups. A more elaborate process consists in the exhaustive methylation process of Hofmann, by which the compound is converted into the hydroxide of a quaternary base and then heated alone or with caustic alkali, when the nitrogen is eliminated as a tertiary amine and an unsaturated hydrocarbon is formed, from which it is often possible to arrive at some ideas as to the structure of the original base (see coniine). Oxidation methods are also frequently used, and lead to the formation of substances of simpler nature from which ideas of structure are obtained. Distillation over zinc dust has been resorted to in some cases, and has led to the formation of pyridine and its homologues, but such drastic reactions as this are, as a rule, not of much use as aids to the determination of structure, since they lead to deep-seated changes which cannot be successfully traced back, in the majority of instances.

Pyridine Group.—*Arecaidine*, $C_7H_{11}O_2N$, was first isolated in 1888-1891 by Jahns from the betel-nut, in which it occurs in combination chiefly with tannic acid, three other alkaloids, namely, arecaine, $C_7H_{11}O_2N$, guvacine, $C_6H_9O_2N$, and arecoline, $C_8H_{13}O_2N$, being also present in the nuts. It crystallizes in plates which contain one molecule of water of crystallization, and in the anhydrous state melts at $223^\circ C$. It possesses an acidic character, since it may be esterified, a fact pointing to the presence of the carboxyl group. It is also of a basic character. The nitrogen atom is attached directly to a methyl group, since when heated with caustic baryta or with lime, methylamine is eliminated, the presence of such a methyl group being also demonstrated by the fact that when the alkaloid is heated under pressure with hydrochloric acid, methyl chloride is obtained. Again, on reduction, the alkaloid combines with two atoms of hydrogen and forms a dihydro-arecaidine, which shows that the grouping $C=C$ exists in the molecule, and thus in all probability it may be considered as

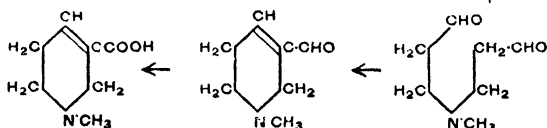
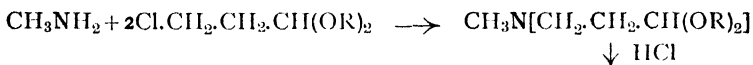


that is, as the carboxylic acid of a methyl piperidine, a result

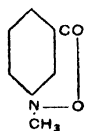
confirmed by the fact that both arecaidine and dihydro-arecaidine are obtained when the methyl chloride of nicotinic acid is reduced by tin and hydrochloric acid.



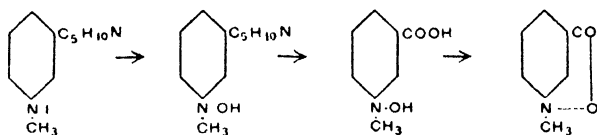
The structure of the alkaloid was definitely settled in 1908 by Wöhl, who prepared it synthetically by the following method. The acetal of β -chloropropionic aldehyde, on condensation with methylamine, yields a tertiary base which, under the action of cold hydrochloric acid passes into the aldehyde of a methyl piperidine carboxylic acid. The aldehyde is then converted into its oxime, and the oxime into the nitrile by dehydration, hydrolysis of the nitrile giving rise to the carboxylic acid, identical with arecaidine.



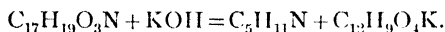
Trigonelline, $\text{C}_7\text{H}_7\text{O}_2\text{N}$, was also first isolated by Jahns in 1885 from the seeds of *Trigonella*, and has since been recognized as occurring in flax, in oats, and in the seeds of *Strophantus hispidus* and *S. Kombé*, where it is found associated with strophanthin and choline. *Trigonelline* is readily soluble in water. When heated with baryta water it yields methylamine, a reaction showing that the group $-\text{N.CH}_3$ is present in the molecule, and again, when subjected to the action of hydrochloric acid at 260°C ., it is converted into methyl chloride and nicotinic acid; these reactions being identical with those of the methyl betaine of nicotinic acid, which was prepared by Hantzsch before Jahns had isolated *trigonelline*. Thus the alkaloid possesses the following constitution:—



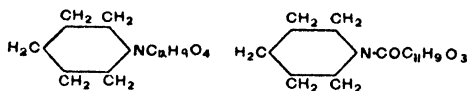
further confirmation of which was given by Pictet and Genequand in 1897, who found that when nicotine iso-methiodide was converted into the hydroxide, and the latter oxidized by potassium permanganate in aqueous solution, it was immediately converted into the methyl betaine of nicotinic acid, identical in every respect with trigonelline.



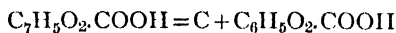
Piperine, $C_{17}H_{19}O_3N$, is found in the fruits of *Piper nigrum* and *Piper longum*. It crystallizes in prisms, is inactive, and melts at $129^\circ C$. Practically the first step taken to elucidate the constitution of this alkaloid was that due to von Babo and Keller, who showed that on hydrolysis with alcoholic potash it gave piperidine (hexahydropyridine) and piperic acid.



Hence one has in piperine the grouping

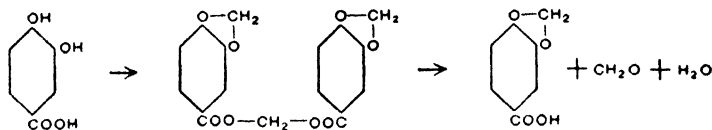


and since the constitution of piperidine is known (from its relation to pyridine), it only remains to determine that of piperic acid. This acid, on oxidation with potassium permanganate, yields piperonal, $C_7H_5O_2 \cdot CHO$, and piperonylic acid, $C_7H_5O_2 \cdot COOH$. It is also an unsaturated acid, since it readily takes up four atoms of bromine, and on reduction combines with four atoms of hydrogen. Piperonylic acid, on the other hand, is a saturated monobasic acid, which, when heated with water under pressure to about $200^\circ C$., is decomposed into protocatechuic acid, $C_7H_6O_4$, and carbon.

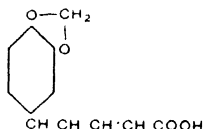


This reaction points to piperonylic acid as being a derivative of protocatechuic acid, confirmation of which fact was given when

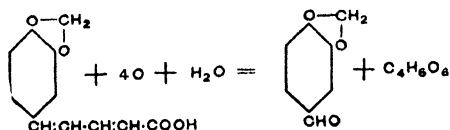
Fittig and Remsen synthesized it by the action of methylene iodide upon protocatechuic acid in the presence of potassium hydroxide,



and thus piperonylic acid appears as the methylene ether of protocatechuic acid. Now, since piperonylic acid possesses the empirical formula $C_7H_5O_2.COOH$, and piperic acid is $C_{11}H_9O_2.COOH$, the difference between the two compounds in question is that of a group C_4H_4 , and this must of necessity lie between the phenyl group in the piperonylic acid and the carboxyl group, for were it in any other position it would mean that another side chain would be present in the piperic acid molecule, and, consequently, on oxidation piperic acid would yield at least a dibasic acid, whereas only the monobasic piperonylic acid is formed. Hence piperic acid must possess the following constitution:—

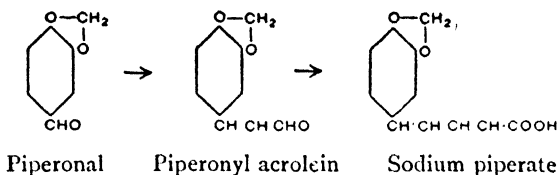


This constitutional formula has received further confirmation from two different sources, firstly, from Dœbner's observation that the acid, on oxidation by potassium permanganate, yields piperonal and racemic acid,

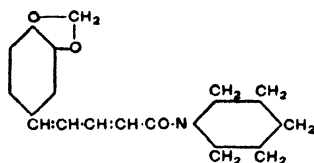


and, secondly, by the synthesis of piperic acid from piperonal by Ladenburg and Scholtz as follows. Piperonal in the presence of caustic alkalis condenses directly with acetaldehyde, water being eliminated from the reacting components and the un-

saturated piperonylacrolein being formed. This aldehyde, on heating with fused sodium acetate and acetic anhydride, behaves like benzaldehyde, that is, it undergoes the Perkin reaction, and the resulting substance obtained is the sodium salt of piperic acid

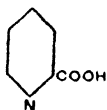


Thus, knowing the constitution of the products of fission of piperine, which are evidently produced by a reaction similar to that by which acetanilide is decomposed into acetic acid and aniline, it would seem most probable that piperine should be represented as

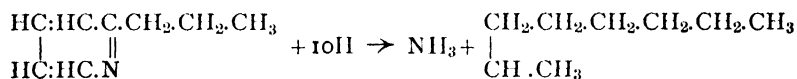


a result which is further confirmed by Rugheimers' synthesis of the alkaloid from piperidine and the chloride of piperic acid.

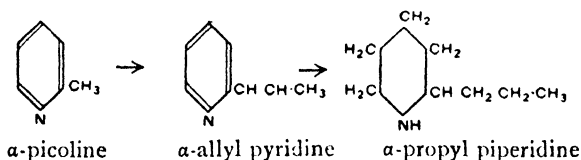
Coniine, $C_8H_{17}N$, is found, together with γ -coniine, $C_8H_{15}N$, and conhydrine, $C_8H_{17}ON$, in the hemlock. It is one of the few alkaloids which are liquids. It is a colourless oil, boiling at $166^\circ C.$, and in solution is dextro-rotatory. It behaves as a secondary base. The first ideas as to the constitution of this substance are due to the researches of Hofmann, who showed that when the alkaloid is distilled over zinc chloride, a basic compound of formula $C_8H_{11}N$ (*conyryne*) is produced, together with hydrogen. Now, since the oxidation of conyryne yields picolinic acid, a monobasic acid of the following structure :—



it follows that conyryne must be a pyridine derivative containing *one* side chain in the α -position, and it is consequently to be regarded as an α -propyl pyridine, $C_5H_4N(C_3H_7)$. The propyl group is the *normal* propyl group, because in the first place α -isopropyl pyridine, which is obtained on heating pyridine and isopropyl iodide to $290^\circ C.$, is not identical with conyryne, and, secondly, on reduction with fuming hydriodic acid at high temperature, conyryne is converted into normal octane (and ammonia), a result that would not be obtainable if the isopropyl group were present.

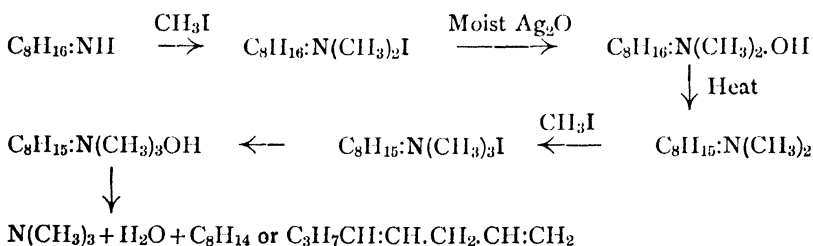


Since conyryne, $C_8H_{11}N$, and coniine, $C_8H_{17}N$, differ by a matter of six hydrogen atoms, it therefore appears to be probable that coniine is a hexahydro-conyryne, that is, a hexahydro- α -propyl pyridine or α -propyl piperidine, a fact confirmed by the synthesis of the alkaloid by Ladenburg from α -picoline as follows. Paraldehyde, when heated with α -picoline to high temperature, is partially converted into α -allyl pyridine, the reduction of the latter with sodium and alcohol yielding α -propyl piperidine.



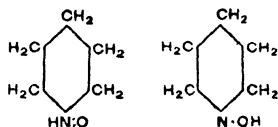
The base so formed resembles natural coniine in all respects except that it is optically inactive, whereas the natural base is dextro-rotatory. The artificial coniine is a racemic mixture, and may be split into its active components by fractional crystallization of the bitartrate of the base, but it is only quite recently that Ladenburg has succeeded in getting the rotation of the synthetic *d*-form to agree with that of the natural *d*-coniine, it being necessary to heat the synthetic product for many hours at $290^\circ C.$ in order to get pure *d*-coniine.

Coniine possesses a certain amount of historical importance, as it was the first alkaloid prepared synthetically. Numerous decomposition products of coniine have been obtained at different times in the hope of elucidating its structure, and of these, perhaps, the most important is the hydrocarbon *conylene*, C_8H_{14} , which was first obtained by Wertheim on heating nitroso-coniine, $C_8H_{16}N.NO$, with phosphoric anhydride. It is also a product of the decomposition of the alkaloid in the destructive methylation process. The alkaloid, on treatment with methyl iodide, yields the methiodide of methyl coniine, from which, by the action of moist silver oxide, the corresponding hydroxide is obtained. On distillation of this hydroxide, the ring system is broken, water is eliminated, and the so-called *dimethylconiine* is formed. This tertiary base readily forms an ammonium salt by direct union with methyl iodide, the hydroxide of which (obtained as before by the action of moist silver oxide on the iodide) on distillation, decomposes, with elimination of the nitrogen atom, as trimethylamine, and the formation of the hydrocarbon conylene.

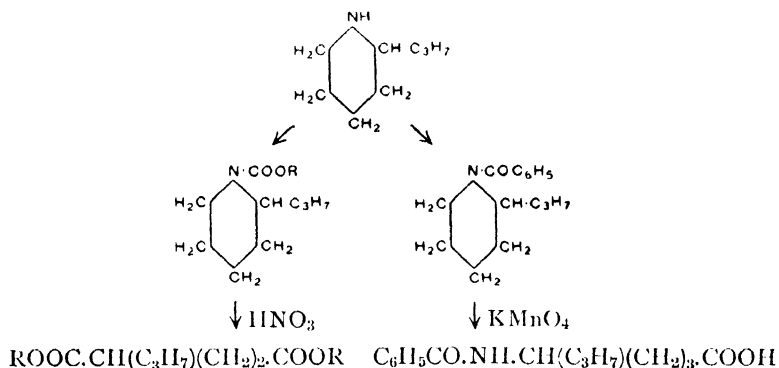


Various oxidation products may be obtained from coniine by working under different conditions, thus with strong oxidizing agents, such as chromic acid, nitric acid, etc., ammonia and normal butyric acid are produced, whilst Wolfenstein, by the action of hydrogen peroxide (in 3% solution), obtained propyl- δ -aminovalerylaldehyde, $H_2N.CH(C_3H_7).CH_2.CH_2.CH_2.CHO$, a coniceine, $C_8H_{15}N$, and butyryl butyric acid, $C_3H_7.CO.CH_2.CH_2.CH_2.COOH$. Possibly too much faith must not be placed on these reactions, since by a similar oxidation of piperidine (of which

coniine is only a *n*-propyl derivative) Wolffenstein obtained what he at first considered to be a δ -aminovalerylaldehyde, $\text{H}_2\text{N}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CHO}$, a view which he modified some few years later, the supposed aldehyde agreeing more nearly with the properties of a piperidinium oxide or oxime.



Other oxidation products have been obtained by Schotten and Baum, the nitrogen atom in the ring being first protected by converting the coniine into its benzoyl derivative; or into a urethane (by the action of chloro-carbonic ester), the ring system then on oxidation, in the first case by the action of nitric acid, and in the second case by potassium permanganate, being broken between the nitrogen atom and a neighbouring carbon atom, and yielding open chain compounds.

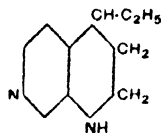


Nicotine, $\text{C}_{10}\text{H}_{14}\text{N}_2$.—Previous to 1901 it was supposed that nicotine was the only alkaloid existing in the leaves of the tobacco plant, but in that year Pictet and Rotschy showed that three other alkaloids, namely, nicotimine, $\text{C}_{10}\text{H}_{14}\text{N}_2$, nicotine, $\text{C}_{10}\text{H}_{12}\text{N}_2$, and nicotelline, $\text{C}_{10}\text{H}_8\text{N}_2$, were also present,

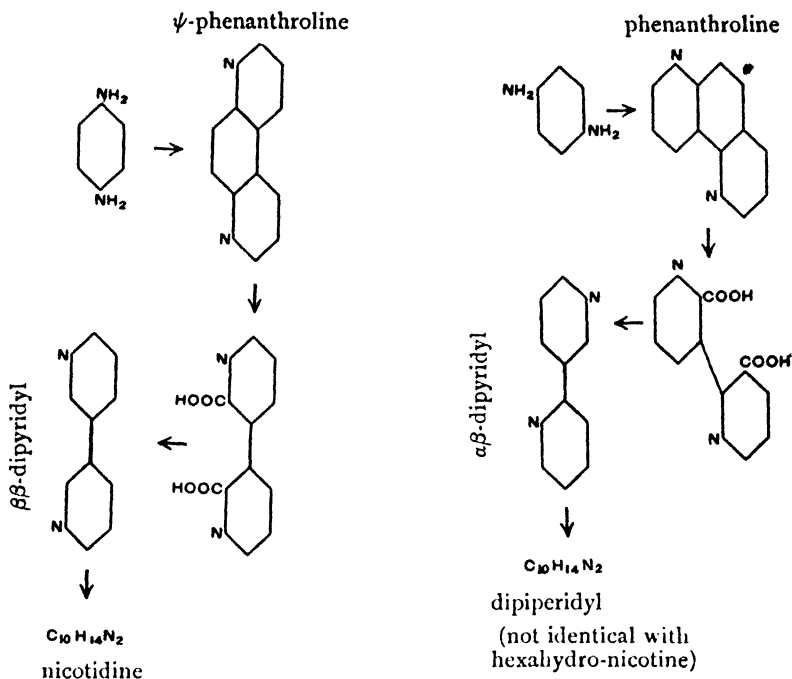
although only in relatively small quantities, since on working up 10 kilos of tobacco extract the authors obtained about 1 kilo of nicotine, 20 grams of nicotine, 5 grams of nicotimine, and 1 gram of nicotelline.

Nicotine may be separated from the other members of the group by distillation of its aqueous alkaline solution in a current of steam. It is, when freshly prepared, a colourless oil of characteristic odour, boiling at 245°C . It behaves as an unsaturated di-acid base. The free alkaloid is strongly lævo-rotatory, its salts, however, are dextro-rotatory. It is a very active poison. On oxidation it yields nicotinic acid, $\text{C}_5\text{H}_4\text{N}.\text{COOH}$ (pyridine- β -carboxylic acid), and is thus in all probability to be considered as a pyridine derivative containing the complex $-\text{C}_5\text{H}_{10}\text{N}$ in the β -position.

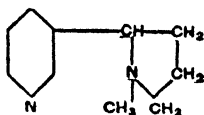
One of the earliest structural formulæ given to nicotine was that of Etard, namely,



which, however, must be ruled out as inadmissible since such a compound could not, under any circumstances, be oxidized to nicotinic acid. Skraup and Vortmann then assumed the possibility of a dipyridyl structure for nicotine, and tried to synthesize the alkaloid as follows. By condensation of meta-phenylene diamine with glycerine and an oxidizing agent, phenanthroline is formed, which, on oxidation yields $\alpha\beta$ -dipyridyl dicarboxylic acid. This acid on elimination of carbon dioxide from the carboxyl groups is converted into $\alpha\beta$ -dipyridyl, para-phenylene diamine by the same treatment yielding $\beta\beta$ -dipyridyl. The $\beta\beta$ -derivative was then reduced in the hope of obtaining nicotine, but the compound obtained $\text{C}_{10}\text{H}_{14}\text{N}_2$ (pyridylpiperidine) was not identical with the alkaloid.

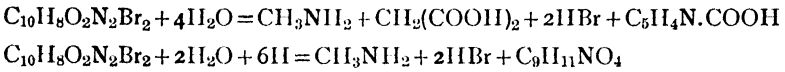


Thus it seems apparent that the ring system attached to the pyridine nucleus is not a six-membered system, and Pinner assumed the possibility of a five-membered ring being present, and assigned to the alkaloid the following constitution:—

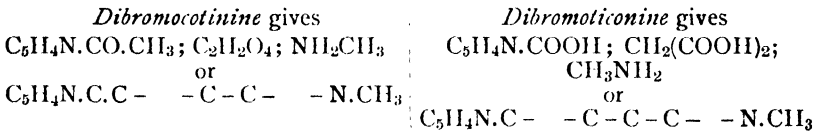


which is that of a β -pyridyl-N-methyl pyrrolidine. The first step taken by Pinner was to oxidize the alkaloid with hydrogen peroxide, and in this way an oxynicotine was obtained of composition $C_{10}H_{14}ON_2$, but no definite ideas as to its structure could be obtained since its decomposition products could not be obtained in an analyzable condition. Again, nicotine could not be regarded as an imide base since acetyl and benzoyl derivatives were not obtainable, although Etard had earlier observed the existence of such derivatives. This discrepancy was explained

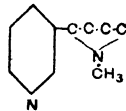
In a similar manner dibromoticonine when heated with baryta yields methylamine, nicotinic acid, and malonic acid, whilst if heated with alkalis in the presence of zinc dust yields methylamine and a derivative $C_9H_{11}O_4N$, which possesses the characteristic properties of an acid.



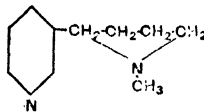
Thus we now have that



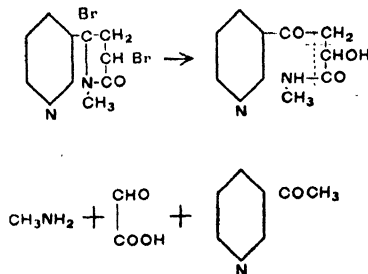
which give for the nucleus of the alkaloid the grouping



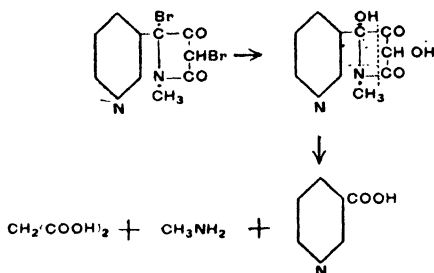
and nicotine is therefore most probably to be represented as



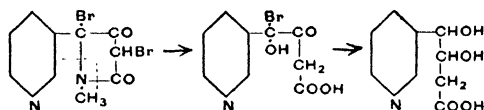
Dibromocotinine is probably a compound of an acid amide type, its structure and decompositions being shown below.



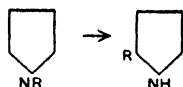
Dibromoticonine similarly is to be represented as



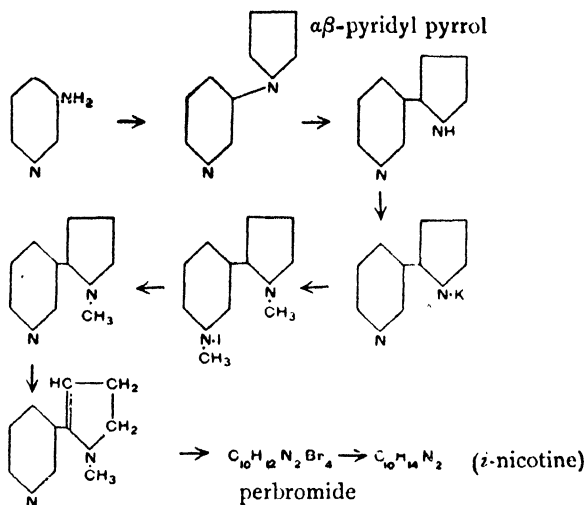
The acid $\text{C}_9\text{H}_{11}\text{NO}_4$ is a pyridyl- $\beta\gamma$ -dihydroxybutyric acid, and is formed from dibromoticonine as shown in the annexed scheme.



The structure given above by Pinner for nicotine has received confirmation at the hands of Pictet, who has succeeded in synthesizing the alkaloid in the following manner. The mucate of β -aminopyridine on dry distillation is converted into *N*- β -pyridyl pyrrol, which, when its vapours are passed through a red-hot tube, yields what must be $\alpha\beta$ -pyridyl pyrrol since Ciamician has shown that *N*-alkyl pyrrols by such treatment are transformed into α -alkyl derivatives.



The potassium salt of the $\alpha\beta$ -pyridyl pyrrol when heated with methyl iodide yields the methiodide of *N*-methyl- $\alpha\beta$ -pyridyl pyrrol, from which the free base is obtained by distillation over lime. Reduction of this base by means of tin and hydrochloric acid yields a dihydronicotyrine, and this by the action of bromine is transformed into a perbromide. By further reduction of the perbromide *i*-nicotine is obtained.



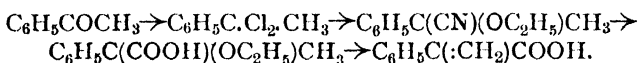
The *z*-nicotine may be resolved by repeated fractional crystallization of the salt it forms with *d*-tartaric acid.

Pyrrolidine Group.—The most important derivatives of this group are *atropine*, $\text{C}_{17}\text{H}_{23}\text{O}_3\text{N}$, which is found in the roots of the belladonna (*Atropa belladonna*), and *cocaine*, $\text{C}_{17}\text{H}_{21}\text{O}_4\text{N}$, found in the leaves of *Erythroxylon Coca*.

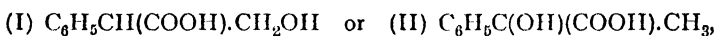
Atropine crystallizes in prisms, and is a strong poison. Its solutions have no action on polarized light. It behaves as a tertiary base and also as an ester, since Lossen showed that on hydrolysis it decomposed into tropic acid and tropine, $\text{C}_{17}\text{H}_{23}\text{O}_3\text{N} + \text{H}_2\text{O} = \text{C}_9\text{H}_{10}\text{O}_3 + \text{C}_8\text{H}_{15}\text{ON}$. Tropic acid also by further heating with baryta water for a considerable time loses a molecule of water, and yields atropic acid, $\text{C}_9\text{H}_8\text{O}_2$, and it is from a study of these products that the structure of the alkaloid has been developed. The constitution of atropic acid (an isomer of cinnamic acid) is shown by its synthesis by Ladenburg and Rügheimer from acetophenone. This ketone is converted in the normal manner by phosphorus pentachloride into the keto-chloride, from which by heating with an alcoholic solution of potassium cyanide a nitrile is formed. This nitrile, on hydrolysis with baryta, is converted into an acid, and by heating the acid,

142 MODERN RESEARCH IN ORGANIC CHEMISTRY

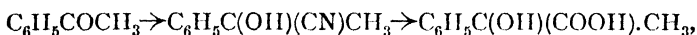
with hydrochloric acid, alcohol is eliminated and atropic acid is produced.



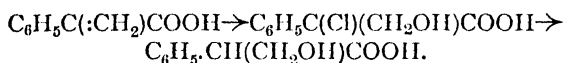
Now, seeing that tropic acid only differs from this acid by the addition of a molecule of water, it must be either



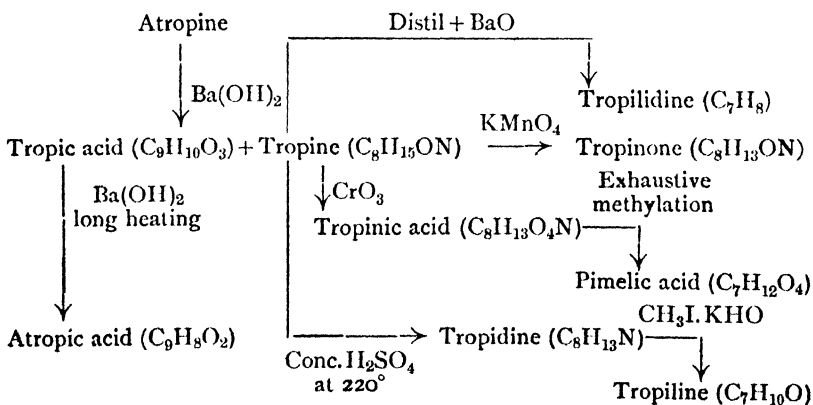
and Fittig and Wurster obtained an isomer of tropic acid (atrolactic acid) by the action of sodium carbonate on the hydrobromic acid addition product of atropic acid. The constitution of this isomer was settled by its synthesis from the cyanhydrin of acetophenone, thus—



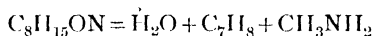
and consequently atrolactic acid is (II) and tropic acid is (I). Further confirmation of this is shown in the synthesis of the latter from the chlorhydrin of atropic acid, which by reduction with zinc and caustic alkali yields tropic acid.



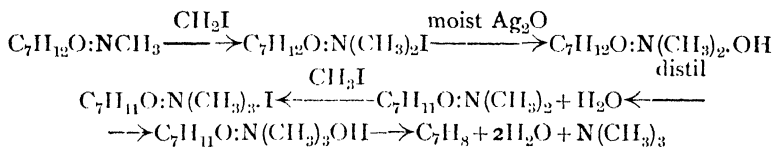
The various splitting products of atropine (derived chiefly from its derivatives tropic acid and tropine), which have been used in elucidating the structure of the alkaloid, are shown in the following chart:—



Knowing the structure of tropic acid, it only remains to determine that of tropine (the basic decomposition product of the alkaloid) in order to assign a constitution to atropine, and the earlier work in this direction was carried out by Ladenburg, who showed that tropine, which is an inactive tertiary base, possesses the character of an alcohol, since it unites with acids to form esters, and who also found that the nitrogen atom is attached to a methyl group, because on distillation of tropine with baryta, tropilidine (a hydrocarbon isomeric with toluene) and methylamine are formed—

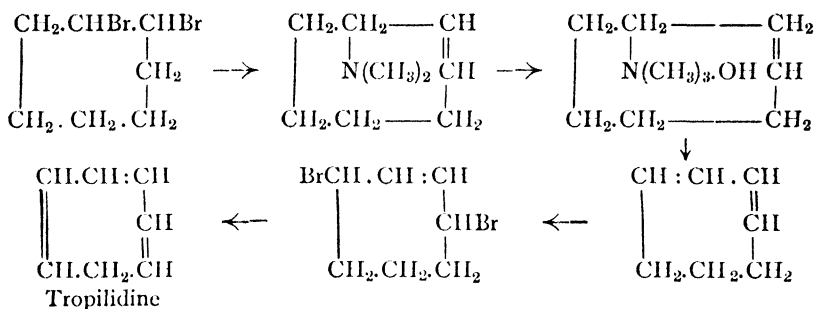


a similar result being obtained if tropine is subjected to the destructive methylation process, the nitrogen atom necessarily in this process being eliminated in the form of trimethylamine.

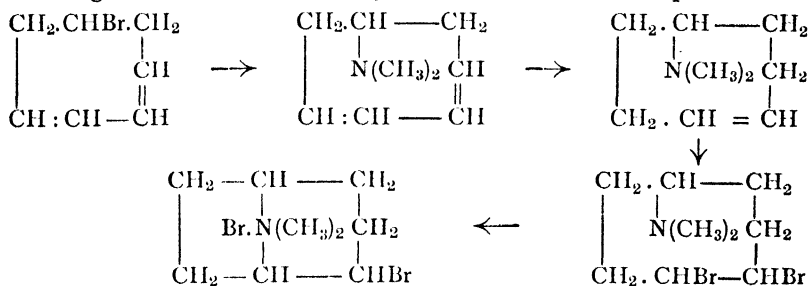


Ladenburg next developed his ideas as to structure from the non-oxygenated compound tropidine ($C_8H_{13}N$), obtained when tropine is heated with concentrated sulphuric acid, and showed that it was an unsaturated compound. This substance forms a hydrobromide, which reacts with a large excess of bromine to give $\beta\beta$ -dibromopyridine, and so it was concluded that tropidine is a partially reduced pyridine with an unsaturated side chain of two carbon atoms, the latter fact being shown by the formation of ethylene dibromide when the reaction product of bromine and tropidine hydrobromide is heated to about $170^\circ C$. The side chain was then shown to be in the α -position by the conversion of tropine into α -ethyl-pyridine by a somewhat complicated series of reactions, and Ladenburg finally concluded that tropidine and tropine possessed the following structures:—

The dibromide of this hydrocarbon when heated with dimethylamine is converted into Δ^2 -dimethylamidocycloheptene, from which by destructive methylation and distillation of the hydroxide, cycloheptadiene is obtained. Cycloheptadiene also forms a dibromide, the bromine atoms, in accordance with Thiele's observations, uniting with the carbon atoms in the 1.4 position of the conjugate system, and the dibromide, when heated with quinoline to 150-165° C., is converted into cycloheptatriene, identical with the tropilidene obtained from tropine.

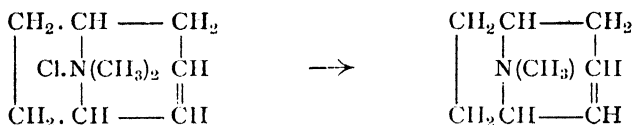


This yields a monohydrobromide, which is converted by dimethylamine into dimethylamidocycloheptadiene, reduction of the latter leading to the formation of a corresponding heptene. This substance, on treatment with bromine in hydrobromic acid solution, is converted into a dibromide which, on purification, rearranges itself into the methyl bromide of bromo-tropane.

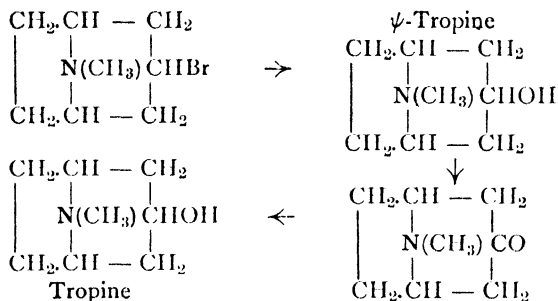


The bromide so produced is then converted into the corresponding methyl iodide of tropidine by eliminating hydrobromic acid (through the agency of sodium hydroxide), and subsequent addition of potassium iodide to the solution, to replace the bromine

atom attached to the nitrogen; and the iodide into the chloride by digestion with silver chloride, the chloride on heating losing methyl chloride and giving tropidine.



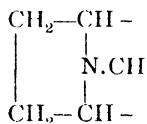
The conversion of tropidine into tropine then follows by heating tropidine hydrobromide with water or dilute sulphuric acid to 200°C ., when ψ -tropine is obtained. Oxidation of this to tropinone and subsequent reduction with zinc dust and hydriodic acid finally yielded tropine—



Cocaine, $\text{C}_{17}\text{H}_{21}\text{O}_4\text{N}$, is one of a number of alkaloids found in the leaves of *Erythroxylon coca*. It crystallizes in prisms, melting at $97\text{-}98^\circ \text{C}$., and sublimes with partial decomposition at a somewhat higher temperature. Its solutions react alkaline, and are laevo-rotatory. On hydrolysis it yields benzoyl ecgonine, $\text{C}_{16}\text{H}_{19}\text{NO}_4$, and methyl alcohol, the former product being in its turn decomposed on treatment with acids or alkalis into ecgonine and benzoic acid. Thus it appears that cocaine is an ester, and may be considered as a methyl benzoyl ecgonine, $\text{C}_8\text{H}_{13}\text{N}(\text{O} \cdot \text{COC}_6\text{H}_5)\text{COOCH}_3$. It is also a tertiary base, and contains an $-\text{N} \cdot \text{CH}_3$ group, since Merck has stated that ecgonine which may be considered as the parent substance of cocaine, when distilled over nearly dry barium hydroxide, yields methylamine.

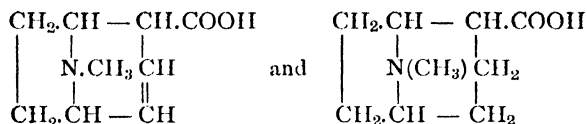
Since hydrolysis of cocaine ultimately leads to ecgonine, it

suffices to determine the structure of the latter compound in order to arrive at the constitution of the alkaloid. This has been arrived at by showing the relation that exists between ecgonine and tropine. Ecgonine has the characters of an acid, a base and an alcohol, since it can form esters, quaternary ammonium salts, and acyl derivatives, consequently it may be represented as $N:C_8H_{13}(OH)COOH$, and as it also contains the $-N.CH_3$ group, as mentioned above, this formula may be developed into $CH_3.N:C_7H_{10}(OH).COOH$. The relation between ecgonine and tropine was first shown in the following manner. Ecgonine, when heated with phosphorus oxychloride or pentachloride, loses a molecule of water and passes into *anhydroecgonine*, $C_9H_{13}O_2N$, which, when heated under pressure with hydrochloric acid to 280° , decomposes into carbon dioxide and tropidine, $C_8H_{13}N$; and consequently anhydroecgonine is to be considered as a tropidine carboxylic acid. Further confirmation of the relation existing between ecgonine and tropine is given by Willstätter's observations that both substances yield the same oxidation products, namely tropinone and tropinic acid. Thus by comparison of the formulæ of the two compounds, viz., $C_9H_{15}O_3N$ and $C_8H_{15}ON$, it would seem that ecgonine might be considered as a carboxylic acid of tropine, with its carboxyl group attached to the carbon atom adjacent to the group $-CH.OH-$, since oxidation yields tropinic acid, a N-methyl pyrrolidine derivative, showing that the complex

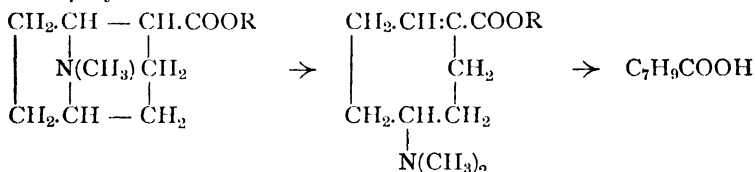


is not affected by oxidation, and that, therefore, the carboxyl group in ecgonine cannot be present in that part of the molecule.

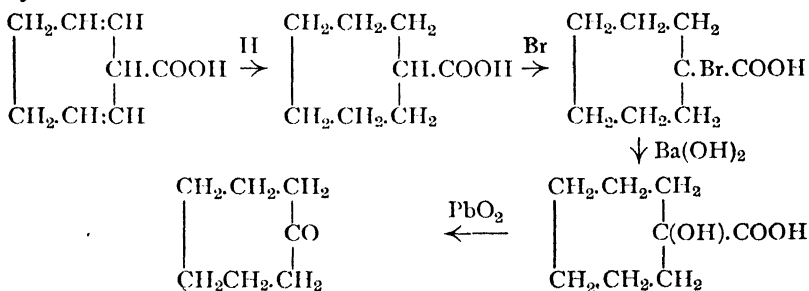
The two most important decomposition products of ecgonine are anhydroecgonine, $C_9H_{13}O_2N$, and hydroecgonidine, $C_9H_{15}O_2N$, the former, as already mentioned, being a tropidine carboxylic acid, which is converted into hydroecgonidine by reduction with sodium and amyl alcohol. Anhydroecgonine contains the carboxyl



Further confirmation of the presence of the cycloheptane ring in the ecgonine molecule was given in 1898 by Willstätter, who showed that hydroecgonidine could be broken down to suberone in the following manner. The destructive methylation of hydroecgonidine ethyl ester leads to the formation of an unsaturated nitrogen compound which, when heated with alkalis, yields an unsaturated acid, $\text{C}_7\text{H}_9\text{COOH}$.

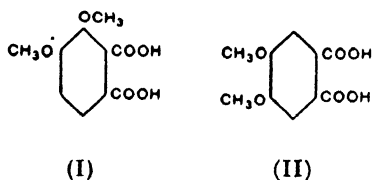


This acid on reduction passes into the saturated acid, $\text{C}_7\text{H}_{13}\text{COOH}$, which on bromination by the Hell-Volhard method, brominates in the α -position. On treatment with baryta water the bromo-acid yields two products, one arising by loss of hydrobromic acid, and consequently being an unsaturated acid, $\text{C}_7\text{H}_{11}\text{COOH}$, the other being a hydroxy-acid formed by replacement of bromine by the hydroxyl group. Oxidation of the hydroxy-acid with lead peroxide converts it into suberone, $\text{C}_7\text{H}_{12}\text{O}$, thus showing the presence of the cycloheptane ring in the ecgonine molecule. The acid, $\text{C}_7\text{H}_9\text{COOH}$, is thus a cycloheptadiene carboxylic acid, probably of the annexed structure, but the positions of the double bonds are only conjectural. The cycle of reactions is shown thus—

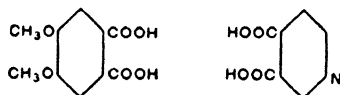


Isoquinoline Group.—This group includes principally the *opium alkaloids* obtained from the sap of various members of the Papaveraceæ; *berberine*, $C_{20}H_{17}O_4N$, and *hydrastine*, $C_{21}H_{21}O_6N$, obtained from the root of the golden seal (*Hydrastis canadensis*), and *corydaline*, $C_{22}H_{27}O_4N$, obtained from the root of *Corydalis cara*. The opium alkaloids may for convenience be divided into two groups, namely, the papaverine group, containing *papaverine*, $C_{20}H_{21}O_4N$, *laudanoline*, $C_{21}H_{27}O_4N$, and *narcotine*, $C_{22}H_{29}O_7N$, as members which have been most thoroughly investigated; and the morphine group, containing *morphine*, $C_{17}H_{19}O_3N$, *codeine*, $C_{18}H_{21}O_2N$, and *thebaine*, $C_{19}H_{21}O_3N$.

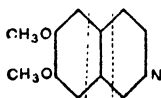
Papaverine Sub-group.—*Papaverine*, $C_{20}H_{21}O_4N$, was first discovered by Merck in 1848. It crystallizes in prisms which melt at 147° , and is a weak, inactive base. The constitution of this alkaloid has been determined in the following manner. The Zeisel reaction shows that four methoxy-groups are present, since it is found that four molecules of methyl iodide are obtained by the decomposition of one molecule of the alkaloid, and again fusion with caustic alkali converts it into dimethylhomopyrocatechin, $CH_3 \cdot (1) \cdot C_6H_4(OCH_3)_2(3-4)$, and a base, $C_{11}H_{11}O_2N$, which on oxidation yields cinchomeric acid, $C_5H_3N(COOH)_2$, and an acid, $C_{10}H_{10}O_6$, that was found to be an isomer of hemipinic acid, and was consequently designated as metahemipinic acid. This latter acid was found to be dibasic, and as it formed both an imide and an anhydride, it followed that the carboxyl groups must be in the ortho position to each other. Also, since on fusion with alkali the acid is transformed into catechol, $C_6H_4(OH)_2(1,2)$, the methoxy groups must be in the ortho position to each other, and so the acid must be represented as—



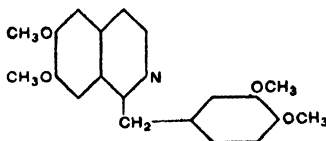
but as it is known that hemipinic acid is (I), metahemipinic acid must be (II). Thus having the two complexes—



it would seem that the base, $C_{11}H_{11}O_2N$, which on oxidation yields these two products, should be a dimethoxyisoquinoline,

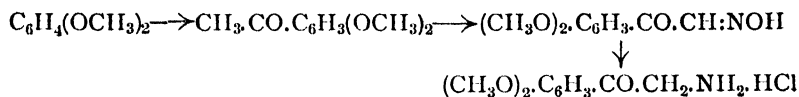


oxidation taking place as shown by the dotted lines, in the one case yielding the nitrogen free dibasic acid, by destruction of the pyridine ring; and in the other case the pyridine dicarboxylic acid by destruction of the benzene ring. Finally, it is now necessary to unite this group with the dimethylhomopyrocatechin molecule in order to arrive at the structure of the alkaloid. The point of union seems to be the α -carbon atom of the isoquinoline complex, for, on oxidation with potassium permanganate, papaverine yields an acid, $C_{12}H_{12}O_4N$, which, on further oxidation, is converted into metahemipinic acid, and α -carbocinchomeric acid, $C_5H_2N(COOH)_3(\alpha\beta\gamma)$. Thus the alkaloid may be formulated as—

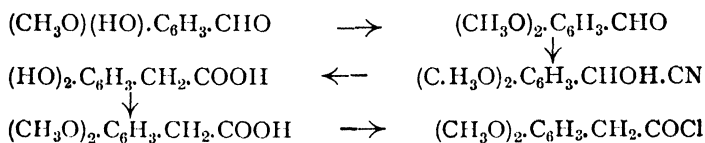


a structure which has been confirmed by Pictet's recent synthesis of the alkaloid, as follows. Veratrol, by the action of acetyl chloride, is converted into aceto-veratrone, the isonitroso-derivative of which on reduction with stannous chloride and hydrochloric acid is transformed into amino-acetoveratrone hydrochloride—

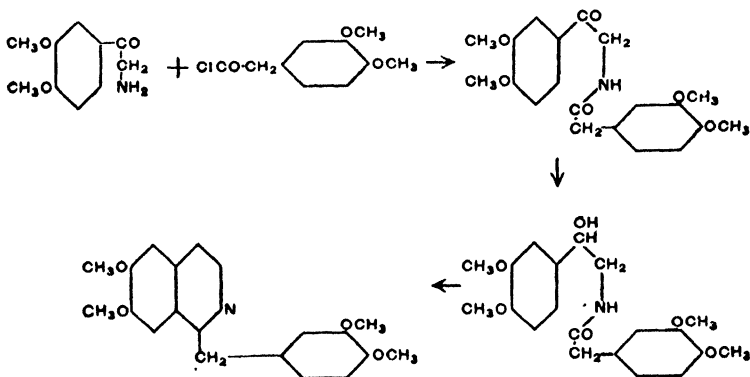
154 MODERN RESEARCH IN ORGANIC CHEMISTRY



As a second starting-point vanillin is taken and by methylation converted into methyl vanillin, from which the cyanhydrin is formed in the usual manner, and is then simultaneously hydrolysed and reduced by hydriodic acid to homoprotocatechuic acid. This acid on methylation is converted into homoveratric acid, and the latter into homoveratroyl chloride—

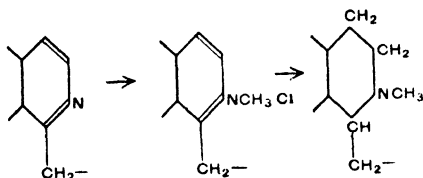


Now homoveratroyl chloride and amino-acetoveratrone hydrochloride condense in the presence of caustic potash to yield homoveratroyl-aminoacetoveratrone, which on reduction in alcoholic solution by sodium amalgam is converted into homoveratroyl-hydroxyhomoveratrylamine. On heating the latter compound in xylene solution with phosphorus pentoxide, it loses water and is transformed into papaverine.

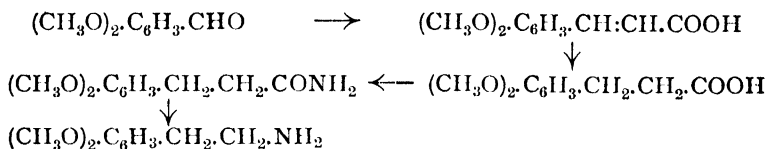


Laudanosine, $\text{C}_{21}\text{H}_{27}\text{O}_4\text{N}$, was first isolated in 1871 by Hesse. Its relation to papaverine was shown by Pictet, who reduced the methochloride of papaverine to racemic laudanosine, and separated the racemic mixture into its components by quinic acid, the

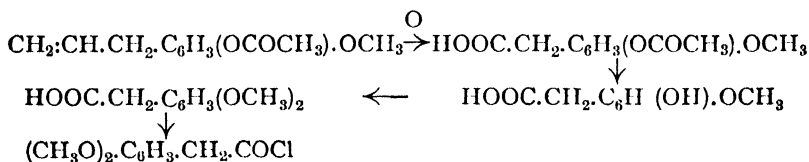
δ -N methyltetrahydro-papaverine so obtained being identical with laudanosine. This reaction may be illustrated in the following manner :—



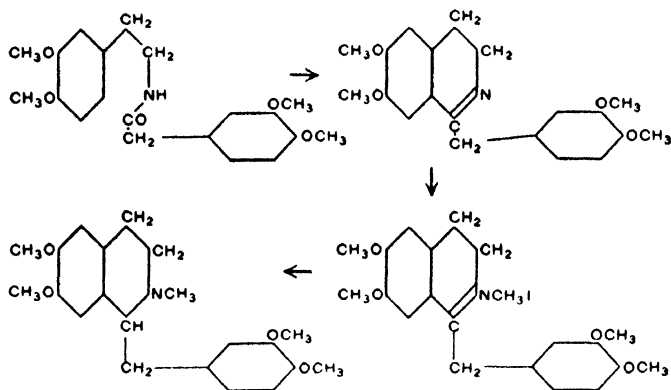
The correctness of this view was again shown by Pictet in 1909 by the synthesis of the alkaloid from eugenol and vanillin in the following manner. Methyl vanillin, when subjected to the Perkin reaction, yields dimethylcaffeic acid, which is then reduced to dimethylhydrocaffeic acid, the amide of the latter, under the influence of bromine and caustic potash, being converted into homoveratrylamine.



Eugenol is acetylated and the acetyl compound oxidized by potassium permanganate, when acetyl-homovanillic acid is formed. This acid on hydrolysis and subsequent methylation yields homoveratric acid, which is then converted into the acid chloride.

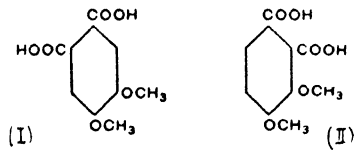


By condensation of the acid chloride with the amine in the presence of caustic alkali, homoveratroyl-homoveratrylamine is produced, which, when heated with phosphorus pentoxide and xylene, yields dihydropapaverine. The dihydropapaverine is then converted into the methiodide and the methyl derivative finally reduced by tin and hydrochloric acid to *dl*-laudanosine.

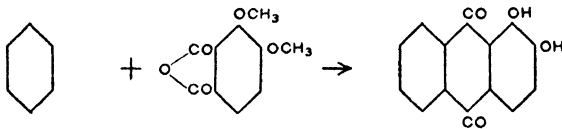


Narcotine, $C_{22}H_{23}O_7N$, is a weak tertiary base, which is insoluble in cold solutions of the caustic alkalis, but is soluble in hot solutions of the alkalis, the salts obtained being formed by the splitting of a lactone ring in the molecule, with consequent assumption of the elements of water. It may be shown by application of the usual reactions that three methoxy groups are present, and also that the nitrogen atom is in combination with a methyl group. The chief decomposition products obtained from narcotine are opianic acid, $C_{10}H_{10}O_5$, and hydrocotarnine, $C_{12}H_{15}O_3N$, which are formed as products of hydrolysis; meconine, $C_{10}H_{10}O_4$, and hydrocotarnine, obtained on reduction; and opianic acid and cotarnine, $C_{12}H_{15}NO_4$, produced when the alkaloid is oxidized with nitric acid.

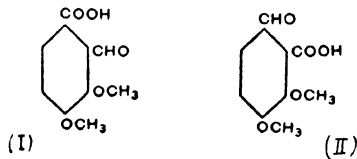
Hemipinic acid, $C_{10}H_{10}O_6$, opianic acid, $C_{10}H_{10}O_5$, and meconine, $C_{10}H_{10}O_4$, are three compounds, which are intimately related, since oxidation of opianic acid yields hemipinic acid, and reduction yields meconine. They are thus related as dibasic acid, aldehyde acid, and internal anhydride of the corresponding alcohol acid. Hemipinic acid is dibasic, and gives an anhydride, consequently its carboxyl groups must be in the ortho-position to each other. It contains two methoxy groups, and on heating with hydriodic acid gives protocatechuic acid, $HOOC(1).C_6H_3(OH)_2(3.4)$. Thus it must be either



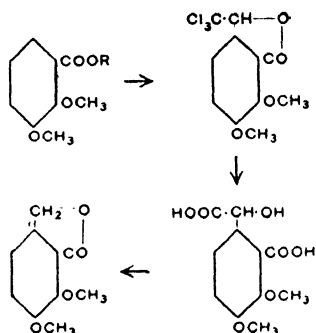
but, as Wegscheider showed that on esterification it could yield *two* different monomethyl esters, it must be (II), for (I) is a symmetrical compound, and could give but one ester. Confirmation of the above structure is given by Lagodzinski's synthesis of alizarine from hemipinic acid and benzene in the presence of aluminium chloride, the reaction product passing into alizarine on subsequent treatment with concentrated sulphuric acid.



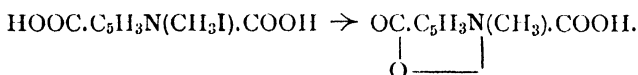
Now, opianic acid, which is a monobasic acid and an aldehyde, and also contains two methoxyl groups, must be either.



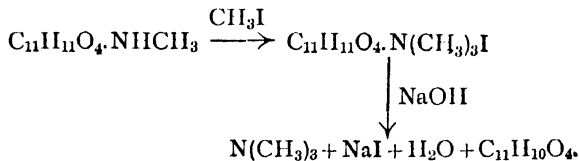
and of these alternatives (II) is correct, for, when heated with hydrochloric acid, opianic acid gives isovanillin, $\text{OHC}(1).\text{C}_6\text{H}_3.(\text{OH})(\text{OCH}_3)(3.4)$, or, when distilled over soda lime, gives methyl vanillin, $\text{OHC}(1).\text{C}_6\text{H}_3.(\text{OCH}_3)_2(3.4)$, which is only possible with a compound of the structure given in (II). Meconine has been synthesized by Fritsch, and its structure as the internal anhydride of the alcohol acid thus confirmed. In this synthesis the methyl ester of 2.3-dimethoxybenzoic acid is condensed with chloral hydrate in the presence of sulphuric acid, and the resulting phthalide derivative hydrolyzed to a hydroxy-acid, which when heated loses water and carbon dioxide and forms meconine.



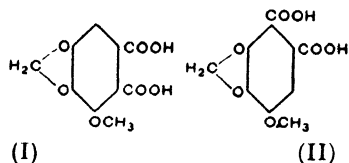
Cotarnine, $C_{12}H_{15}O_4N$, is a secondary base and also an aldehyde, and contains one methoxy group. Its salts are of the type $C_{12}H_{13}O_3N.HCl$, which shows that water is eliminated in their formation, and that their structure is thus different from that of the parent substance. Cotarnine, on oxidation with nitric acid, yields apophyllenic acid, $C_8H_7O_4N$, whose structure, as the methyl betaine of cinchomeronic acid, was shown by its synthesis by Roser on heating the methiodide of cinchomeronic acid.



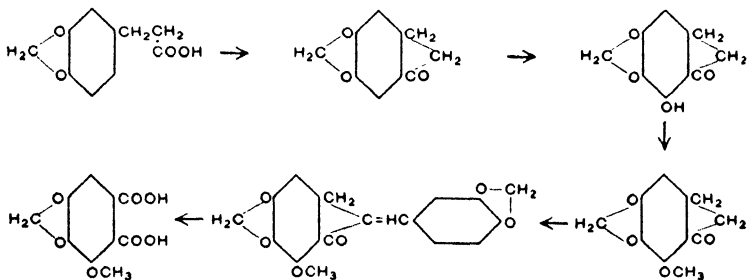
but beyond showing in this way the possibilities of a pyridine ring in cotarnine, nothing further was elucidated by the above oxidation process. Further ideas as to the structure, however, were obtained by the destructive methylation of the base, when an unsaturated aldehyde cotarnone, $C_{11}H_{10}O_4$, was produced, from which the dibasic cotarnic acid, $C_8H_6O_2(COOH)_2$, was obtained by oxidation with potassium permanganate.



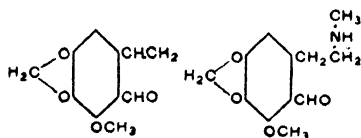
Now, since cotarnic acid forms an anhydride, contains a methoxy group, and on reduction with phosphorus and hydriodic acid yields gallic acid, it must be either



The recent synthesis of cotarnic acid by W. H. Perkin has shown that the acid must possess the structure represented by the formula (I). The starting point in this synthesis is methylene dioxyphenyl propionic acid, which condenses in the presence of phosphorus pentoxide to 5,6-methylene dioxy-1-hydrindone. This latter compound is then nitrated, reduced to the amino-derivative, and the amino-group replaced by the hydroxyl group in the usual manner, a considerable loss of material, however, taking place at this stage of the operations. The hydroxy-compound is then methylated by means of dimethyl sulphate, and the methyl ether condensed with piperonal, by the agency of caustic alkali. The piperonyl compound on oxidation with potassium permanganate yielded cotarnic acid, which was recognized by its characteristic methyl-imide.

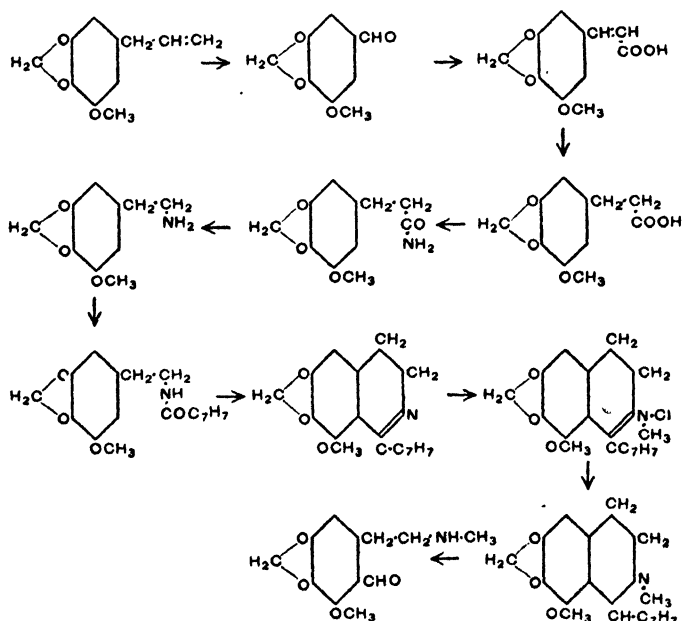


Thus cotarnone and cotarnine are respectively

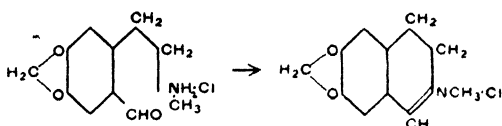


This structural formula of cotarnine has recently (1910) been confirmed by Salway, who has succeeded in synthesizing the base

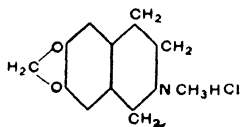
from myristicin as follows. By oxidation of myristicin, myristicin-aldehyde is obtained, and is then converted into 3-methoxy-4.5-methylene dioxycinnamic acid. This acid is now reduced to the corresponding phenyl propionic acid, which is next transformed into its amide, and the latter converted by the Hofmann reaction into 3-methoxy-4.5-methylenedioxyphenylethylamine. The phenyl acetyl derivative of this base is then heated (in xylene solution) with phosphoric anhydride, and two isomeric dihydroisoquinoline derivatives are obtained. These may be separated by the fractional recrystallization of their hydrochlorides, and the 8-methoxy-6.7-methylenedioxy-1-benzyl-3.4-dihydroisoquinoline so obtained, when converted into its methochloride, and subsequently reduced with tin and hydrochloric acid, yielded 1-benzyl-hydrocotarnine. On oxidation of the benzyl compound with manganese dioxide and sulphuric acid, cotarnine is formed.



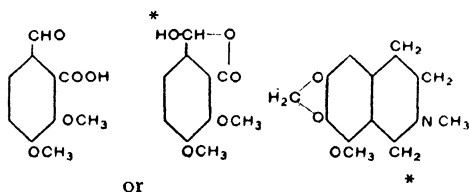
The hydrochloride of cotarnine would consequently be formed thus:—



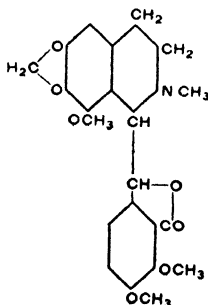
which would give for its reduction product, hydrocotarnine hydrochloride,



and now, since narcotine yields opianic acid and hydrocotarnine on hydrolysis and contains neither carboxyl or aldehydic groups, and also behaves as a tertiary base, it may be assumed that the union of these two complexes has occurred by elimination of water from the points marked * below :—



which leads to the following structure for the alkaloid :—



Morphine Sub-Group.—This sub-group contains morphine,

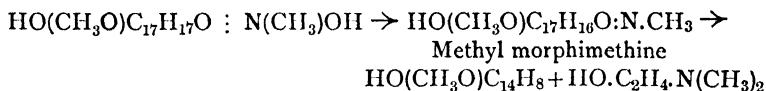
$C_{17}H_{19}O_3N$; codeine, $C_{18}H_{21}O_3N$; thebaine, $C_{12}H_{21}O_3N$, and pseudomorphine ($C_{17}H_{18}O_3N$)₂.

Morphine was first isolated by Serturmer in the early part of the nineteenth century, and was the first basic compound obtained from the plant kingdom. It crystallizes in prisms which melt at about 247° C. Its solutions are lævo-rotatory. It behaves as a tertiary base, and contains two hydroxyl groups, one of which is phenolic, the other being alcoholic in character. It is a powerful reducing agent. Acids convert morphine into apomorphine, $C_{17}H_{17}O_2N$, by elimination of water, and also effect condensation to more complicated derivatives. *Codeine* is the methyl ether of morphine. It is also a tertiary base, its solutions being lævo-rotatory. It contains one hydroxyl group. Although mild oxidizing agents convert morphine into pseudomorphine, an analogous reaction does not take place with codeine, the reason being that the formation of pseudomorphine from morphine is due to the presence of the free phenolic hydroxyl group there present, such a state not occurring in codeine where the phenolic hydroxyl group is methylated. Phosphorus tribromide converts codeine into bromocodeine, $C_{17}H_{17}O(OCH_3).NBr.$, which, when warmed with water, is transformed into isocodeine hydrobromide, $C_{17}H_{18}O_2(OCH_3).N.HBr.$ The close relationship existing between morphine and codeine was shown by Grimaux, who converted morphine into codeine by direct methylation with methyl iodide and caustic alkali, and by Matthiessen and Wright, who, by the action of concentrated hydrochloric acid at 100° C. on codeine, obtained a derivative they called chloro-codide, and which on heating with hydrochloric acid to 150° C. decomposed into methyl chloride and apomorphine.

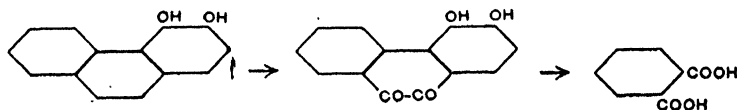


Thus both morphine and codeine contain the complex $C_{17}H_{17}ON-$, and the structure of this group has been investigated chiefly by Vongerichten, Knorr, and Pschorr. One of the earliest observations made was, that on distillation of morphine over zinc dust, phenanthrene is obtained, a result leading to the conclusion that morphine is a derivative of phenanthrene. Further

confirmation must, however, be sought, for pyrogenetic processes such as the above are not reliable operations from which to draw conclusions, owing to the tendency to molecular rearrangement that frequently takes place in such processes. Such confirmation is, however, obtained in the destructive methylation of codeine, the methyl hydroxide of which on distillation yields methylmorphimethine, which in its turn, when heated with acetic anhydride, is decomposed into methyl-dihydroxyphenanthrene and dimethylhydroxyethylamine,



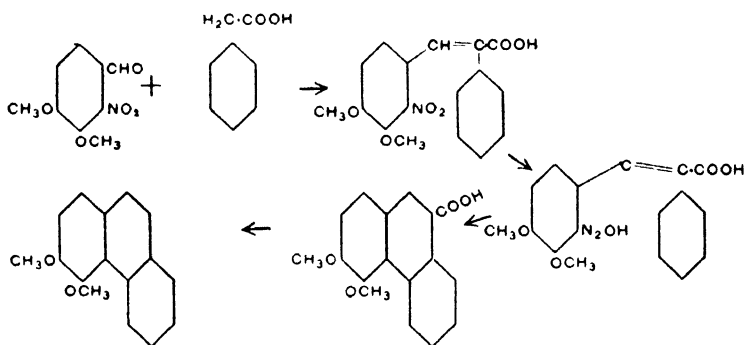
The phenanthrene derivative is phenolic, the parent dihydroxyphenanthrene being known as *morphol*, oxidation of the acetyl derivative yielding dihydroxyphenanthrene quinone [in the form of its diacetyl derivative], which, since it contains the hydroxyl groups intact, shows that they are not attached to the adjacent carbon atoms of the $\text{C}_{14}\text{H}_{10}$ nucleus. Again, that they are both contained in one ring is shown by the fact that potassium permanganate oxidizes the quinone to phthalic acid, thus



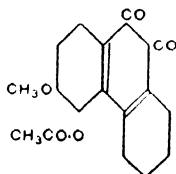
The two hydroxyl groups are shown to be in the ortho-position, since an alkali fusion of morphine yields protocatechuic acid, and by the behaviour of morphol to mordanted fibre, towards which it acts as an alizarine. Further confirmation is met with in the synthesis of dihydroxyphenanthrene and its derivatives as follows. 3-Hydroxyphenanthrene quinone may be directly converted into morphol quinone by nitration, reduction of the nitro-compound, diazotization of the amino-quinone and subsequent boiling with water, this series of reactions being the first direct synthesis of a morphine decomposition product directly from phenanthrene. Again, in 1900, Pschorr, by the following series of reactions, prepared 3,4-dimethoxyphenanthrene identical with the dimethyl morphol previously obtained by Vongerichten from

164 MODERN RESEARCH IN ORGANIC CHEMISTRY

methyl morphol, which in its turn was prepared from codeine. The Perkin condensation of *o*-nitrovanillin methyl ether and sodium phenylacetate yields α -phenyl-2-nitro-3,4-dimethoxy cinnamic acid. This acid is reduced to the amino-acid which is then diazotized, and the solution of the diazo-compound in sulphuric acid (in the presence of copper powder) loses nitrogen, and is converted into 3,4-dimethoxyphenanthrene-9-carboxylic acid. On distillation, the acid decomposes into 3,4-dimethoxyphenanthrene (dimethyl morphol) and carbon dioxide.

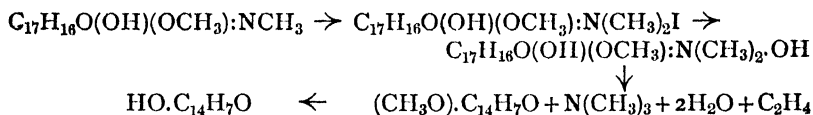


By a similar set of reactions starting out from *o*-nitroacetyl-isovanillin, 3-methoxy-4-acetoxyphenanthrene-9-carboxylic acid is formed. Oxidation of this acid yields the corresponding phenanthrene-quinone,

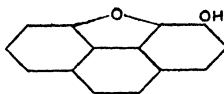


identical with acetyl-methylmorphol quinone, showing thus that methyl morphol is 3-methoxy-4-hydroxyphenanthrene.

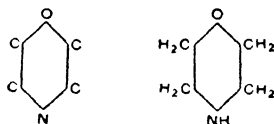
Methylmorphimethine on treatment with acetic anhydride is converted into a stereo-isomer, from which by destructive methylation and distillation of the methyl hydroxide, methyl morphenol is obtained, the latter substance when heated with hydriodic acid passing into *morphenol*, C₁₄H₇O(OH),



and since morphenol readily passes into morphol on reduction it is most probably to be represented as



The base, $\text{C}_4\text{H}_{11}\text{ON}$, was shown by Knorr to be identical with one previously prepared by Ladenburg from dimethylamine and ethylene chlorhydrin, and is thus a hydroxyethyl-dimethylamine (ethanol-dimethylamine) $\text{HO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{N}(\text{CH}_3)_2$. This result led Knorr to conclude that morphine contained an oxazine ring, and the parent base corresponding to this ring system was designated as *morpholine*.

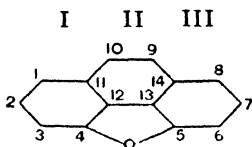


Oxazine ring

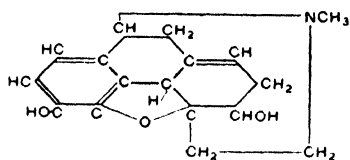
Now codeine, on oxidation, yields a ketone *codeinone*, $\text{C}_{18}\text{H}_{19}\text{O}_3\text{N}$, and this ketone, on heating with acetic anhydride, is decomposed into 3-methoxy-4.6-dihydroxyphenanthrene and hydroxyethyl-dimethylamine, which indicates also that codeine is a derivative of 3.4.6-trihydroxyphenanthrene. In his later work Knorr has come to the conclusion that the oxazine ring in all probability does not exist in the pre-formed state in these alkaloids, since the synthetic phenol ethers of ethanol-dimethylamine and of methyl morphol do not behave like α -methylmorphimethine towards sodium ethoxide, the assumption of an oxazine ring requiring these ethers and the methine base to have the same constitution and to behave in a similar fashion; and again, Freund's results, obtained from the action of magnesium phenyl bromide on thebaine, suggest that a "bridge" oxygen atom has taken part in the reaction. Further, from an examination of the

166 MODERN RESEARCH IN ORGANIC CHEMISTRY

decomposition products of morphine, codeine, and thebaine, it is concluded that all three are derivatives of 3,6-dihydroxyphenanthrylene oxide

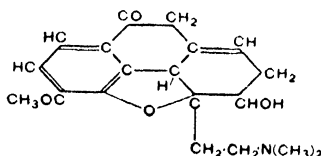


and the following conclusions are deduced. The hydroxyl group at 3 is phenolic, whilst that at 6 is alcoholic in character, the oxygen linking between 4 and 5 being indifferent. The group $\text{CH}_2\text{CH}_2\text{NCH}_3$ is attached to the phenanthrene nucleus as a side ring ether at 9 or 10, this result being arrived at by comparison of the alkaloids of the group with papaverine. Again, the ring (II) is a dihydrobenzene ring containing two extra hydrogen atoms at 9 and 10, whilst (III) is a tetrahydrobenzene ring. Thus finally Knorr suggests for morphine the constitution



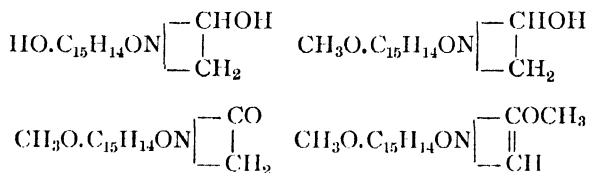
The position of attachment of the side chain is shown as follows. The decomposition of α -methylmorphimethine shows that it must be attached to ring (III). Again, codeinone methiodide decomposes, when heated with alcohol to 150°C ., into dimethylamino-methyl ether and 4,6-dihydroxy-3-methoxyphenanthrene, whilst in a similar manner ψ -codeinone obtained from ψ -codeine yields the same ether and 4,8-dihydroxy-3-methoxyphenanthrene, so that ψ -codeine must contain its carbonyl group at position 6 and codeine at position 8, and hence in the conversion of codeine into ψ -codeine the hydroxyl group must migrate from 6 to 8, and since both codeine and ψ -codeine yield the same desoxycodine, the place of attachment of the side ring must remain intact during the migration of the hydroxyl group, so that the side chain cannot be attached to position 8. Position 6 is excluded, since codeinone

has its carbonyl group there, and similarly position 7 is excluded, since the Claisen reaction shows that codeinone contains the grouping $-\text{CH}_2\text{CO}-$, so that position 5 alone remains for the point of attachment of the $-\text{CH}_2\text{CH}_2\text{N}-$ chain. Positions 13 and 14 are excluded, because the side chain is found attached to ring (III) even in thebenine, which is completely aromatic in character. The double bond between 8 and 14 is shown by the ketonic character of hydroxymethylmorphimethine, which is produced when hydroxycodine is boiled with an aqueous solution of sodium hydroxide, and since hydroxycodine, on oxidation with chromic acid, yields Vongerichten's acetylmethylmorphol quinone (see above), it follows that hydroxycodine must contain its alcoholic hydroxyl group at 9 or 10. Hence hydroxymethylmorphimethine must be



Hence, if morphine is to be represented as above, which seems highly probable in the light of Knorr's work, codeine is the 3-methyl ether of morphine.

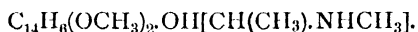
Thebaine, $\text{C}_{19}\text{H}_{21}\text{O}_3\text{N}$, is a tertiary base which contains no hydroxyl groups, but, on the other hand, possesses two methoxy groups. The relationship existing between morphine, codeine, and thebaine may be represented by the following formulæ:—



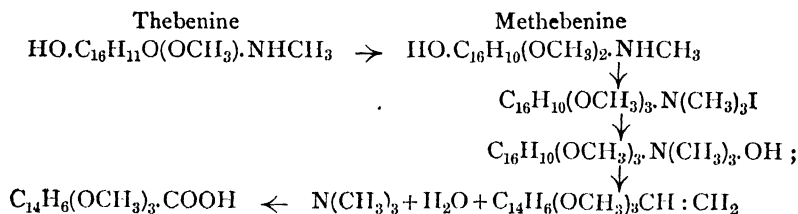
since Knorr found that thebaine, on hydrolysis with dilute sulphuric acid, yields a certain amount of codeinone, whilst Freund, by the action of bromine on thebaine, obtained an additive product which spontaneously decomposed into methyl

bromide and bromocodeinone. Thus thebaine appears as the methyl ether of the enolic form of codeinone.

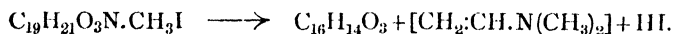
Among the various decomposition products of thebaine that have been investigated are *thebenine*, $C_{18}H_{19}O_3N$ [which is formed by the action of dilute hydrochloric acid on the alkaloid, one methoxy group being hydrolyzed], and *thebaol*, $C_{16}H_{14}O_3$. The methyl ether of thebenine (methebenine) has been shown by Pschorr to be phenolic in character, so that the third oxygen atom (which is not accounted for by the methoxy groups), is therefore phenolic, and not part of a furan ring. The hydroxyl group in methebenine cannot be methylated until the secondary nitrogen atom has been converted into a quaternary nitrogen atom, and the resulting salt, when heated with the alkaline hydroxides, yields trimethylamine and an unsaturated phenanthrene derivative, which may be oxidized to trimethoxyphenanthrene tricarboxylic acid. Thus all three oxygen atoms in methebenine are linked directly to the phenanthrene nucleus, and it probably is to be represented as



The above reactions could be thus represented

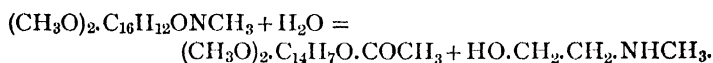


thus showing the relation of thebaine to phenanthrene. Again, thebaine methiodide, when warmed with sodium ethoxide, yields tetramethyl ethylene diamine, and the non-nitrogenous *thebaol*, $C_{16}H_{14}O_3$, the diamine resulting probably from the decomposition of an intermediately formed dimethylvinylamine and a small quantity of dimethylamine which is also produced.

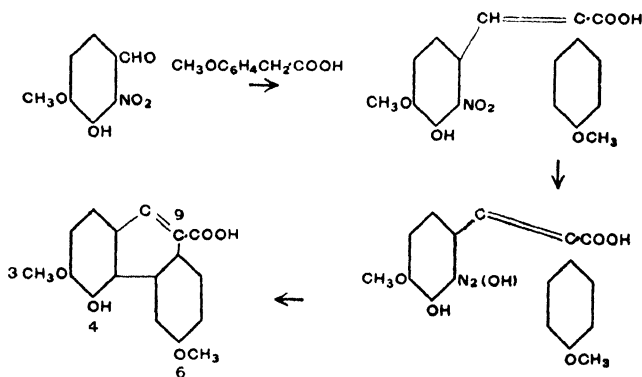


Thebaol is also formed when thebaine methyl iodide is warmed with acetic anhydride in the presence of silver acetate. Thebaine

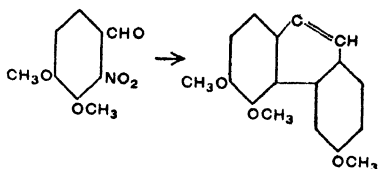
alone on treatment with acetic anhydride yields acetyl thebaol and methyl hydroxyethylamine.



Thus thebaol is derived from a compound containing three hydroxyl groups, and since on distillation over zinc dust it yields phenanthrene it is probably a trihydroxyphenanthrene derivative. This latter conclusion receives proof by the following series of reactions. Chromic acid oxidizes thebaol to thebaol quinone $(\text{CH}_3\text{O})_2\text{C}_{14}\text{H}_5\text{O}_2\cdot\text{OH}$, which, by further oxidation with potassium permanganate, is converted into *o*-methoxyphthalic acid, a result indicating that the two methoxy groups are not present in one and the same ring; thebaol quinone has been synthesized by Pschorr by condensing *vic*-(*o*)nitroisovanillin with *p*-methoxyphenyl acetic acid, the resulting nitro-cinnamic acid derivative being then reduced to the amino-acid and diazotized. The diazo compound when boiled in alkaline solution is converted into 4-hydroxy-3,6-dimethoxyphenanthrene-9-carboxylic acid, the acetyl derivative of which oxidizes directly to acetyl thebaol quinone, so that thebaol is a derivative of 4-hydroxy-3,6-dimethoxyphenanthrene.

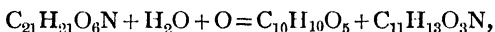


Similarly by the condensation of *vic*-(*o*)nitrovanillin methyl ether and *p*-methoxyphenyl acetic acid, methyl thebaol is formed.

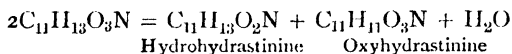


Thus thebaine contains the same type of grouping as morphine and codeine, and can also be converted into codeinone, so that the conclusion that it is the methyl ether of the enolic form of codeinone seems justified. For the sake of convenience of reference, the chief decomposition products of these three alkaloids are shown in the following chart.

Hydrastine, $C_{21}H_{21}O_6N$, is found in the root of the golden seal (*Hydrastis canadensis*). It crystallizes in prisms which melt at $132^\circ C.$, and behaves as a tertiary base. In neutral solutions it is lævo-rotatory, in acid solution dextro-rotatory. It contains two methoxy groups. The constitution of this alkaloid has been determined chiefly by the investigations of Freund and his pupils in the following manner. On oxidation with a somewhat diluted nitric acid it yields opianic acid and hydrastinine, $C_{11}H_{13}O_3N$,

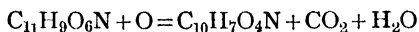


from which Freund concludes that it is a meconyl-hydrohydrastinine. Now, since hydrastinine, on heating for a short time with a concentrated solution of potassium hydroxide, is converted into a mixture of hydrohydrastinine and oxyhydrastinine,



a reaction resembling Cannizzaro's, in that it consists of a simultaneous oxidation and reduction process, it seems that hydrastinine must be regarded as an aldehyde, $C_{10}H_{12}NO_2$, whilst hydrohydrastinine and oxyhydrastinine are the internal anhydrides of the corresponding alcohol and acid. Further confirmation of the aldehyde character of hydrastinine is given by the fact that it forms an oxime. It also possesses the character of a secondary base, and contains a methyl group attached to the nitrogen atom. On oxidation with potassium permanganate, hydrastinine is converted into hydrastinic acid, $C_{11}H_9O_6N$, which, by further oxida-

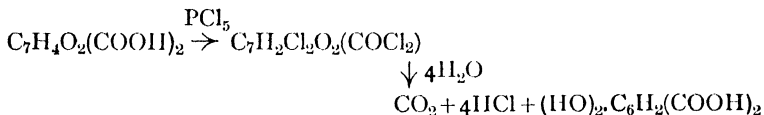
tion with nitric acid is transformed into what must be regarded as the methyl imide of hydrastic acid, $C_{10}H_7O_4N$,



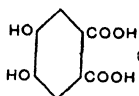
for, on hydrolysis, the latter compound is decomposed into methylamine and the dibasic hydrastic acid $C_7H_4O_2(COOH)_2$.



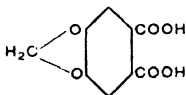
Hydrastic acid contains its carboxyl groups in the ortho-position to each other, since it forms an anhydride and an imide, and on treatment with phosphorus pentachloride yields an acid chloride, which, when boiled with water, is converted into a dihydroxyphthalic acid,



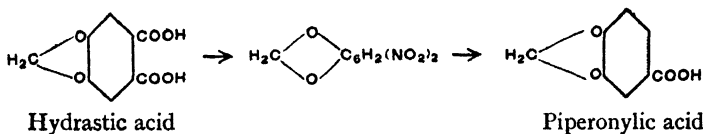
identical with the dihydroxyphthalic acid obtained by Rossin on heating metahemipinic acid with hydriodic acid, therefore represented as



Thus hydrastic acid would appear to be the methylene ether of 4,5-dihydroxyphthalic acid.

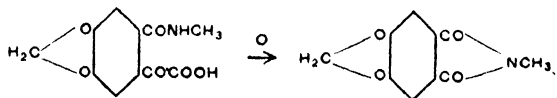


Further confirmation of this structure is given by the fact that fuming nitric acid converts it into the methylene ether of dinitro-pyrocatechin, which has also been obtained by the action of fuming nitric acid on piperonylic acid.

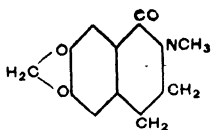


172 MODERN RESEARCH IN ORGANIC CHEMISTRY

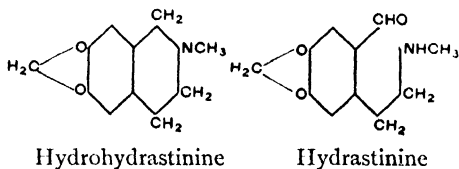
Consequently the easiest way of formulating hydrastinic acid in order to show its conversion into the methyl imide of hydrastic acid on oxidation will be



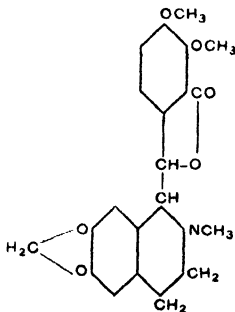
and the production of this hydrastinic acid by the oxidation of oxyhydrastinine will be explained if the latter is written as



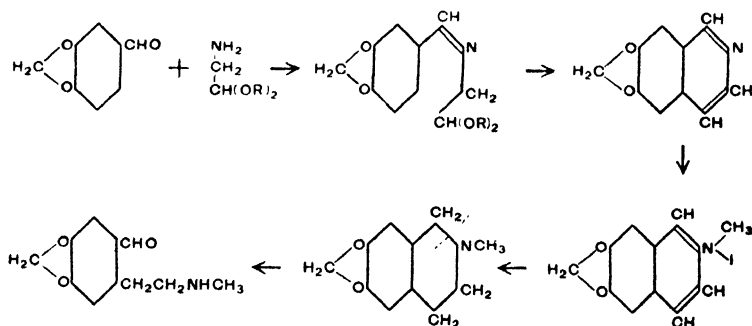
thus leading to the following formulæ for hydrohydrastinine and hydrastinine.



Since hydrastine decomposes on oxidation into opianic acid and hydrastinine, the connection between these two portions in the molecule must be effected by the carbon atoms from which the aldehyde groups of the opianic acid and hydrastinine are obtained, and consequently the alkaloid must be represented by the annexed formula.



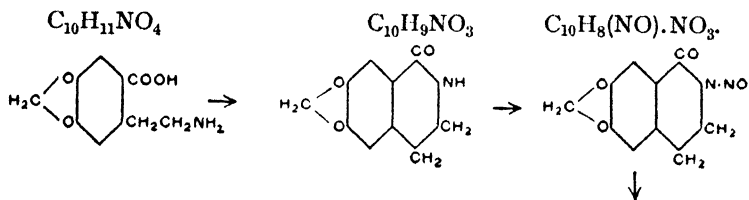
The constitution for hydrastinine, given above, has received further confirmation by its synthesis at the hands of Fritsch, as follows. Piperonal condenses with amido-acetal to form piperonal acetalamine, which, on treatment with sulphuric acid, is transformed into *Bz*-2,3-methylenedihydroxyisoquinoline. The methiodide of the latter compound on reduction is converted into methylene dihydroxy-methyl-tetrahydroisoquinoline or hydrohydrastinine, and this compound on oxidation with potassium bichromate and sulphuric acid passes into hydrastinine.



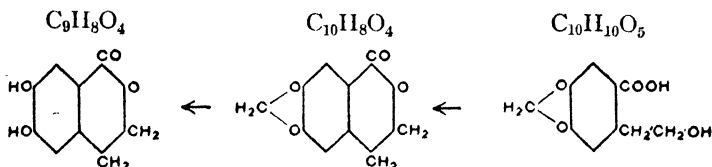
Berberine, C₂₀H₁₇O₄N, is found widely distributed in the vegetable kingdom. It crystallizes in yellow prisms which contain a variable amount of water of crystallization, and in the anhydrous condition melts at 120° C. It behaves as a weak tertiary base and contains two methoxy groups. The earlier investigations as to the constitution of berberine give very little insight as to its structure, the chief facts observed being that alkaline potassium permanganate oxidizes it to hemipinic and hydrastic acids, whilst concentrated nitric acid oxidizes it to berberonic acid, C₅H₂N(COOH)₈(αγβ¹), results pointing to the presence of a pyridine ring and two benzene rings in the molecule. Our knowledge of the method by which these ring systems are linked together is due to the researches of W. H. Perkin, jun., on the products of oxidation of the alkaloid by potassium permanganate. Perkin found that beside hemipinic and hydrastic acids, the following six oxidation products were formed :—

Oxyberberine	$C_{20}H_{17}O_5N$
Dioxyberberine	$C_{20}H_{17}O_6N$
Berberal	$C_{20}H_{17}O_7N$
Anhydroberberilic acid	$C_{20}H_{17}O_8N$
Berberilic acid	$C_{20}H_{19}O_9N$
Berilic acid	$C_{20}H_{15}O_8N$

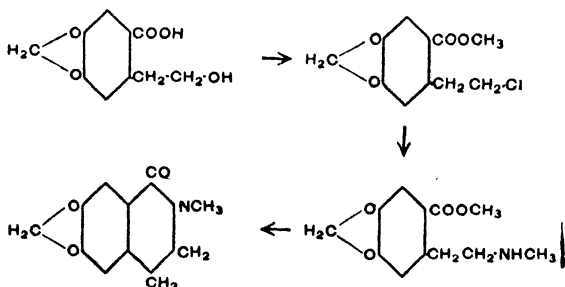
and of these the two that throw most light on the constitution of the alkaloid are berberilic acid and berberal. Berberilic acid is a dibasic acid, which, when heated above $170^{\circ}C.$, passes into the monobasic anhydroberberilic acid, an internal anhydride of berberilic acid, and also a free acid, since under certain conditions it can form salts, and also an acid chloride, amide, and anilide. When berberilic acid is boiled with dilute sulphuric acid, it is decomposed into hemipinic acid, and a base of composition, $C_{10}H_{11}O_4N$. The latter, when heated to $180^{\circ}C.$, loses a molecule of water and forms an internal anhydride, $C_{10}H_9O_3N$. The nitroso-derivative of this anhydride on hydrolysis with caustic alkali loses nitrogen, and is transformed into a monobasic acid, $C_{10}H_{10}O_5$, which, on heating, again yields an internal anhydride, $C_{10}H_8O_4$. No further results were obtained by the oxidation of this anhydride, but it was found that if it were heated under pressure to $170^{\circ}C.$ with hydrochloric acid, it decomposed with elimination of carbon and formation of a substance of composition $C_9H_8O_4$. This decomposition product gave an intense catechol reaction on the addition of ferric chloride, and also reduced Fehling's solution and warm ammoniacal solutions of silver nitrate. It also gave a white precipitate on the addition of lead acetate. These reactions and decompositions indicate the presence of piperonyl derivatives, and consequently the above series of compounds can be formulated as follows :—



ω-aminoethylpiperonylcarboxylic acid



It will be noticed that the compound $C_{10}H_9O_3N$ closely resembles oxyhydrastinine, from which it differs in composition by the presence of the group $>NH$ instead of $>N.CH_3$, and for this reason Perkin called it noroxyhydrastinine. It was converted into oxyhydrastinine by the following series of reactions. The nitrosamine, $C_{10}H_8(NO)NO_3$ (see above), on heating with caustic soda, is decomposed into nitrogen, and the acid, $C_{10}H_{10}O_5$ (*ω*-hydroxyethylpiperonylic acid), the anhydride of the latter by the action of phosphorus pentachloride, yielding a compound, $C_{10}H_8O_3Cl_2$, which is readily hydrolyzed to the acid, $C_{10}H_9O_4Cl$ (*ω*-chloroethylpiperonylic acid). The methyl ester of this acid is then heated with an alcoholic solution of methylamine to $130^\circ C.$, and the product obtained warmed with alcoholic potash, when methyl alcohol is split off and oxyhydrastinine is formed.

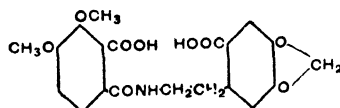


This series of reactions thus shows the close relation existing

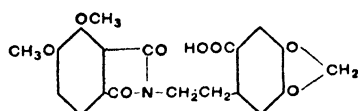
176 MODERN RESEARCH IN ORGANIC CHEMISTRY

between berberine and hydrastine, and also that berberine may be considered as a derivative of isoquinoline.

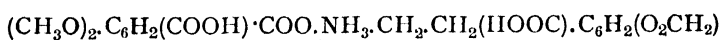
Since berberilic acid on hydrolysis yields hemipinic acid, and ω -aminoethylpiperonyl carboxylic acid, it must be



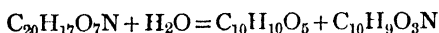
which consequently gives for anhydroberberilic acid,



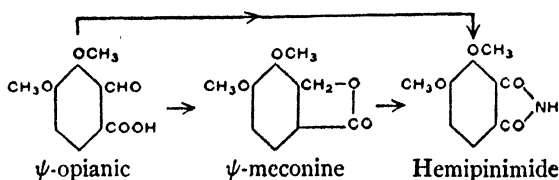
a conclusion shown to be correct since, on evaporation of aqueous solutions of hemipinic acid and ω -aminoethylpiperonylic acid, a hemipinate of the acid is formed, which passes into anhydroberberilic acid when heated.



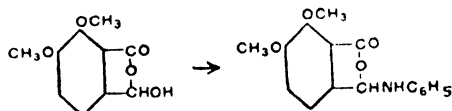
Berberal, $\text{C}_{20}\text{H}_{17}\text{O}_7\text{N}$, crystallizes in plates, which melt at 150°C . ; it possesses aldehydic properties, and on hydrolysis is decomposed with formation of ψ -opianic acid and noroxyhydrastinine.



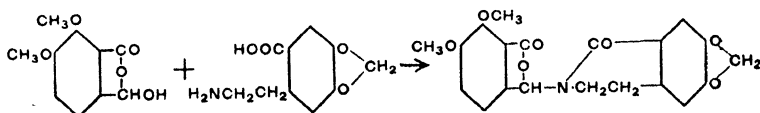
The ψ -opianic so obtained possesses the properties of an orthoaldehyde acid, is monobasic, and contains two methoxy groups. When fused with caustic potash it yields protocatechuic acid. Its oxime when heated is converted into hemipinimide. On reduction with sodium amalgam the acid is converted into ψ -meconine, which thus, taken in conjunction with the other reactions, leads to the following structural formulá for the acid :—



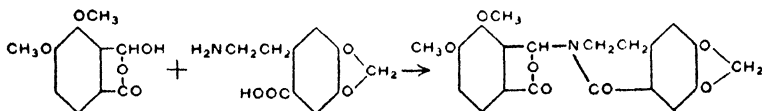
Now opianic acid condenses with ω -aminoethylpiperonylic anhydride to form isoberberal, $C_{20}H_{17}O_7N$, which has properties exactly similar to berberal; and Liebermann has shown that when opianic acid reacts with aniline in the cold, an anilino-opianic acid is formed, the opianic acid reacting in the tautomeric hydroxyphthalide form.



From a study of this and similar reactions it seems clear that in the condensations of opianic acids with bases it is always the carbon atom of the aldehyde group which is attached to the nitrogen atom in the final product, and in this way the formation of isoberberal may be represented by the following scheme.



Again, since ψ -opianic acid is very similar in structure and in its reactions to opianic acid, it may be assumed that it will condense with basic substances in an exactly similar manner to opianic acid, and as ψ -opianic acid and ω -aminoethyl piperonylic anhydride condense to form berberal this reaction must take place as follows:—

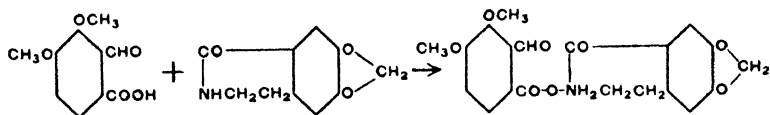


which, of course, establishes the structure of berberal.

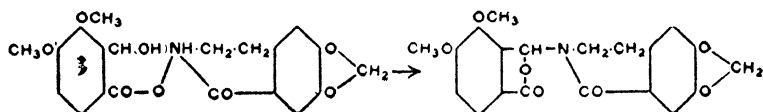
Perkin points out that the condensations shown above are probably not so simple as suggested by Liebermann, since, in the formation of berberal and isoberberal, the first stage in the process is the formation of the salt of the acid with the base,

178 MODERN RESEARCH IN ORGANIC CHEMISTRY

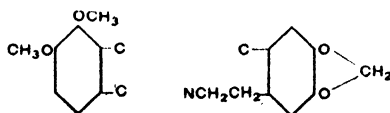
thus from ψ -opianic anhydride and ω -aminoethylpiperonyl anhydride, the salt



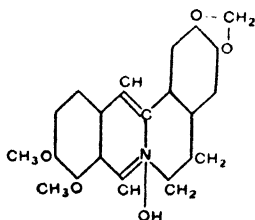
is produced, and when heated to 180° C. is transformed into berberal, aldol formation probably taking place, followed by rearrangement.



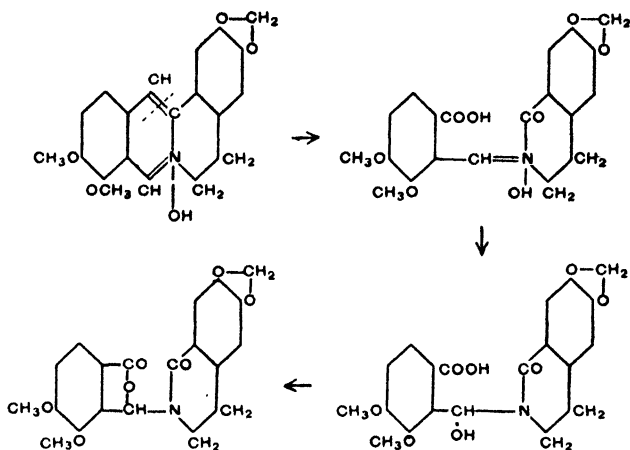
Thus, knowing the constitutional formulæ of berberilic acid and berberal, it is evident that the alkaloid must contain the groupings



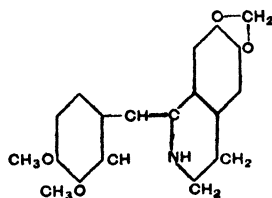
and as the position of the methoxy groups is determined by the facts mentioned above, the simplest structure that can be given to the alkaloid in order to explain its properties and decompositions is



The oxidation to berberal can then be explained by the following scheme :—



The salts of berberine are derived from the hydroxylic formula given above, but the alkaloid probably itself exists in the corresponding aldehydic modification. Gadamer, from the action of barium hydroxide on a solution of berberine sulphate, obtained a brownish red strongly alkaline solution, which, on the addition of excess of sodium hydroxide, gave a modification of berberine, insoluble in water, faintly alkaline, and also aldehydic in character. This form he named *berberinal*. It forms an oxime, reacts with magnesium alkyl iodides to form homologues of berberine, and undergoes the Cannizzaro reaction. On the above formulation of berberine it would be represented as

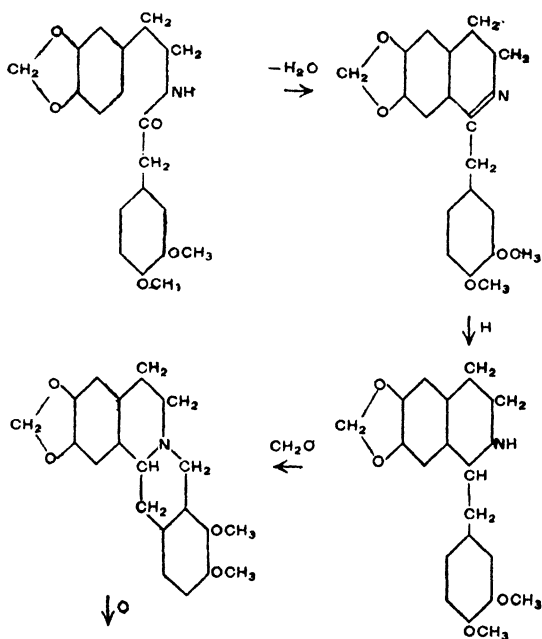


which brings it into line with the formula given for hydrastine (p. 172).

All doubts as to the constitution of berberine may now be considered as settled, since the alkaloid has recently been synthesized by Pictet.

In this synthesis, homoveratryl chloride is condensed with

homopiperonylamine, and the resulting anilido-compound when heated in xylene solution with phosphorus pentoxide is converted into veratryl-methylene dioxy-dihydroisoquinoline. The isoquinoline compound so formed is then reduced with tin and hydrochloric acid, and the reduction product condensed with methylal, when tetrahydro-berberine is formed. Oxidation of tetrahydro-berberine with dilute nitric acid then yields berberine nitrate, identical with that obtained from the alkaloid itself. The stages in the reaction are shown in the following diagram :—

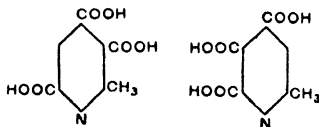


Berberine

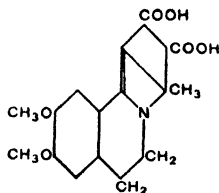
Corydaline, $C_{22}H_{27}O_4N$, is the chief alkaloidal constituent of the root of *Corydalis cava*. Its solutions are alkaline, possess a bitter taste, and are dextro-rotatory. The action of concentrated hydriodic acid on the alkaloid shows that it contains four methoxy groups. It does not contain a methyl group attached to nitrogen. It has the properties of a tertiary base. For our knowledge of

the constitution of corydaline we are indebted to the researches of Dobbie and Lauder, who showed that on oxidation with a hot solution of potassium permanganate, hemipinic acid and meta-hemipinic acid were formed, this result pointing to the presence of two benzene rings in the nucleus. At the same time a nitrogen containing product *corydaldine*, $C_{11}H_{13}O_3N$, was obtained, and it may be assumed that an isoquinoline nucleus is present, since the oxidation of corydaldine yields meta-hemipinic acid.

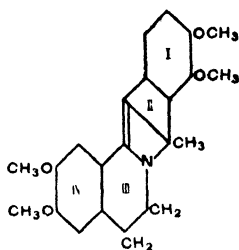
Mild oxidants, such as nitric acid, or an alcoholic solution of iodine, convert corydaline into dehydrocorydaline, $C_{22}H_{23}O_4N$, which may be further oxidized to the dibasic corydic acid $C_{18}H_{17}O_6N$. This acid in its turn may be oxidized by potassium permanganate into a tribasic acid, corydilic acid $C_{17}H_{15}O_8$, meta-hemipinic acid, and α -methyl pyridine tricarboxylic acid, which is either



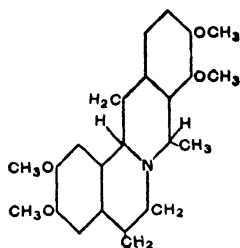
since further oxidation converts it into pyridine 2.3.4.6-tetracarboxylic acid. These results point to corydilic acid possessing the following structure:—



As corydilic acid is formed by the oxidation of dehydrocorydaline, the two carboxyl groups probably result from the destruction of another ring containing two methoxy groups, since dehydrocorydaline, like corydaline itself, contains four methoxy groups, so that dehydrocorydaline must be represented as

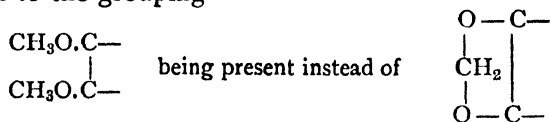


which gives for corydaline itself



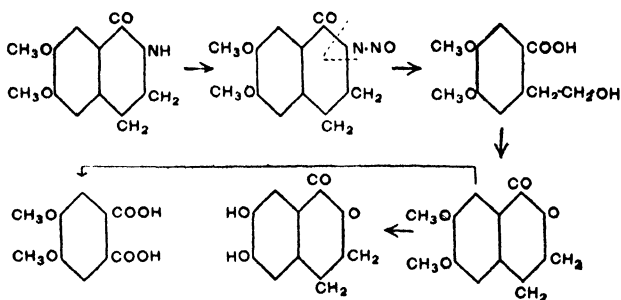
The formula for dehydrocorydaline given above accounts quite well for the various oxidation products obtained from it, corydic acid being formed by the destruction of ring (I), and corydalic acid from this by the destruction of ring (III).

Corydaldine closely resembles noroxyhydrastinine, from which it only differs by the carbon and hydrogen content CH_4 , and since corydaldine contains two methoxy groups, whilst noroxyhydrastinine has not any, it would seem that the difference is to be ascribed to the grouping



Corydaldine shows a very remarkable likeness to berberine in that it yields decomposition products very similar to those obtained from ω -aminoethylpiperonyl carboxylic acid, thus it forms a nitroso-derivative, which, when warmed with solutions of the caustic alkalis, is transformed into the sodium salt of ω -hydroxyethyl veratric acid, nitrogen being eliminated during

the progress of the reaction. The free acid on liberation from its solution loses water and passes into its anhydride, which contains two methoxy groups, since on oxidation with potassium permanganate it is converted into metahemipinic acid. A further argument in favour of its constitution is given by the fact that on heating with hydrochloric acid it yields ω -hydroxyethyl catechol carboxylic anhydride identical with that obtained by Perkin from berberine. These reactions may be illustrated in the following way :—



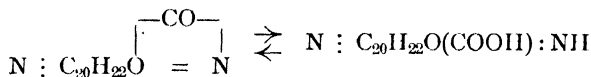
Thus the presence of the isoquinoline nucleus may be considered as definitely determined. Again, the formation of hemipinic acid by the oxidation of the above anhydride shows that hemipinic acid is derived from the benzene ring of the isoquinoline complex, hence the ring, destroyed when corydaline is oxidized by dilute nitric acid, is the ring which yields hemipinic acid when the alkaloid is oxidized by potassium permanganate, and consequently the benzene ring and the isoquinoline ring each contain two methoxy groups.

Quinoline Group.—The principal members of this group are the alkaloids strychnine, $C_{21}H_{22}O_2N_2$, and brucine, $C_{23}H_{26}O_4N_2$, the latter apparently being the dimethoxy-derivative of the former.

Strychnine is found in nux-vomica, the seed of *Strychnos nux-vomica*, and in other plants of the genus *Strychnos*. It crystallizes in prisms which melt at 269° , and is lævo-rotatory. It is a tertiary base, and forms salts with only one equivalent of acid. It does not contain a methoxy-group. Many investigations

have been made in order to determine the structure of this alkaloid, but few deductions have been drawn by the earlier workers as to its constitution. The presence of an aromatic nucleus may be concluded from the fact that sulphonic acids have been obtained, whilst nitric acid and the halogens also yield substitution derivatives. Strychnine is readily oxidized, but very little light has been thrown on the structure of the molecule from a study of the oxidation products. The most important researches from which any idea as to constitution can be drawn are those of Tafel, Leuchs, and Perkin. Tafel has shown that the action of alkalis on strychnine is one of hydrolysis, a molecule of water being added, with the resulting formation of strychnic acid, $C_{21}H_{24}O_3N_2$, and isostrychnic acid, $C_{21}H_{24}O_3N_2$, this result being obtained by the use of baryta water or of sodium methoxide as hydrolyzing agents. Strychnic acid contains the groups $-COOH$ and $>NH$, the presence of the latter group being shown by the formation of a nitrosamine. It is also a tertiary base, and on treatment with methyl iodide yields methyl strychnic acid methiodide. From these results, taken in conjunction that when heated, strychnic acid reverts to strychnine,

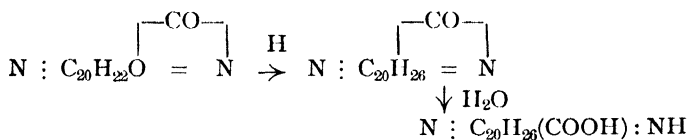
Tafel concluded that the alkaloid contained the group $\begin{array}{c} \diagup CO \\ | \\ \equiv N, \end{array}$
 the two substances being related thus:—



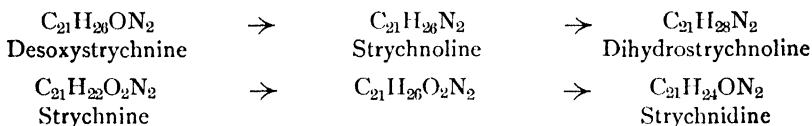
such a grouping readily explaining the fact that strychnine only combines with one equivalent of an acid, the second nitrogen atom being present in the form of the non-basic group $-CO.N$.

The presence of this grouping receives further confirmation by a study of the reduction products of strychnine. By heating the alkaloid with hydriodic acid and phosphorus an atom of oxygen is eliminated, and a mon-acid base, $C_{21}H_{26}ON_2$ (desoxystrychnine) is formed, which, on hydrolysis with sodium ethoxide, is converted into desoxystrychnic acid, $C_{21}H_{28}O_2N_2$, an imino-acid, resembling strychnic acid in properties. Thus the groups

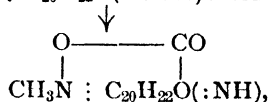
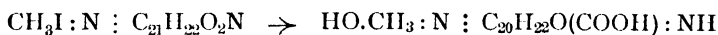
N : and .CO.N : of the strychnine molecule are unaltered by reduction, and the reaction may be formulated.



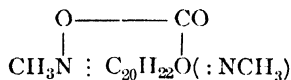
Desoxystrychnine, on reduction with sodium and amyl alcohol, is converted into strychnoline $\text{C}_{21}\text{H}_{26}\text{N}_2$ (the group $-\text{CO}-\text{N}:$ becoming $-\text{CH}_2.\text{N}:$), which, on electrolytic reduction, becomes dihydrostrychnoline, $\text{C}_{21}\text{H}_{28}\text{N}_2$. The electrolytic reduction of strychnine itself yields tetrahydro-strychnine, which readily loses water and passes into strychnidine



The presence of the quinoline complex in the molecule has been determined in the following way. Nitration yields picric acid and a monobasic acid, dinitrostrychol carboxylic acid $(\text{NO}_2)_2.\text{C}_9\text{H}_2\text{N}(\text{OH})_2.\text{COOH}$. This acid, when heated to 200°C . with water, loses carbon dioxide and is transformed into dinitrostrychol $(\text{NO}_2)_2.\text{C}_9\text{H}_3\text{N}(\text{OH})_2$, a substance which Tafel regards as dinitro-dihydroxyquinoline. Again, strychnine methiodide, on treatment with silver hydroxide, yields methyl strychnine

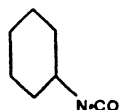


a substance showing all the properties of a betain and of a secondary base. It combines with methyl iodide to form dimethyl strychnine

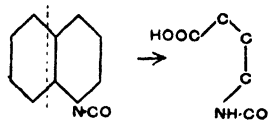


which behaves as a tertiary base, yields a nitrosamine, condenses with benzaldehyde to form a leuco-base resembling leuco-malachite green, and combines with diazobenzenesulphonic acid

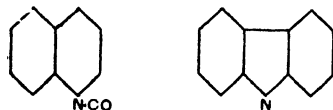
to form a yellow dyestuff, properties which show its great resemblance to the dialkyl anilines and to N-methyltetrahydroquinoline. From this behaviour Tafel concludes that strychnine contains a quinoline nucleus, and that the $-NCH_3$ group in dimethylstrychnine, and hence the $-NH$ group in methylstrychnine and the $-N.CO-$ group in strychnine is combined by one linking direct to the benzene ring, and that the alkaloid must therefore contain the grouping



Oxidation of strychnine and of brucine (*i.e.* dimethoxystrychnine) with chromic acid gives a monobasic acid, $C_{15}H_{17}O_2N_2.COOH$, which is a carbazole derivative, since it yields carbazole when distilled over zinc dust. Again, since the oxidation of brucine yields the same acid as the oxidation of strychnine, the two methoxy-groups must have disappeared, and it follows that the benzene ring of the quinoline complex in the two alkaloids is broken down during oxidation.

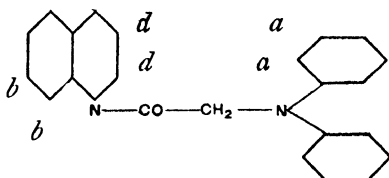


Knowing the presence of the groupings

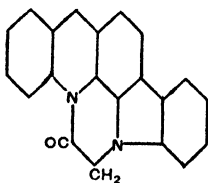


and taking into account the number of hydrogen atoms in strychnine which point to the pyridine and carbazole nuclei being almost completely reduced, Perkin has arrived at the following conclusions concerning the structure of the molecule. As these groupings contain C_{22} and strychnine only C_{21} , at least one carbon atom is common to both. Now, since the basic nature of strychnine is due to the carbazole nitrogen atom, the

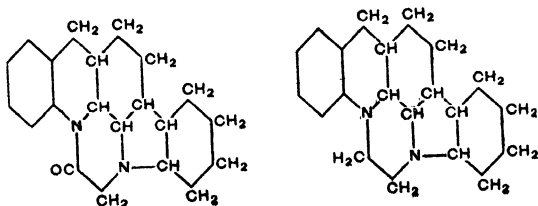
attempt to construct a formula on the assumption that one carbon atom is common to both would lead to the nitrogen atom of the carbazole residue being rendered tertiary by union with a carbon atom of the quinoline nucleus, whilst the $>CO$ group would unite with the carbazole nucleus, thus leading to a formula which cannot represent strychnine. As an alternative, it may be assumed that two carbon atoms are common to both, and that the skeleton which now contains C_{20} is completed by an additional carbon atom between the CO group and the basic nitrogen atom, thus giving



further fusion taking place between the carbon atoms at *aa* and *bb*, or *aa* and *dd*, the latter being taken as preferable, since the former would yield a seven-membered ring which would not seem likely to be formed by the elimination of water from strychnic acid, such elimination with formation of a six-membered ring being, however, quite usual. Thus the strychnine skeleton may be represented as



which leads to desoxystrychnine and dehydrostrychnoline being

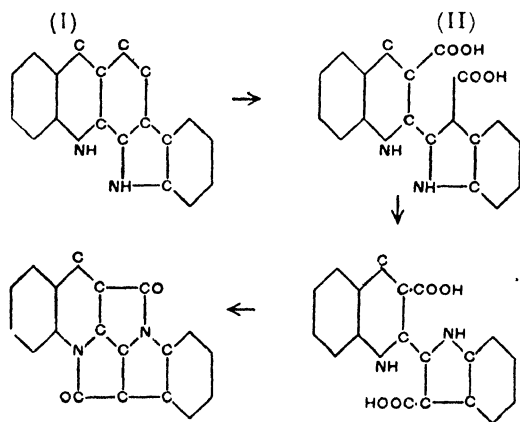


188 MODERN RESEARCH IN ORGANIC CHEMISTRY

This skeletal structure also leads to an explanation of Leuchs' investigations and to a possible formula of strychnine itself. Leuchs found that strychnine when dissolved in acetone and oxidized by potassium permanganate gave a dibasic acid (strychninonic acid) which was ketonic in character, since it yielded an oxime and a carbazone. This acid has the composition $N : C_{17}H_{18}(:N.CO)(CO).(COOH)_2$. On reduction with sodium amalgam it yields strychninolic acid, the group $>CO$ becoming $>CH.OH$, and this alcohol acid, when left in contact with dilute alkali for some time, is decomposed into glycollic acid and strychninolone, $C_{19}H_{18}O_3N_2$, which has neither basic nor acidic properties. Now to produce such a substance as strychninolone it seems evident that reaction must take place between two $COOH$ groups and basic nitrogen atoms, and since two such atoms are required for the process, it follows that the grouping $:N.CO.CH_2.N:$ of the original molecule must lose $.CO.CH_2-$, which is therefore the source of the glycollic acid

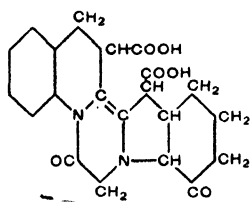


thus also giving basic nitrogen atoms to react with carboxyl groups. Hence, as the simplest way of representing the production of strychninolone, we have the the following scheme:—

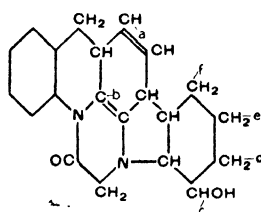


On the basis of the formulæ (I) and (II) above, the following

structural formulæ can be given to strychninonic acid and to strychnine.

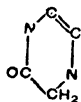


Strychninonic acid



Strychnine

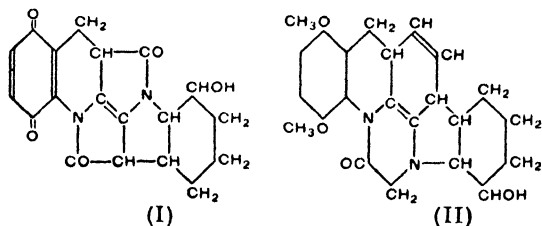
The positions assigned to the double linkages shown in the above formula are based on the following considerations. If the formula assigned to strychninonic acid is correct, one must clearly be at *a*. Position *b* is chosen for another, because it must be situated in a stable part of the molecule, otherwise it would undergo oxidation during the preparation of strychninonic acid, but experience shows such groupings as



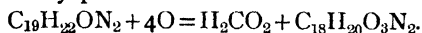
are not readily oxidized. The keto-acid (strychninonic acid) must arise from the oxidation of the $-CHOH$ group in strychnine, and this group cannot be in position *g*, for then strychninonic acid would be a derivative of benzoyl acetic acid. Positions *e* and *f* would make strychninonic acid a γ or δ hydroxy acid, but it shows no tendency to lactonize as such acids would. Of the other two available positions for the hydroxyl group, *c* was chosen preferably to *d*, by comparison of strychnine with quinine and other natural products in which such a group occurs.

Brucine has been shown by Leuchs to oxidize in a similar manner to brucinonic acid, which may be reduced to brucinolic acid, and the latter then converted into brucinolone. Now, brucinolone on oxidation with nitric acid yields a quinone, the methoxy groups present being eliminated, and this quinone, on

reduction, is converted into a quinol. Perkin is of the opinion that under these conditions a paraquinone would result, which by comparison with strychninolone should therefore possess the structure (I). Consequently, brucine would then be represented by the configuration (II).



Cinchonine, $C_{19}H_{22}ON_2$, and *quinine*, $C_{20}H_{24}O_2N_2$, are found with many other alkaloids, in cinchona bark, and are very closely related, cinchonine containing an unsubstituted quinoline nucleus, whilst quinine contains a *p*-methoxy-group in the same nucleus. The cinchona bases are bitertiary and contain a hydroxyl group. Cinchonine is an unsaturated base containing the group $-CH:CH_2$ since it combines with two atoms of halogen, or with one molecule of an halogen hydride; and is instantaneously attacked by potassium permanganate in acid solution, one carbon atom being eliminated as formic acid, cinchotenine, $C_{18}H_{20}O_3N_2$, being simultaneously produced.

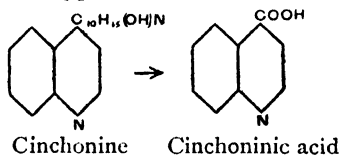


Cinchotenine contains the original hydroxyl group of the alkaloid since it is readily acylated, and in addition is a carboxylic acid, the carboxyl group probably arising from the oxidation of the vinyl group $-CH:CH_2$ in cinchonine.

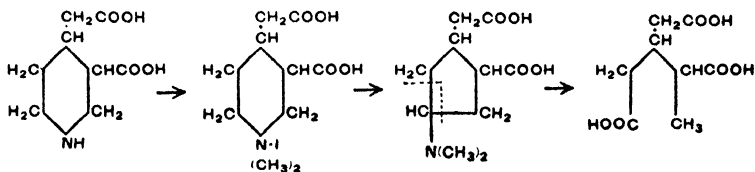
By the distillation of cinchonine with caustic alkalis, various quinoline and pyridine derivatives are produced.

The fact that cinchonine is a quinoline derivative is shown by the production of cinchoninic acid (quinoline $-\gamma$ -carboxylic acid) $C_9H_8N.COOH$, in quantity, when the alkaloid is oxidized with chromic acid. Further oxidation products, called respectively meroquinine, $C_9H_{15}O_2N$, and cincholeuponic acid, $C_8H_{18}O_4N$, are also obtained, whilst quite recently Rabe has shown that by a slight modification of the conditions another derivative, which

he designates as cinchoninone, $C_{19}H_{20}ON_2$, may be isolated. Thus cinchonine may be considered as a quinoline derivative with a side chain in the γ -position, this chain of necessity containing the hydroxyl group of the alkaloid, otherwise a hydroxy-cinchoninic acid would appear on oxidation.



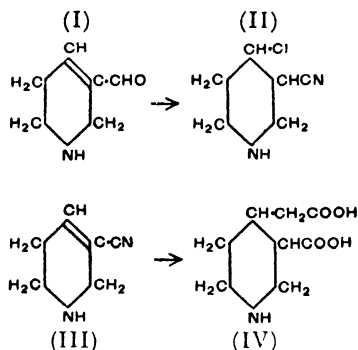
The constitution of cincholeuponic acid has been determined by Skraup from a study of its decomposition products, and has received confirmation at the hands of Wohl and Losanitsch, who have synthesized the acid. Cincholeuponic acid is a saturated dibasic acid, and contains the group $>NH$. The carboxyl groups are in the ortho-position, since the acid gives a fluorescein reaction when heated with zinc chloride and resorcinol. Again, the hydrochloride of the acid when heated with dilute sulphuric acid, to a high temperature, yields γ -picoline, and as the methiodide of methylcincholeuponic ester on treatment with caustic alkali is converted into a cyclopentane derivative which readily decomposes into dimethylamine and a tribasic acid when fused with potassium hydroxide, Skraup concluded that the acid was to be represented as



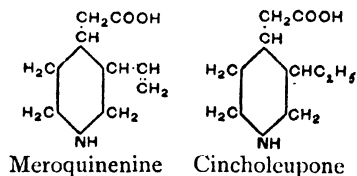
Wohl and Losanitsch synthesized the acid from iminodipropionacetal, which on treatment with hydrochloric acid passes into Δ_3 - β -tetrahydropyridine aldehyde (I), the hydrochloride of the aldoxime of this latter compound on treatment with thionyl chloride yielding the hydrochloride of 4-chloropiperidine-3-nitrile (II). By elimination of hydrochloric acid from (II), Δ_3 -tetrahydropyridine nitrile (III) is produced, and on condensation with

192 MODERN RESEARCH IN ORGANIC CHEMISTRY

sodio-malonic ester yields an addition product, which on hydrolysis gave, among other products, two stereo-isomeric 4-pipecoline-3- ω -dicarboxylic acids (IV), these representing the two possible racemic cincholeuponic acids.

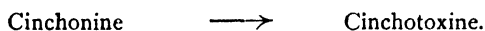


Meroquinene, $C_9H_{13}O_2N$, is a secondary base which also contains a carboxyl group. On oxidation with sulphuric and chromic acids it yields cincholeuponic and formic acids, whilst a modified reduction with hydriodic acid in the presence of zinc dust yields cincholeupone, $C_9H_{17}O_2N$. Energetic reduction by hydriodic acid and phosphorus produces β -ethyl- γ -methyl pyridine, which is also formed when meroquinene is heated with hydrochloric acid and mercuric chloride at $250^\circ C$. These results lead to the formulation of meroquinene and cincholeupone as



The results thus far obtained show that cinchonine contains a quinoline and a piperidine residue, which are of necessity united by a chain of carbon atoms attached to the γ -carbon atoms in each nucleus, this chain, on oxidation, giving rise to the carboxyl groups in meroquinene and cinchoninic acid. This chain must also contain the hydroxyl group of the alkaloid since this group does not appear in either oxidation product. Further light is

thrown on the constitution of the cinchona alkaloids by the examination of the "toxins," a series of isomeric bases formed when the alkaloids are heated with dilute acetic acid for twenty-four hours. These bases contain the :CO and :NH groups, and differ from the alkaloids by their greater toxic properties, hence their name. Brunner showed that these toxins yield a monoisonitroso derivative, and hence do not contain the group $-\text{CH}_2\text{CO}\cdot\text{CH}_2-$ as was at one time thought probable.

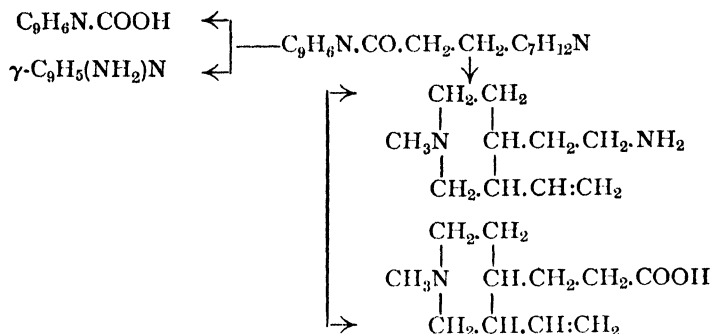


Cinchotoxine is a strong base, in which one nitrogen atom is tertiary and the other secondary in character. It is also a ketonic substance yielding an oxime and a hydrazone, absence of the aldehydic grouping being shown by the fact that methyl-cinchotoxine is not oxidized to an acid by silver oxide, and that dehydration of the oxime does not yield a nitrile.

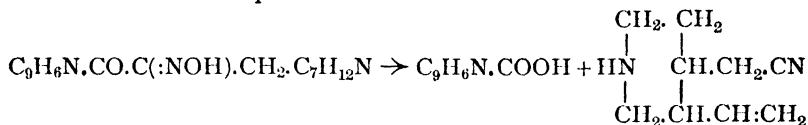
In the conversion of cinchonine into cinchotoxine, that is of a tertiary base with a hydroxyl group into a secondary base with a keto-group, the groupings must undergo molecular rearrangement as follows:—



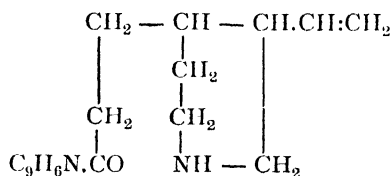
Koenigs considered that the :CO group in cinchotoxine was placed between two methylene groups, whilst Rabe, from the fact that it yields only a monoisonitroso-derivative, was of the opinion that the group is adjacent to the quinoline nucleus. A decision was arrived at by submitting the oxime of N-methyl cinchotoxine to the Beckmann reaction (using phosphorus pentachloride), the products obtained being cinchoninic acid (6%) and γ -aminoquinoline (43%), corresponding to the quinoline nucleus, together with N-methyl- β -vinyl- γ -aminoethylpiperidine and N-methyl homo-meroquinine, from the piperidine nucleus,



These results show that the :CO group in the toxins, and hence the .OH group in the alkaloid is linked to that carbon, which is directly attached to the quinoline nucleus. A similar result follows when the Beckmann transformation is applied to monoisonitrosocinchotoxine, the products obtained being cinchoninic acid and meroquinenine nitrile.

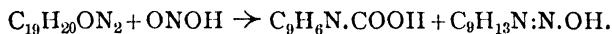


Thus cinchotoxine is to be formulated as—

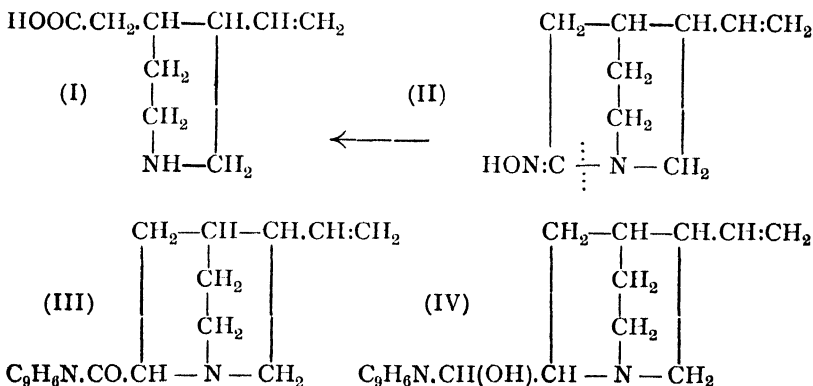


Rohde and Antonaz have arrived at a similar result from a study of the action of amyl nitrite and sodium ethoxide on the sodium salt of cinchotoxine. In this reaction the nitrite behaves as an oxidizing agent, and cinchoninic acid is formed in rather small quantity. The acid may, however, be obtained in quantitative yield by the action of nitrobenzene on the sodium salt in absolute alcohol. The products from the other portion of the molecule could not, however, be isolated, but it was shown that no meroquinenine was present, a fact which is accounted for by the assumption that the grouping $-\text{CH}_2.\text{CO}.\text{CH}_2-$ is absent, the :CO group being directly linked to the quinoline nucleus.

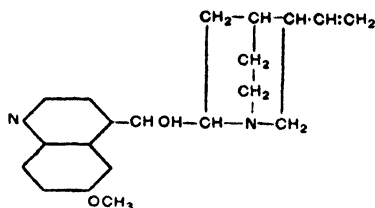
The intermediate oxidation product cinchoninone, $C_{19}H_{20}ON_2$, obtained by Rabe in 1907, has the properties of a base, a phenol, and a ketone, whilst it also exhibits keto-enolic tautomerism. The production of a ketone, here seems to point definitely to the alkaloid cinchonine containing a secondary alcohol grouping $>CHOH$. Cinchoninone forms an oxime, and gives a benzoyl derivative, but since both nitrogen atoms are tertiary in character, it follows that the acyl group must be linked to an oxygen atom. On treatment with nitrous acid, cinchoninone yields cinchoninic acid and an oxime, $C_9NH_{13}:NOH$,



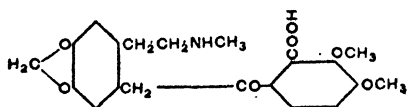
a reaction analogous to the preparation of diacetyl monoxime from ethyl methylacetoacetate, and hence pointing to the existence of the grouping $.CO.CH<$. The oxime still contains the tertiary nitrogen atom of the other portion of the molecule, and on hydrolysis yields meroquinenine and hydroxylamine. Hence, knowing the constitution of meroquinenine (I), that of the oxime must be (II), which leads to cinchoninone being (III) and cinchonine (IV).



In precisely the same manner quinine yields a ketonic derivative quinone, $C_{20}H_{22}O_2N_2$, and this on treatment with nitrous acid is decomposed into quininic acid and meroquinenine. Consequently, as quininic acid is known to be *p*-methoxyquinoline- γ -carboxylic acid, quinine must be



The formula given above for cinchonine is also rendered probable by analogy with narcotine, for just as cinchonine may be converted into cinchotoxine, so Rabe has shown that narcotine when heated with dilute acetic acid passes first, probably, into its isomer, gnoscopine, and then decomposes into cotarnine and meconine, together with a keto-base nornarceine—



from which it would appear probable that narcotine and cinchonine contain the group $>N.CH.CH(OH)-$ in common.

BIBLIOGRAPHY

A complete list of references to papers dealing with the alkaloids has not been attempted, but only the more important papers are given in each case. From the list given, cross references to the earlier work may in most cases be obtained, and these may be supplemented by recourse to Pictet's "Les Alcaloides Végétaux," and Guareschi's "Alkaloide."

- Arecaidine** . . . Jahns, *Ber.* 1888, **21**, 3404; 1890, **23**, 2972; 1891, **24**, 2615.
 Wohl, *Ber.* 1907, **40**, 4712.
- Trigonelline** . . . Jahns, *Ber.* 1885, **18**, 2518; 1887, **20**, 2840.
 Hantzsch, *Ber.* 1886, **19**, 31.
 Pictet and Genequand, *Ber.* 1897, **30**, 2117.
- Piperine** . . . v. Babo and Keller, *Jour. Prak. Chem.* 1857, **72**, 53.
 Fittig and Remsen, *Ann.* 1873, **168**, 94
 Doebner, *Ber.* 1890, **23**, 2375.
 Ladenburg and Scholtz, *Ber.* 1894, **27**, 2958.

- Coniine** . . Hofmann, *Ber.* 1884, **17**, 825; 1885, **18**, 109.
Ladenburg, *Ber.* 1886, **19**, 439, 2578; 1889, **22**, 1403;
1894, **27**, 3062; 1897, **30**, 485; 1906, **39**, 2486.
Wertheim, *Ann.* 1862, **123**, 157; 1864, **130**, 269.
Wolfenstein, *Ber.* 1895, **28**, 1459.
Schotten and Baum, *Ber.* 1882, **15**, 1947; 1883, **16**,
643; 1884, **17**, 2548; 1886, **19**, 500.
- Nicotine** . . Pictet and Rotschy, *Ber.* 1907, **34**, 696.
Skraup and Vortmann, *Monats.* 1882, **3**, 599; 1883,
4, 591.
Pinner, *Ber.* 1891, **24**, 61, 1378; 1892, **25**, 292, 765;
1894, **27**, 1053, 2861; 1895, **28**, 456, 1932.
Pictet and Crepieux, *Ber.* 1895, **28**, 1904; 1898, **31**,
2018.
- Atropine** . . Lossen, *Ann.* 1864, **131**, 43; 1866, **138**, 230.
Ladenburg and Rugheimer, *Ber.* 1880, **13**, 376, 2041;
Ann. 1883, **217**, 74.
Fittig and Wurster, *Ann.* 1879, **195**, 153.
Ladenburg, *Ber.* 1879, **12**, 942; 1880, **13**, 252; 1881,
14, 227, 2126, 2403; 1882, **15**, 1028, 1140; 1883,
16, 1408; 1884, **17**, 157; 1887, **20**, 1647; 1890, **23**,
1780, 2225; 1902, **35**, 1159, 2295; *Ann.* 1883,
217, 74.
Merling, *Ber.* 1881, **14**, 1829; 1882, **15**, 286; 1883,
16, 1238; 1891, **24**, 3108; 1892, **25**, 3123; *Ann.*
1883, **216**, 329.
Willstätter, *Ber.* 1896, **29**, 393, 936, 1575, 1636, 2216,
2228; 1897, **30**, 731, 2679; 1898, **31**, 1534; 1901,
34, 129, 3163; 1902, **35**, 1870; *Ann.* 1901, **317**, 204,
267, 307; 1903, **326**, 1, 23.
- Cocaine** . . Lossen, *Ann.* 1865, **133**, 351.
Einhorn, *Ber.* 1888, **21**, 3029; *Ann.* 1894, **280**, 96.
Liebermann, *Ber.* 1890, **23**, 2518; 1891, **24**, 606.
Willstätter, *Ber.* 1897, **30**, 702; 1898, **31**, 2498, 2655.

Opium Alkaloids.

- Papaverine** . . Goldschmiedt, *Monats.* 1883, **4**, 714; 1885, **6**, 372, 667,
954; 1886, **7**, 485; 1887, **8**, 510; 1888, **9**, 42, 327,
349, 762, 778; 1889, **10**, 156, 673, 692; *Ber.* 1884,
17, 491.
Koenigs and Nef, *Ber.* 1887, **20**, 622.
Pictet, *C.R.* 1909, **149**, 210; *Ber.* 1909, **42**, 2943.
- Laudanosine** . . Pictet and Athanasescu, *Ber.* 1900, **33**, 2346.
Pictet, *C.R.* 1909, **148**, 925; *Ber.* 1909, **42**, 1979.

198 MODERN RESEARCH IN ORGANIC CHEMISTRY

- Narcotine** . . . Beckett and Wright, *Jour. Chem. Soc.* 1875, **28**, 583.
 Wöhler, *Ann.* 1844, **50**, 1.
 Matthiessen and Wright, *Ann.* (Suppl. 7), 1871, 63.
 Wegscheider, *Monats.* 1882, **3**, 384; 1883, **4**, 262.
 Lagodzinski, *Ber.* 1895, **28**, 1427.
 Fritsch, *Ann.* 1898, **301**, 352.
 Vongerichten, *Ann.* 1881, **210**, 79.
 Roser, *Ann.* 1886, **234**, 116; 1888, **249**, 156; 1889, **254**, 334.
 W. H. Perkin, *Jour. Chem. Soc.* 1909, **95**, 1977.
 Salway, *ibid.* 1910, **97**, 1208.
- Morphine, Codeine, and Thebaine** . . . Matthiessen and Wright, *Ann.* (Suppl. 7), 1871, 364.
 Beckett and Wright, *Jour. Chem. Soc.* 1874, **27**, 1038; 1875, **28**, 23, 315.
 Vongerichten, *Ber.* 1896, **29**, 65; 1897, **30**, 2439; 1898, **31**, 2924, 3198; 1899, **32**, 1521; 1900, **33**, 352, 1824; 1901, **34**, 767, 1162, 2722; 1902, **35**, 4410; 1907, **40**, 2827, 4146.
 Hesse, *Ann.* 1871, **157**, 43; 1884, **222**, 203.
 Knorr, *Ber.* 1889, **22**, 181, 1113; 1894, **27**, 1144; 1897, **30**, 910, 918; 1898, **31**, 1071; 1899, **32**, 736, 742; 1903, **36**, 3067, 3074; 1905, **38**, 3143, 3172; 1906, **39**, 1409, 3252, 4409, 4412; 1907, **40**, 376, 2032, 2040, 3341, 3844, 3860, 4883; *Ann.* 1898, **301**, 1; 1899, **307**, 71.
 Pschorr, *Ber.* 1900, **33**, 1810; 1902, **35**, 4400, 4412; 1905, **38**, 3160; 1906, **39**, 3124; 1907, **40**, 1980, 1998, 2001, 3652.
 Freund, *Ber.* 1895, **28**, 941; 1897, **30**, 1357; 1899, **32**, 168; 1905, **38**, 3234; 1906, **39**, 844.
 Bucherer, *Jour. Prakt. Chem.* 1907, (ii), **76**, 428.
- Hydrastine** . . . Freund, *Ber.* 1886, **19**, 2797; 1887, **20**, 88, 2400; 1889, **22**, 456, 1156, 2322, 2329; 1890, **23**, 404, 2897, 2910; 1891, **24**, 2730; 1893, **26**, 2488; *Ann.* 1892, **271**, 311.
 Rossin, *Monats.* 1891, **12**, 486.
 Fritsch, *Ann.* 1895, **286**, 1.
- Berberine** . . . Schmidt, *Ber.* 1883, **16**, 2589.
 W. H. Perkin, *Jour. Chem. Soc.* 1889, **55**, 63; 1890, **57**, 991; 1910, **97**, 305.
 Gadamer, *Arch. Pharm.* 1901, **239**, 648.
 Pictet, *Ber.* 1911, **44**, 2480.
- Corydaline** . . . Dobbie and Lauder, *Jour. Chem. Soc.* 1892, **61**, 244, 605; 1894, **65**, 57; 1895, **67**, 17, 25; 1897, **71**, 657;

- 1899, **75**, 670; 1901, **79**, 87; 1902, **81**, 145, 157; 1903, **83**, 605.
- Strychnine** . . . Tafel, *Ber.* 1890, **23**, 2731; *Ann.* 1891, **264**, 33; 1892, **268**, 229; 1898, **301**, 285, 336; 1899, **304**, 49.
Hanssen, *Ber.* 1884, **17**, 2849; 1885, **18**, 777, 1917; 1887, **20**, 451.
Leuchs, *Ber.* 1908, **41**, 1711, 4393; 1909, **42**, 2494, 2681, 3703.
W. H. Perkin, *Jour. Chem. Soc.* 1910, **97**, 305.
- Cinchonine** . . . Koenigs, *Ber.* 1879, **12**, 97; 1894, **27**, 900, 1501; 1895, **28**, 1986, 3143, 3148; 1897, **30**, 1326, 1332; 1898, **31**, 2358; 1901, **34**, 4322, 4336; 1902, **35**, 1349, 2554, 2980; 1907, **40**, 648, 2873; *Ann.* 1906, **347**, 143.
v. Miller and Rhode, *Ber.* 1894, **27**, 1187, 1279; 1895, **28**, 1056; 1900, **33**, 3214.
Skraup, *Ber.* 1895, **28**, 12; *Monats.* 1895, **16**, 159; 1900, **21**, 879; *Ann.* 1879, **197**, 376.
Wohl and Losanitsch, *Ber.* 1907, **40**, 4698.
Rabe, *Ann.* 1906, **350**, 180; 1909, **365**, 353; *Ber.* 1907, **40**, 3280, 3655; 1908, **41**, 62.
Rohde and Antonaz, *Ber.* 1907, **40**, 2329.

CHAPTER V

THE RELATION BETWEEN THE COLOUR AND CONSTITUTION OF CHEMICAL COMPOUNDS

THE gradual development of synthetic chemistry in recent years, and the increasing knowledge of the relative structure of chemical compounds, has led to a desire to express a relation between the structure of compounds and their physical properties. In this way many important generalizations have been made, and, knowing the constitutional formula of a compound, one is able to deduce in many cases a number of its physical constants with a fair degree of accuracy. Since the colour of a substance is one of its most striking properties, many attempts have been made by different investigators to deduce a connection between the colour and structure of compounds.

At first, it was only "colour" of wave length between the limits of the visible spectrum that was taken into consideration, but recently much investigation has taken place in the (to the eye) invisible "ultra-violet" region of the spectrum, and it is from these ultra-violet spectra that much information is to be obtained in the elaboration of the present-day dynamic theories of colour.

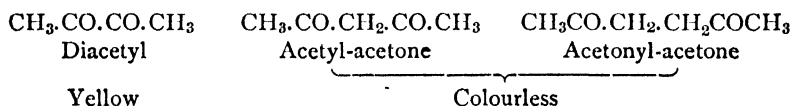
The first attempt to correlate colour with structure was due to Otto Witt, and was known as the auxochrome-chromophore theory, and it may be noted in passing that it still gives, in a limited number of cases, the best explanation of the known facts (Kauffmann, *Ber.* 1906, 39, 1959). In the development of this theory it was noticed that the introduction of certain groups into carbon compounds tended to cause a colourless compound to become coloured, and as a result of this property Witt designated these groups as "chromophores." The introduction of a single chromophoric group, however, has not usually a sufficiently

marked effect in the production of colour of visible wave length ; but if certain other groups are introduced in addition into the chromophoric nucleus (or chromogen), the auxiliary effect is almost always sufficient to produce visible colour. This second group of radicals is known as the auxochrome group, but it must be borne in mind that auxochromes alone do not produce colour when they are introduced into a colourless molecule. Thus, on this theory a coloured compound is to be regarded as consisting of a neutral radical to which are attached one or more chromophores, and one or more auxochromes.

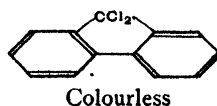
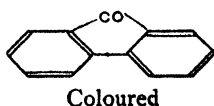
The principal chromophoric groups are the *carbonyl* $>C:O$, *thionyl* $>C:S$, *nitrile* $-C\equiv N$, *azo* $-N:N-$, *azoxy* $-N:N-O$, *nitroso*

$-N:O$, and *nitro* $-N\begin{matrix} //O \\ //O \end{matrix}$ groups, and of these the carbonyl, azo

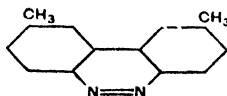
and nitro-groups are the most important. The carbonyl group by itself does not produce visible colour, but two carbonyl groups in juxtaposition usually produce coloured substances. When the two groups are more remote from each other, colourless substances again result, striking examples of such results being seen in the case of the simple α , β and γ diketones.



In the aromatic series, the presence of one carbonyl group often appears to have a disproportionately large effect, but this may perhaps be explained by the conception of the double bonds in the molecule as possessing an auxochromic character. Thus fluorenone is highly coloured, and that the colour does in this case depend on the presence of the carbonyl group is shown by the fact that if the ketonic oxygen be replaced by chlorine, the resulting di-chloro derivative is colourless.



In both the aromatic and aliphatic series it is invariably found that compounds containing the azo-grouping are highly coloured, even the simplest members of the series, namely diazomethane and diazoethane, being yellow. It is, however, in the benzene series that the effect is most marked, azobenzene, for example, crystallizing in the form of large scarlet plates. The azo-group is regarded as one of the strongest chromophores, though when found as a constituent group of a closed ring system, its effect is not nearly so marked, as, for example, in tolazone, which is only slightly coloured.



The nitro-group is also a most important chromophore, not so much by reason of the magnitude of its effect, but rather by reason of the ease with which it may be introduced, and the generality of its action.

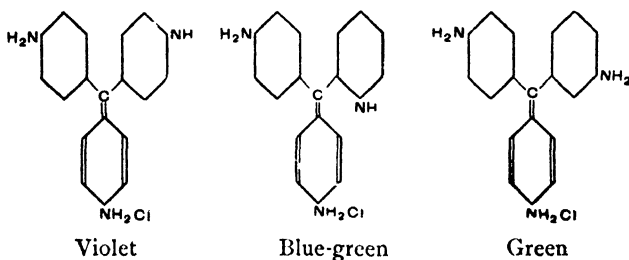
The chief auxochromes, arranged in order of magnitude of effect by Kauffmann, mainly on the evidence of magnetic rotation constants, are the *acetoxy* ($-\text{OCOCH}_3$), *methoxy* ($-\text{OCH}_3$), *acetamino* ($-\text{NHCOCH}_3$), *amino* ($-\text{NH}_2$), and *dimethyl* and *diethyl* amino groups. In addition to these there is also the hydroxyl group, the auxochromic effect of which varies considerably with its orientation in the molecule. As has been mentioned, Witt's theory assumes the action of the auxochrome to lie in intensifying the effect of the chromophore. This action is explained to be due to a finer display of forces within the molecule, caused by the strain consequent on the introduction of the auxochrome. Thus, as Kauffmann says, "The benzene ring is no dead unalterable structure, but a most delicate picture, which on the slightest touch at once alters its properties, to a greater or less extent, in reply."

Among the auxochromic groups it is found that the amino-group and its derivatives exert a greater effect than the hydroxyl group and its corresponding derivatives, for example, whilst paranitro-aniline is coloured bright yellow, paranitro-phenol is

quite colourless. Again, alkylation of the amino-group tends to produce more colour, whilst the alkylation of the hydroxyl group has apparently no settled effect, thus Liebermann has shown that the alkylation of alizarine and isoanthraflavic acid causes the absorption bands to move toward the violet end of the spectrum, whilst similar treatment of anthraflavic acid and quinalizarin moves the bands towards the red end. The introduction of several auxochrome groups has a cumulative effect, but in the case of single groups the maximum effect appears when the auxochromic group is in the ortho- or para-position to the chromophore. This is well illustrated in the case of the fuchsine dyestuffs, the effect of the position of the auxochromic group

(NH_2) in relation to the chromophore $\left(= \text{C}_6\text{H}_4 = \right)$

being shown in the colour transition from violet to blue-green and green, in the annexed examples.



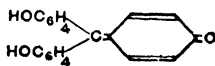
The auxochrome-chromophore theory as thus outlined has undoubtedly been of great use in the development of the theory of colour, since it has satisfactorily generalized what might have been merely a disjointed collection of facts, but in many cases it is unsatisfactory, in that it occasionally leads to anomalies. This is seen, perhaps, best in the azo-series, where addition of the auxochromes $-\text{NH}_2$ and $-\text{OH}$ has no effect in the direction indicated by theory, or indeed in some cases has a precisely opposite action.

The next development in theory was due to Armstrong in 1888, and was known as the "quinonoid" theory of colour. All quinones appear to be highly coloured compounds, and Arm-

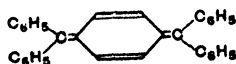
strong pointed out that most coloured compounds could be formulated as quinone derivatives, and this quinonoid structure was regarded by him as the cause of colour. The simplest quinone (benzoquinone) is of a deep golden yellow colour, and that the colour effect is due to the special grouping in the molecule, and not merely to mutual reinforcement by the carbonyl groups is clearly shown by the fact that cyclohexane-dione-1-4 is colourless, while the colour effect still persists in other quinonoid compounds. In considering examples based on this theory it is not necessary that the quinone oxygen atoms should be present, any other group united to the carbon atoms in the position 1,4, provided that it is a bi-valent group (the double bonds being essential), will suffice, thus, for example, in quinone diphenyl-dimide,



which is brown red in colour, the group $\text{C}_6\text{H}_5\text{N}=\text{}$, satisfies the necessary conditions, whilst in the "aurine" group of dyestuffs a simple quinone grouping is present.



Again, a series of coloured hydrocarbons such as, for example, tetraphenyl-*p*-xylylene,

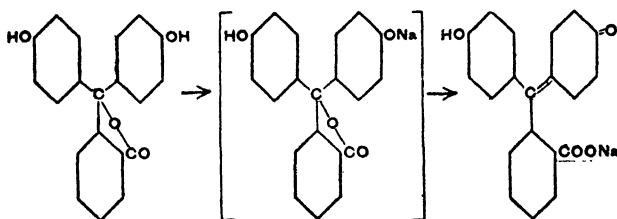


also afford a striking example of the effect of a quinonoid grouping in producing colour.

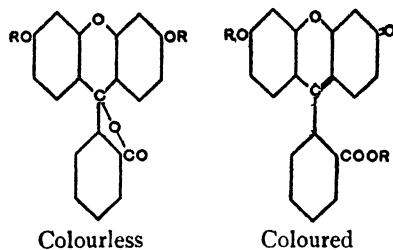
The almost universal presence of a quinonoid structure in coloured compounds gave great support to this theory, which was, however, subject to much hostile criticism, and it seems necessary to point out that although all quinones may be coloured it does not *necessarily* follow that all coloured substances should be quinonoid in structure. In view of this obvious fact it cannot be too strongly urged that when a coloured substance admits of a quinonoid formulation, all the evidence,

both chemical and physical, should be thoroughly considered, and the case treated on its merits.

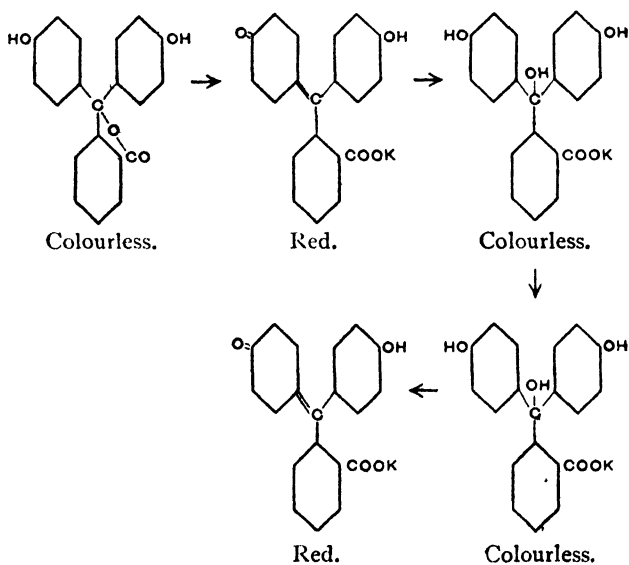
Among cases which have given rise to considerable discussion as to the validity of the quinonoid theory of colour, that of phenol-phthalein and its alkali salts has caused, perhaps, the most interest. This substance is in neutral or acid solution, quite colourless, but in the presence of caustic alkali exhibits a deep red colour. According to Ostwald, the phenomenon is to be ascribed to simple ionization. He regards phenol-phthalein as unionized, but yielding in alkaline solution a coloured ion. On the quinonoid theory the change is attributed to a change of configuration from the benzenoid to the quinonoid type of structure, it being assumed that the lactone ring in the molecule is broken, and the salt of a quinonoid carboxylic acid is produced.



Somewhat later it was found that the addition of excess of alkali or alcohol to the solution, tended to destroy the colour initially produced. According to the ionization theory one has to suppose that excess of these reagents would tend to repress any electrolytic dissociation in the solution, and so the number of coloured ions in the solution would gradually diminish, and the colour of the solution become gradually fainter and fainter as ionization diminished. The quinonoid theory found considerable support in the work of Nietzki, who showed that by working under suitable conditions, two isomeric ethers could be obtained from the potassium salt of fluorescein, one being colourless and unaffected by the addition of aqueous alkali, the other, coloured, losing one ethoxy-group under the influence of alkali. This result necessitates that the non-coloured and coloured compounds should be represented as

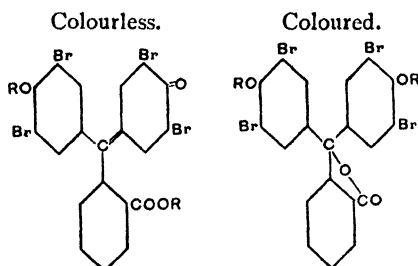


Further evidence favouring the quinonoid formulation of the coloured alkali salts of phenol-phthalein is given by the work of Perkin and Green. These authors suggest that the colour changes produced by the addition of an excess of alkali may be due to the destruction of the quinonoid grouping by the addition of a further molecule of alkali, and consequent production of a colourless carbinol compound, which on heating becomes dehydrated, and reverts to the red quinonoid form.



A conclusive proof of the quinonoid character of this type of compound was given by Meyer and Marx in 1907, when they succeeded in preparing a coloured ether of a brominated phenol-

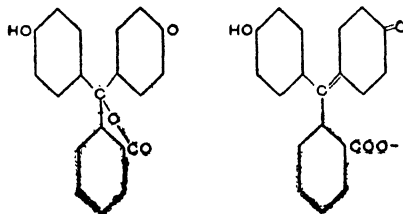
phthalein, which very easily isomerized into a colourless ether.¹



The change from the colourless phenolphthalein to its red alkali salt is thus apparently to be regarded as accompanied by a radical change in structure of the two substances. This view does not necessarily militate against any idea of ionization, for undoubtedly the phenolphthalein salts do contain a red ion, the chief point to be borne in mind is that the process of salt formation is accompanied by a change of constitution. It is possible that the ionic and chemical theories are here complementary, since for a substance to act as an indicator it must be a weak acid or a weak base, but the ion which it forms must possess a different structure from the parent substance, the latter body thus being a ψ -acid or a ψ -base. Phenolphthalein may be regarded then, as showing the following equilibrium in solution:—



X_u and X_v representing respectively:—



X_u is the more stable configuration, and the acid is very weak (the dissociation constant of phenolphthalein as measured by

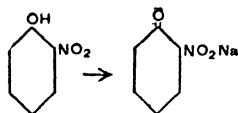
¹ Somewhat later in the same year they obtained similar ethers of the non-brominated phenolphthalein.

208 MODERN RESEARCH IN ORGANIC CHEMISTRY

Salm being 8.0×10^{-10}). Therefore $X_v.O.H$ and its ions are only present to a very small extent in neutral solution, and the absorption due to X_u is observed (this absorption is in the ultra-violet region of the spectrum, and the substance thus appears colourless). The addition of bases (*i.e.* hydroxyl ions) removes the hydrogen ions, and the colour due to the X_v configuration then makes its appearance.

The quinonoid structure of the phenolphthalein salts has also been adversely criticized by Silberrad, who has prepared compounds of similar type, which he claims cannot possibly undergo change to a quinonoid structure. But, as has been pointed out by Green, this difficulty is removed if the presence of quadrivalent oxygen in the molecule be assumed (see p. 231).

Much discussion has also taken place with regard to the constitution and colour of the azo-compounds, reference to which will be made later. No review of the quinonoid theory can be considered as complete without reference to its extension to the case of the nitro-compounds, more especially to the nitro-phenols, for it is in connection with these compounds that Hantzsch's generalization that "a fundamental change of colour on salt formation is due to a change in the structure of the compound," was substantiated. The nitrophenols are in general, weakly coloured substances, their alkyl derivatives being usually colourless. On the other hand, their alkali salts are, as a rule, highly coloured, and it was first suggested by Armstrong that this change of colour was due to an intramolecular change, salt formation being accompanied by the production of a quinonoid structure.



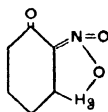
The experimental confirmation of this hypothesis was chiefly due to Hantzsch, who in a series of papers developing a theory of ψ -acids had pointed out that a marked change in properties of a substance on salt formation always connoted a structural change. This idea, of course, gave to Armstrong's conjecture an air of probability, and

by the isolation of two isomeric ethers of *o*-nitrophenol, one coloured and the other colourless. The coloured ether is labile, and passes readily into the colourless stable form, which is identical with *o*-nitroanisole. The two forms may, therefore, be represented by the general formulæ—

$\text{CH}_3\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2$
True nitrophenol ether
Colourless ; stable

$\text{O}:\text{C}_6\text{H}_4:\text{NOOCH}_3$
aci-Nitrophenol ether
Coloured ; labile

This structure of the *aci*-compounds receives corroboration from a consideration of certain coloured mercury compounds which do undoubtedly possess such an orthoquinonoid configuration. Thus the mercury salt of *o*-nitrophenol when heated, undergoes internal condensation with the production of a compound, which, by analogy, with compounds prepared by Dimroth, and by comparison with similar compounds obtained from trinitrophenol, can only be represented as—



This compound is thus similar to the ether, and is coloured. The free nitrophenols, which are coloured, are assumed to consist of a solid solution or equilibrium mixture of the two dynamic isomerides, the colour intensity depending upon the proportion of the *aci*-constituent present. Every case of colour in the nitrophenol group is explained in the light of these facts. In the case of picric acid it may be noted that the *aci*-ethers are red in colour, whilst the alkali salts are much lighter in colour, and this is explained by the existence of two series of *aci*-ethers, a light and a dark coloured one, the metallic picrates corresponding to the light coloured series.

The change of colour in the nitrophenols is not only brought about by conversion into their salts, but also by rise of temperature, and by solvents, thus, whereas light petroleum gives a colourless solution, water, with its greater ionizing power, produces a certain amount of the *aci*-form. Hantzsch does not admit that

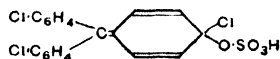
ionization alone produces colour, but considers the change is entirely structural in the first instance, and ionization is only a secondary phenomenon, and draws the conclusion that the idea of chromophore and auxochrome as separate factors in colour production does not hold, but that the phenomenon of colour is the effect of a chemical interchange which is promoted by their association in the same compound.



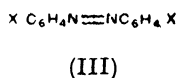
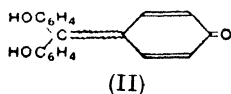
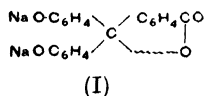
This hypothesis of Hantzsch has been criticized adversely by Kauffmann, who defends the auxochrome theory on the grounds of the change in position of the absorption band produced in benzene by the introduction of substituent groups, and on the existence of coloured ethers, such as nitroquinol dimethyl ether, the existence of Hantzsch's colourless ether being ascribed to the weak auxochromic character of the methoxy group. Hantzsch defends his position by pointing out that the absorption spectra cannot determine the presence or absence of auxochromic groups, because no relation has been shown to exist between them, and he also doubts the purity of the yellow form of nitroquinol dimethyl ether. Hantzsch considers that all nitro-compounds are colourless, and that the true nitroquinol dimethyl ether is thus colourless and exists as such in solutions in non-dissociating or feebly dissociating solvents, basing his claim on the fact that the molecular refraction of the ether in feebly dissociating solvents is only slightly greater than the calculated value, whilst in solutions in strongly dissociating solvents a pronounced exaltation of the value is observed. In a later paper Kauffmann, however, points out that Hantzsch contradicts himself, since he has already pointed out that nitrobenzene shows absorption in the extreme violet, which is only another way of saying that it is not colourless; and also that it is known that substances containing auxochromes in the benzene nucleus exhibit abnormally high molecular refraction, consequently the true nitroquinol ether must be that form existent in solutions in highly dissociating solvents, that is the yellow modification.

Reference may be made here to an idea mooted in 1905 by

Baeyer, who found that the sulphates of *p*-trichloro-, and *p*-triiodo-triphenyl carbinols are highly coloured salts which show no tendency to lose halogen on treatment with silver nitrate, a result hardly compatible with the view that these compounds possess a quinonoid structure,



for the chlorine atom in the quinone nucleus of such a compound should be easily detachable. Acting on Gomberg's idea that the yellow solutions of triphenylmethyl chloride in certain solvents are due to ionization, Baeyer introduces a distinction between an ionizable and a non-ionizable valency, the ionizable bond being represented as $\sim\sim\sim$. In the triphenylmethane series this is called the carbonium bond and is responsible for the colour. On this principle the sodium salt of phenolphthalein is represented as (I), aurin as (II), and the azo-series as (III).



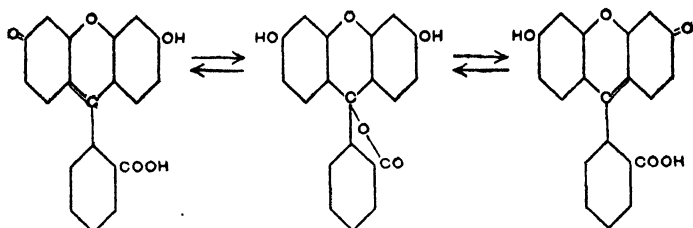
Owing to its vague and somewhat indefinite powers, this idea of the carbonium valency has not received much support.

Thus far a somewhat restricted view of colour has been taken, as, for example, in the work of Hantzsch, whose explanation of colour phenomena is a statical one, depending upon a particular structure, and it would seem advisable that the previous conceptions should be extended. Colour is produced by selective absorption of part of the spectrum and, in addition to the ordinary spectrum, the rays of which affect the eye and so produce visible colour; there are other rays of exactly the same nature which differ from ordinary light rays only in rapidity of vibration. The human eye is unable to detect and appreciate waves longer than those of red light or shorter than those of violet light. The rays of the invisible spectrum though without effect on the eye may be detected by the photographic plate, and it has been shown by Hartley and others that many substances which are

designated as colourless show selective absorption in the invisible (to the eye) ultra-violet region of the spectrum. There is no essential physical difference between selective absorption in the ultra-violet and in the visible spectrum, the distinction commonly drawn between "coloured" and "colourless" substances being in most cases a subjective one, depending on the limited capabilities of the human eye, and consequently any thoroughly scientific treatment of the subject of colour must recognize the existence of these theoretically "coloured" substances. Since absorption of light means absorption of energy the question may be asked, "To what use is this energy put?" and it seems most reasonable to consider that it is used up either in causing or reinforcing certain vibrations in the molecule, the frequencies of these vibrations being equal to those of the particular wave-lengths of the light absorbed. The view appears still more reasonable when the numerous cases in which light either induces or modifies reactions is taken into account.

By increasing the molecular weight of a compound one may suppose that the vibrations of the molecule, associated with the absorption of light, would become slower, and in this way the absorption might be shifted from the ultra-violet region into the visible spectrum. By such means a colourless body might become coloured; but there is no need to suppose a constitutional change has taken place to explain the production of colour, since it may be merely the result of adding to the weight of the vibrating structure, thereby rendering it less active. By taking into consideration such ideas as these a dynamical foundation for the relation of colour to structure has been introduced, one of the earliest attempts at such being given in 1900 by Hewitt to explain the phenomenon of fluorescence. Fluorescence is the absorption of radiant energy of definite wave-length, and the emission of the same energy after it has been reduced in vibration frequency, and, in the opinion of Hewitt, one would consequently expect to find that it is thus a property of substances which are capable of existing in tautomeric forms. If one of the forms is symmetrical in structure, then in order to pass into the other configuration, either of two displacements is

necessary, these being equal in magnitude but opposite in sign; for instance, with fluorescein itself the phases may be represented.

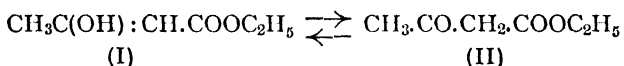


and a molecule which shows a tautomerism of this type might undergo continual and frequent change. The energy absorbed when the molecule possesses one configuration will consequently be emitted to an appreciable extent when it passes into the other configuration. Since it may be considered as certain that the vibration frequencies are different in the two forms (for the absorption spectra of the diethyl ethers of the quinonoid and lactone structure are quite different), every opportunity is given for the transformation and degradation of the energy which is necessary to explain the fluorescence.

The next attempt to show that intramolecular activity is the true explanation of colour came in 1905 from Baly and his co-workers, who have made a study of the absorption spectra of a large number of compounds. In carrying out these observations the usual method of procedure is to determine the variation of absorption with concentration, of solutions of substances, and to express these results in the form of a curve, a characteristic and quantitative record of the absorption or colour thus being obtained. By using this method it is found that substances of similar structure give the same type of curve, and this fact has been used with some degree of success to settle doubtful cases of constitution, although it may be urged in objection to the method that preconceived notions as to constitution may lead a too hasty observer to imagine and to exaggerate similarities in curves. Taking all facts into consideration, one is led from the study of absorption curves to adopt a modified view of Hantzsch's original

“Umlagerungs” theory, and to say that a change in the absorption curve of a compound affords evidence of some internal change in the molecule. Baly has gone somewhat further than this, and has offered some suggestions as to the nature of the vibrations associated with selective absorption, and finally comes to the conclusion that the origin of colour exists in the vibration of the valencies.

From the reactivity of certain diketones to chemical reagents, and from certain peculiarities shown by their absorption spectra, Baly was led to the conclusion that the diketones could not be adequately represented by static formulæ, since their properties indicate a state of dynamic isomerism. It is found, for example, that the carbonyl group in aceto-acetic ester is far more reactive towards sodium bisulphite than would be expected from current ideas on steric hindrance, the reactivity being greater than either that of acetone or methyl ethyl ketone. Usually the presence of a heavy group adjacent to the active group either retards or inhibits the reaction, and consequently it might be expected that aceto-acetic ester would be the least reactive of the above-mentioned compounds. It is evident, then, that some new influence has appeared which tends to mask or modify the steric hindrance due to the more voluminous group. Acetone shows very little sign of tautomeric change, whilst, on the contrary, aceto-acetic ester exhibits a very marked keto-enolic tautomerism. Baly ascribes the reactivity of the carbonyl group in such compounds to the actual process of tautomeric change,



thus, when a molecule of configuration (I) passes into the form represented by (II), it may be assumed from analogy with the behaviour of atoms in the nascent state that this “nascent carbonyl group” is endowed with a much greater reactivity than that possessed by the ordinary non-nascent carbonyl group, which is present in such a compound as acetone.

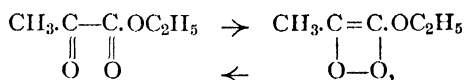
This reactivity need not, however, be occasioned purely by the wandering of the hydrogen atom from oxygen to carbon;

it may be due to some finer display of forces within the molecule, which manifests itself in the production of the characteristic absorption band in the β -diketone spectrum. The condition into which the hydrogen atom is thrown as a result of this play of forces may be termed a condition of "potential tautomerism," and the hydrogen atom will consequently possess a reactivity somewhat similar to that of an hydrogen ion.

Ethyl pyruvate, $\text{CH}_3\text{CO}\cdot\text{COOC}_2\text{H}_5$, is another ketonic substance which is extremely reactive toward sodium bisulphite, and when its absorption spectrum is examined it is found to give a band much nearer the red end of the spectrum than the band shown by aceto-acetic ester. The origin of this band may be attributed to

- (i) the keto-enolic transformation $\text{CH}_3\text{CO} - \rightarrow \text{CH}_2\text{:C(OH)} -$
- (ii) the interaction of the :CO group with the COOC_2H_5 group.

The first of these explanations is impossible, since if keto-enolic change were responsible for the absorption, the band should occupy approximately the same position in the spectrum as that of aceto-acetic ester and its derivatives. Again, the ethyl pyruvate molecule is lighter than that of ethyl aceto-acetate, and one would expect the band of pyruvic ester to be lower down in the ultra-violet spectrum than that of aceto-acetic ester, whereas the reverse is the case. As other α -diketones give similar results, Baly considered that the band in question was due to the action of the two carbonyl groups on each other, and that it was produced by the change



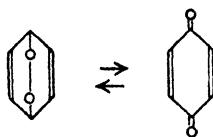
these formulæ representing different phases of the substance. This special type of oscillation was called "isorropesis" (ισορροπία , an equipoise). The isorropesis band of the α -diketones is in the blue region of the spectrum, and consequently these compounds appear yellow.

In order to account for isorropesis (*i.e.* oscillations between the residual affinities of adjacent atoms) it is absolutely necessary to have some exciting or disturbing influence present, thus, for

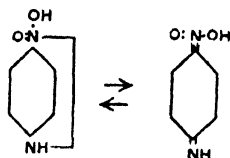
216 MODERN RESEARCH IN ORGANIC CHEMISTRY

example, in diacetyl $\text{CH}_3\text{CO}\cdot\text{CO}\cdot\text{CH}_3$ this influence is furnished by the hydrogen atoms of the methyl groups. In this compound there is an attraction exerted on the hydrogen atoms by the oxygen atoms, with the result that the residual affinities on the two oxygen atoms tend to undergo alteration, evidence of this potential isomerism existing in the incipient formation of a keto-enol type of band in the absorption curve of diacetyl. Hence the residual affinities of the two oxygen atoms are being slightly disturbed, and it is owing to this disturbance that the new oscillation occurs.

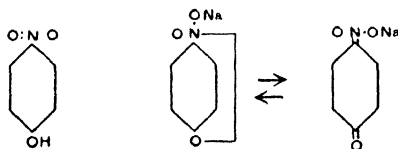
The dioxime of diacetyl is colourless, yet apparently there exists a condition for isorropesis in the molecule, although no selective absorption is shown. This condition is, however, explained by Baly on the assumption that the residual affinity of the nitrogen atoms exerts no attraction on the hydrogen atoms of the methyl group, and consequently no disturbance is set up, therefore there is no isorropesis and no colour. Having in this way attempted to express the idea that intramolecular activity is the cause of colour, Baly proceeded to defend his position by an extended study of absorption spectra. He found that the peculiarities exhibited by the aliphatic diketones were reproduced in the quinones, and the two phases of benzoquinone were therefore represented as



When once isorropesis had been detected in quinones, the extension of the theory to include all colour at once followed, for it simply became a new expression of the old quinonoid theory, the quinonoid structure being regarded as the statical representation of such an internal oscillation as affects the visible region of the spectrum. The colour of the nitroanilines and nitrophenols is ascribed in the same way to oscillations set up by the change of the residual affinities of the nitrogen and oxygen, and the two nitrogen atoms respectively :—



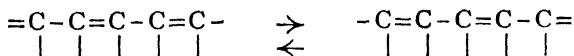
p-nitrophenol in alcoholic solution, and its sodium salt, are represented by—



The free nitrophenol is static and colourless, the sodium salt dynamical and coloured. In a recent paper Baly has abandoned his original view that the colour and absorption of the nitrophenols and nitroanilines is due to the existence of the quinonoid configuration, and considers that, in nitro-compounds generally, the absorption bands are due to isorropesis between the nitro-group and the residue of the molecule.

Very little greater generalization is apparently given by this theory than by the older theory, and it can scarcely be said that the newer phraseology gives any clearer explanation. It, however, claims consideration, since an attempt is made to recognize that not the mere orientation of the groups in the molecule, but an internal vibration among the groups, is the cause of colour.

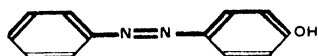
In 1907 Hewitt and Mitchell, in a paper dealing with the azo-compounds, attempted to give to the quinonoid theory a dynamic interpretation. By a consideration of the ordinary formulæ it is made clear that compounds of a quinonoid type can be represented as containing a chain of atoms linked together alternately by single and double bonds. If now in such a substance, a system of vibration—



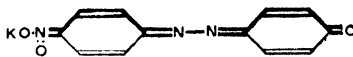
be assumed, it is obvious that the longer the chain of alternate single and double bonds, the longer will the vibration take to travel the

218 MODERN RESEARCH IN ORGANIC CHEMISTRY

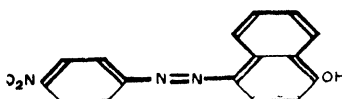
whole length of the system, hence the slower the molecular vibration. With slower molecular vibration it is clear that a greater proportion of red rays will be absorbed; or, expressed otherwise, the compound will appear more blue in shade. The method of experiment adopted was to compare the absorption curve of the azophenol with that of its *p*-nitroderivative and the sodium salt of the nitro-compound, so that in this manner the effect of the introduction of the nitro-group could first be ascertained, and secondly a direct lengthening of the chain, without the introduction of a new substance, was obtained. Thus, with the azophenol and azo- α -naphthol compounds and their salts the configurations may be expressed—



5 double, 4 single

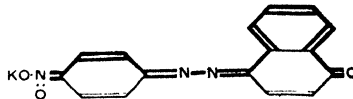


6 double, 5 single



7 double, 6 single.

Alcoholic soln. RED.



8 double, 7 single.

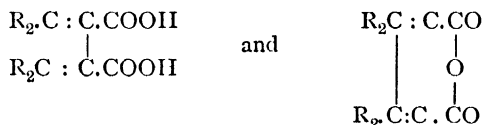
Alcoholic soln. VIOLET BLUE.

As Hewitt and Mitchell observe, the chief oscillation frequency is less, the longer the chain of alternate double and single linkages which exist in the molecule, and in estimating the number present, one is only justified in following the structure round one side of the ring until a para-position is reached, for if carried further, the action becomes retrogressive, and consequently no part of the particular displacement under consideration, but a part of the succeeding or return displacement. Many compounds were examined from this standpoint, and it was found that in each case the theory fitted in with the experimental facts. No attempt has yet been made to give any connection between the length and nature of the chain and the wave-length of the

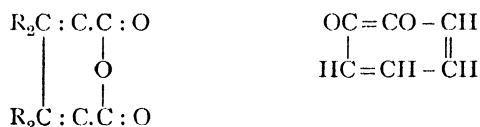
light absorbed, but it would certainly appear that on theoretical as well as on practical grounds the discovery of such a relationship is not improbable.

One may note that two series of compounds exist which cannot be brought into harmony with any of the colour theories yet proposed, namely, the fulgenic acids (and fulgides) and the fulvenes.

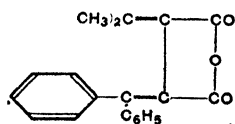
In the case of the fulgenic acids and fulgides, which are respectively of the type—



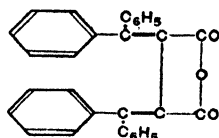
the auxochrome-chromophore theory leads perhaps to the fewest anomalies. The double bonds, carbonyl groups, and, when present, the phenyl groups are regarded as colour centres, the density of grouping of these being alleged to afford sufficient explanation of the colour produced. Adherents of the quinonoid theory have, however, suggested that the fulgides can be formulated as analogues of benzo-(*o*)-quinone—



but one cannot consider that this is the case, for the essential quinonoid grouping must of necessity be absent from a five-membered ring system containing an oxygen atom as a constituent. The phenyl derivatives, which are the most highly coloured, contain a chain of alternate single and double bonds, and it is noteworthy that the longer this chain is, the deeper the colour becomes.



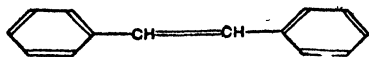
5 double, 4 single
Citron yellow



6 double, 5 single
Blood red

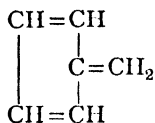
220 MODERN RESEARCH IN ORGANIC CHEMISTRY

The chain, however, is not long enough of itself to explain the colour, for stilbene, which contains a chain of five double and four single linkages, is colourless.



It may be claimed that the colour is due to isorropesis, between the carbonyl groups, but this also appears insufficient, for if isorropesis alone is responsible for the colour, then other dibasic acids of similar type should be coloured.

The simplest member of the fulvene class is—



and here again no theory has been sufficient to explain the colour of these compounds. The chromophoric double bonds are too few in number, and the chain of alternate double and single linkings is too short. The most successful explanation, perhaps because the least definite, is that which makes the fulvenes distantly analogous to benzoquinone.

Despite the activity shown in the experimental investigation of this subject, it is obvious that as yet no real relationship between colour and constitution has been determined, but it does appear probable that the final theory of selective absorption will be one which takes full cognizance of colour (using the term in its broadest sense) as an essentially dynamic property, the molecule being regarded not as a rigid structure, but as one whose components are held together by restraining influences, and which are capable of rapid oscillations. Although in particular groups much valuable generalization has been made, there is still very much unsolved, and it seems that progress will be made by a systematic study of selective absorption coupled with *chemical* evidence of constitution. In this way it may become possible to recognize in a general manner the groupings associated with the production of the vibrations giving rise to certain types of absorption, and hence to predict colour.

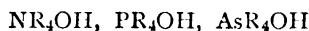
BIBLIOGRAPHY

- O. Witt, *Ber.* 1876, **9**, 522.
Kauffmann, *Ber.* 1906, **39**, 1959, 4237 ; 1907, **40**, 2352, 4243.
Armstrong, *Proc. Chem. Soc.* 1888, **4**, 27 ; 1892, **8**, 101, 103, 189, 194 ; 1893, **9**, 52, 55, 63, 206 ; 1896, **12**, 42.
Nietzki, *Ber.* 1897, **30**, 175.
Perkin and Green, *Jour. Chem. Soc.* 1904, **85**, 398.
Meyer and Marx, *Ber.* 1907, **40**, 1437.
Hewitt, *Analyst*, 1908, p. 85.
Salm, *Z. f. Elektrotech.*, 1904, **10**, 342.
Silberrad, *Jour. Chem. Soc.* 1906, **89**, 1787 ; *Proc. Chem. Soc.* 1908, **24**, 204, 209.
Hantzsch, *Ber.* 1906, **39**, 1073, 1084, 2472, 3072 ; 1907, **40**, 1556.
Baeyer, *Ber.* 1905, **38**, 569, 1156.
Hewitt *Z. f. phys. Chem.* 1900, **34**, 1.
Baly, *Jour. Chem. Soc.* 1905, **87**, 766, 1332, 1347, 1355 ; 1906, **89**, 502, 514, 966, 982 ; 1907, **91**, 1572 ; 1908, **93**, 1747, 2108.
Hewitt and Mitchell, *Jour. Chem. Soc.* 1907, **91**, 1251 ; see also Proc. VII International Congress of Applied Chemistry.

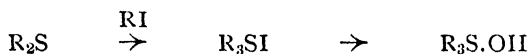
CHAPTER VI

SALT FORMATION, PSEUDO-ACIDS AND BASES

IN the study of organic compounds one finds that ammonia and allied compounds (*e.g.* phosphine, arsine, etc.) are capable of giving rise to salts, to which correspond the strong bases of the type



derived from the corresponding "X"-onium salts. A similar type is also found corresponding to the weak acid H_2S , which gives rise to the strong sulphonium bases $\text{R}_3\text{S.OH}$; the salts in this case being obtained by the action of alkyl iodides on the neutral alkyl sulphides.

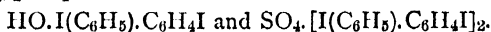


An examination of such compounds shows that in nearly all cases the grouping elements are of a positive type. An instructive example is seen in the case of iodine, which, in the form of phenyl iodide, can in chloroform solution combine with chlorine to produce phenyl iodide chloride, the latter substance passing into iodosobenzene on treatment with alkali. Iodosobenzene possesses the properties of a weak base, and to some extent acts as an oxidizing agent, and its basic nature goes to prove the basic character of iodine in such compounds. It is also found that the introduction of an iodoso-group into benzoic acid reduces the acidic strength very greatly, iodoso-benzoic acid being a much weaker acid than benzoic acid, and partaking more of a phenolic nature. These facts led V. Meyer in 1894 to attempt the isolation of derivatives of the iodonium base, $\text{HI}(\text{OH})_2$, in which effort he was to a certain extent successful, the diphenyl iodonium hydroxide and various salts being prepared. In the first experiments, iodosobenzene was placed in well-cooled sulphuric acid,

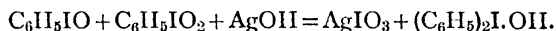
and it was found that the solution became brown and lost the power of liberating iodine from potassium iodide (a property shown by iodosobenzene). The solution is found to contain the sulphate of the new base, from which the iodide can be precipitated by the addition of potassium iodide. Since the iodide on distillation decomposes into phenyl iodide and di-iodobenzene, it must correspond to the molecular formula $C_{12}H_9I_3$,



and the base and its sulphate must consequently be $C_{12}H_9I_2.OH$ and $(C_{12}H_9I_2)_2SO_4$, or

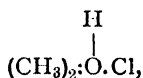


Numerous other salts have been obtained from the sulphate by double decomposition. The simple diphenyl iodonium hydroxide is obtained by triturating iodoso-benzene with moist silver oxide, the reaction depending on the fact that on exposure to sunlight the iodoso-compound is partly converted into iodoxy-benzene, $C_6H_5IO_2$, the two then reacting with the moist silver oxide as follows:—



This hydroxide is a powerful base, but is only known in aqueous solution. It forms well-defined crystalline salts, and absorbs carbon dioxide with avidity. On the addition of sodium sulphide to the solution a yellow precipitate, resembling arsenic trisulphide, is produced, whilst if ammonium sulphide be used the precipitate resembles antimony sulphide.

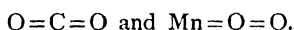
The most recent element to be brought into the positive salt-forming groups is oxygen, the quadrivalency of which was suggested as long ago as 1864 by Naquet from the analogy existing between oxygen and sulphur, selenium and tellurium, all of which act as quadrivalent elements. It was not, however, until 1875 that Friedel isolated the hydrochloride of dimethyl ether, which was formulated by Wurtz as—



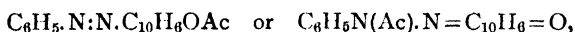
a conclusion accepted by Friedel, who was of opinion that the valency of the oxygen atom was dependent on the temperature in

224 MODERN RESEARCH IN ORGANIC CHEMISTRY

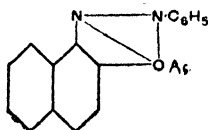
this case. Van't Hoff indulged also in some speculations regarding oxygen, based on analogy to sulphur, and concluded that in oxygen and sulphur compounds, two bonds were prominent, whilst the third and fourth bonds, although weaker, are positive, and give to sulphur its basic nature, a similar condition existing with oxygen, thus rendering possible the combination of oxygen with the chlorides of less basic elements. At a somewhat later period (1876-1888) Baeyer and Fischer obtained addition products of fluorescein and sulphuric acid, whilst Dale and Schorlemmer similarly combined aurine with acids, and Wallach prepared such compounds from cineol and halide acids. The existence of these compounds was explained on the old valency theory, but it is obvious that a simpler explanation is possible if based on the higher valency of oxygen as was advocated by Heyes in 1888, to distinguish between such oxides as sulphur dioxide, carbon dioxide, etc., on the one hand, and barium peroxide, manganese dioxide, etc., on the other. Heyes considered the possibility of the existence of quadrivalent oxygen, and formulated his oxides as—



This idea was then applied by Meldola to the case of benzene-azo- β -naphthol, the acetyl derivative of which can be formulated as—

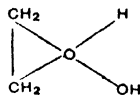


and in order to decide the question of structure Meldola isolated the reduction products of the acetyl compound, and obtained aniline, β -acetoxy- α -aminonaphthol, acetanilide, and α -amino- β -naphthol, from which he suggested that the acetylated azo-compound might be formulated as—



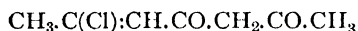
thus necessitating the presence of quadrivalent oxygen. This view, however, is not generally accepted, since Auwers, in 1904, showed that in hydrazones the acetyl group can wander from an

oxygen atom to a nitrogen atom, a process which will readily explain the formation of four different substances by the reduction of Meldola's acetyl derivative. Again, the anomalous behaviour of ethylene oxide in precipitating metals as hydroxides from solutions of their salts suggests the quadrivalency of the oxygen atom, the oxide in aqueous solution being represented as



for in no other way does the production of metallic oxides seem possible.

This idea, however, of quadrivalency for oxygen was not generally accepted until the work of Collie and Tickle (1899) on dimethyl-pyrone was published. It had been shown at an earlier period that dehydracetic acid, when heated under pressure with fuming hydrochloric acid, yielded a compound, $C_7H_{11}O_3Cl$, which was shown by Feist to lose water, when dried over sulphuric acid, and to pass into $C_7H_9O_2Cl$. From this behaviour Feist concluded that it should be represented as a derivative of diacetyl-acetone.

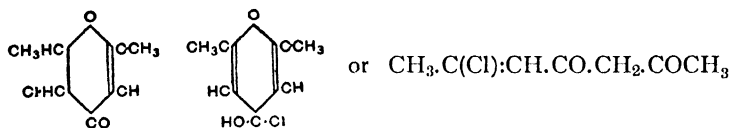


Collie and Tickle, however, pointed out that such a formula does not agree with the reactions of the compound, since it gives no colour reaction on the addition of ferric chloride, whereas diacetyl acetone gives a colour reaction. Again when dissolved in water it behaves as a mixture of dimethyl pyrone and hydrochloric acid, a reaction which seems very unlikely if the structure of the compound is, as advocated by Feist, with a chlorine atom directly united to carbon. The same substance can be prepared by the direct union of dimethyl pyrone and hydrochloric acid, and in aqueous solution possesses a strongly acid reaction, while from such a solution the dimethyl pyrone may be extracted by means of chloroform, and the amount of hydrochloric acid directly determined by titration. The compound in question may be recrystallized from water, and is relatively stable whilst in its reactions it behaves exactly as the salt formed from a strong

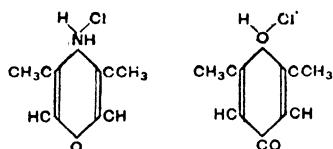
226 MODERN RESEARCH IN ORGANIC CHEMISTRY

acid and a weak base. A similar series of salts were also obtained from other acids, such as hydriodic acid, nitric acid, hydrobromic acid, chlorplatinic acid, picric acid, etc., but the sulphate and acetate have not been obtained.

The ordinary graphic formulæ based on the simpler valency relations obviously fail to account for the existence of such salts, since, for example, the above hydrochloride would have to be represented as—



which will not allow for the production of dimethyl pyrone and hydrochloric acid when the hydrochloride is decomposed by water. But regarding these compounds as salts of weak bases and strong acids, and bearing in mind their resemblance to the corresponding $\alpha\alpha$ -dimethyl- γ -lutidone compounds, a solution of the difficulty is obtained by the consideration of the oxygen atom as quadrivalent, thus—



and, moreover, if oxygen can replace P, N, and S in bases, then these oxygen compounds can be regarded as derivatives of the hypothetical *oxonium hydroxide* $\text{OH}_3.\text{OH}$, just as the similar compounds of nitrogen, phosphorus, sulphur, and iodine are regarded as derived from the hypothetical bases NH_4OH , PH_4OH , H_3SOH , and $\text{H}_2\text{I.OH}$, and these salts can consequently be designated as *oxonium*¹ salts. The solutions of such salts have the characteristic properties that are to be expected in the salts arising from the combination of a weak base and a relatively

¹ A compound derived from dimethyl pyrone, in which the oxygen atom is in ternary oxonium combination, can be obtained by the action of dimethyl sulphate on the pyrone. To compounds of this type Kehrman naturally assigned structure I (A=acid radical), but Baeyer (*Ber.* 1910, 43, 2337) has

strong acid, in that they exhibit the phenomenon of hydrolytic dissociation, and consequently give a strong acid reaction in aqueous solution. The hydrolysis is not, however, complete in the case of a moderately concentrated solution of dimethyl pyrone picrate, for Walden in 1901 compared the partition coefficient of picric acid between benzene and water both with and without the addition of dimethyl pyrone, and found that the ratio

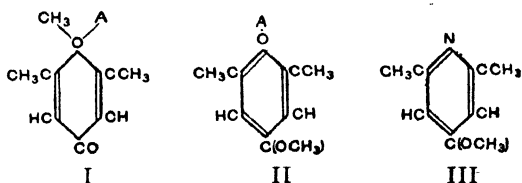
$$\frac{\text{Concentration of benzene solution}}{\text{Concentration of aqueous solution}}$$

is less when the dimethyl pyrone is present, and so concludes that in the aqueous solution the pyrone exists in the form of a picrate. Other methods have also led to the same conclusion, thus from measurements of the depression of the freezing point of aqueous solutions of the hydrochloride, the amount of the depression obtained, if no compound existed in solution, should be equal to the sum of the depressions produced by the known amount of the pyrone and of hydrochloric acid present, whereas the actual values obtained are less than this sum. Again, if no compound were formed, the electrical conductivity of the solution should be the same as the conductivity of a solution of pure hydrochloric acid of the same concentration, but if any appreciable amount of the salt exists in solution this will of necessity give

+

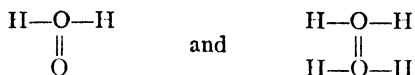
rise to a certain amount of $C_7H_8O_2 \cdot H$ ions and of Cl ions, which means that the number of hydrogen ions in the solution would be less than the number present in a solution of pure hydrochloric acid of the same concentration, and consequently the electric conductivity would be greatly reduced. Actual experiments

recently shown that structure II should be employed instead, since ammonia converts the compound in question into γ -methoxy-lutidine (III).

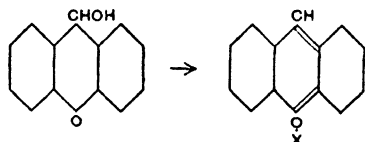


show that this is the case, and that the conductivity tends to decrease more and more as the solution becomes more concentrated.

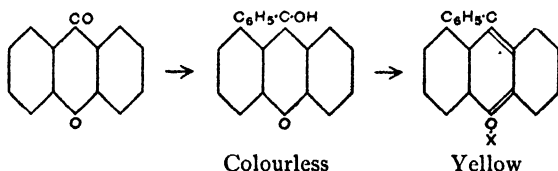
Many instances may be given in which this idea of oxonium salts offers an explanation of observed facts. Thus Brühl in 1897 drew attention to the fact that the observed molecular refraction in the case of hydrogen peroxide is much greater than the calculated value, and advocated the quadrivalency of oxygen both in the peroxide and also in water, the two compounds being represented as shown :—



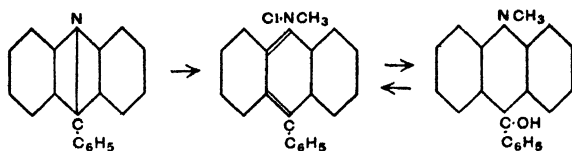
It has been known for many years that the colourless xanthinol dissolves in hydrochloric or sulphuric acid to form a yellow solution, showing a strong green fluorescence, a result which may be explained on the assumption—



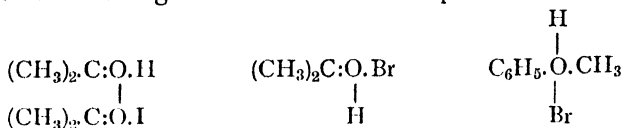
Confirmation of this is given by Werner's isolation of the ferri-chlorides of compounds of such types, and by Hewitt's preparation of the salts of fluoran and fluorescein with mineral acids, whilst a similar type of reaction may be seen in the case of xanthone derivatives, thus—



a condition in this latter case which may possibly be comparable with that obtaining in the acridine series.

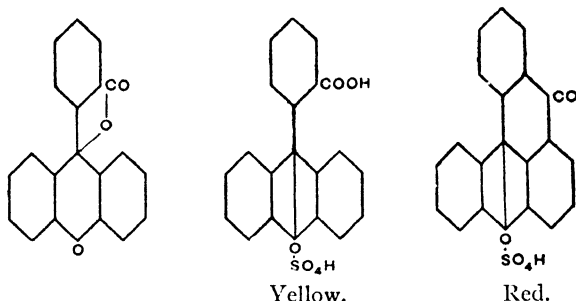


Baeyer and Villiger in 1901 and 1902 made an exhaustive examination of many substances in which the possibility of quadrivalent oxygen was existent, and isolated and examined compounds of ethers, alcohols, acids, esters, aldehydes, and ketones, with oxalic, ferrocyanic, ferricyanic, chlorplatinic, and other acids, and have in all cases explained in a satisfactory manner their results, by the assumption of the quadrivalency of oxygen. Walker and his co-workers have found that many organic substances containing oxygen and nitrogen dissolved in the liquefied acids and yielded conducting solutions, and also that there was strong evidence in favour of the existence of additive compounds, facts which can receive a satisfactory explanation in the case of nitrogen on the assumption of change from the trivalent to pentavalent condition, whilst a similar explanation of change of valency could be given in the case of oxygen. Archibald and M'Intosh have obtained definite compounds of hydriodic acid with diethyl, methyl amyl, and phenyl methyl ethers, acetone, and ethyl and propyl alcohols. Hydrobromic acid forms similar compounds except in the case of ethyl alcohol, and hydrochloric acid also, except in the cases of methyl and propyl alcohols. These substances are all colourless crystalline compounds of definite melting point, and their structure is explained on the assumption that oxygen possesses valencies higher than that usually assigned to it. The following structural formulæ have been given to some of these products—

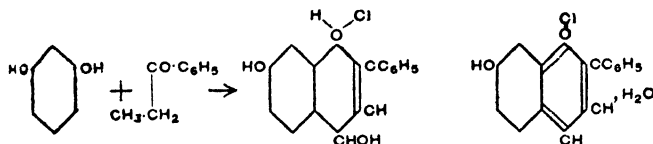


the authors assuming that the lower the temperature at which the reaction is carried out the higher will be the valency of the oxygen atom. Further examples of the production of oxonium

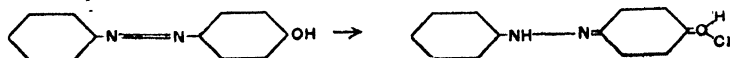
salts are seen in the cases of the coeroxonium salts obtained by Decker from the action of fuming sulphuric acid on fluoran and its derivatives, these compounds dissolving in the acid with production of a yellow salt from which water is eliminated and a stable red salt is ultimately obtained.



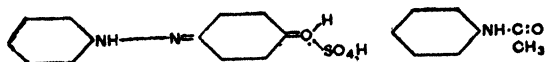
Perkin, in 1908, also obtained pyranol salts by the condensation of resorcinol and resorcylic aldehyde with ketones in the presence of hydrochloric acid, and found that they gave well-defined platinum-chlorides and ferrichlorides.



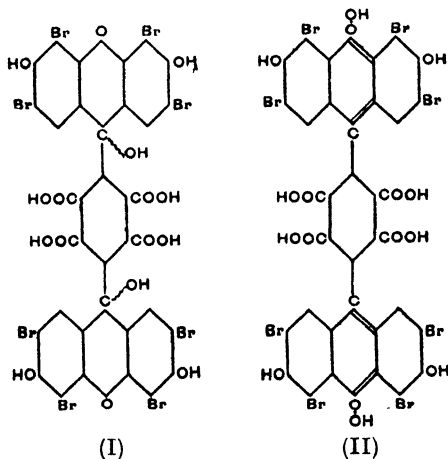
Finally, as further examples of oxonium salts may be mentioned the hydrochlorides of the hydroxyazo-compounds and their ethyl ethers, which have been prepared by Hewitt and his co-workers in recent years,



a structure which agrees with the colour changes noticed on dissolving the azophenols in acid, and with the results of nitration in the presence of concentrated sulphuric acid, the ordinary ortho-para law being obeyed, since the benzene nucleus in acetanilide and in the sulphate of benzene-azo-phenol may be considered as analogous.

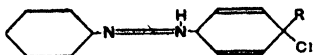


In some of the cases cited above, opposition has been brought forward to the oxonium salt theory, and a carbonium structure has been given to the salts. Baeyer, from a consideration of the salts of the triphenyl carbinol dyestuffs, came to the conclusion that their colour was due to an abnormality of one valency of the central carbon atom of the grouping, and he assumed that this bond differed essentially from the others, and was, in fact, an ionizing valency, thus $(\text{CH}_3\text{O}\cdot\text{C}_6\text{H}_4)_3\text{C}\cdot\text{HSO}_4$ was written as $(\text{CH}_3\text{O}\cdot\text{C}_6\text{H}_4)_3\text{C}\sim\text{HSO}_4$. This idea was extended by Silberrad to the case of octobromo-3,3¹-6,6¹-9,9¹-hexahydroxydixanthyl benzene tetracarboxylic acid, which was written as (I), and he concludes that such coloured substances can in nowise be regarded as quinonoid in type, the colour being due to the latent chromophoric action of the 9,9¹-xanthyl carbon atoms. It, however, seems strange that the analogy of the xanthyl group to the acridines should have escaped notice, and since the existence of quadrivalent oxygen is scarcely to be doubted after the work of Baeyer and Villiger and others, these xanthyl derivatives may perhaps thus be considered as quinonoid oxonium hydroxides (II).

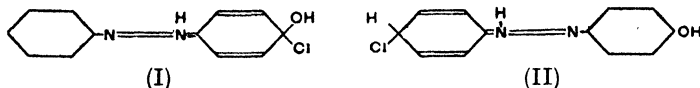


F. Baker has used the carbonium idea for the formulation of the salts of the azophenols and their ethers, but, as Hewitt points out, there are grave objections against such a structure which

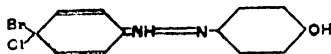
involves nitrogen in a quinquevalent condition never before observed. The general formula of such salts is given by Baker as



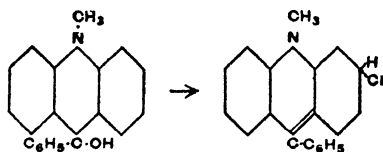
and this has met with hostile criticism from Hewitt and Fox, who indicate that it is not apparent whether Baker intends to represent the hydrochloride of benzeneazophenol as (I) or (II).



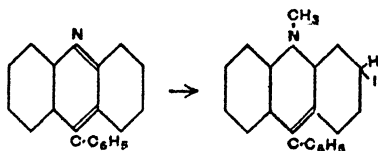
for a compound of structure (I) should not be so readily attacked by substituting agents, whilst against (II) may be urged the fact that the hydrochloride of *p*-bromobenzeneazophenol and the hydrobromide of *p*-chlorobenzeneazophenol are absolutely different, whereas such a structure would require them to be identical, viz. :—



Gomberg also is in favour of the carbonium structure for the salts of the acridine series, which he writes as shewn,

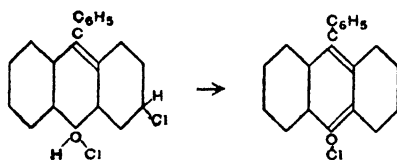


addition taking place on the carbon atom as against the nitrogen atom. If this view is accepted, then one should assume

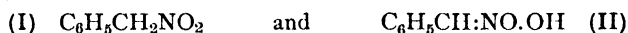


which seems to be counter to the general ideas of salt formation, for a common-sense point of view would indicate that in a stable

salt it seems obviously preferable to assume that the negative element is attached to the element capable of forming a strong base, so that if a choice is to be made between carbon and nitrogen then one would by preference attach the negative element to nitrogen. The same idea has also been extended to the xanthenols, the intensely coloured hydrochloride of the phenyl xanthenol being represented by the formula (I), but Kehrman is of the opinion that this salt when heated passes with elimination of hydrogen chloride into the coloured oxonium chloride (II).



In order to account for the existence of certain types of compounds which do not contain hydrogen directly replaceable by metal, but which are capable of changing into a salt forming isomeride, Hantzsch, in 1899, introduced his conception of *pseudo-acids*. A well-known example of such a case is seen in phenylnitromethane, which, as ordinarily prepared, is a colourless liquid, soluble to a certain extent in water and without action upon ferric chloride solution. On treatment with sodium ethoxide it forms a sodium derivative, which, on acidification with dilute acid, passes into a solid form of the nitro-compound. This modification is relatively unstable, and, on keeping, gradually passes back again into the liquid form. The solid form is probably hydroxylic in structure, since its aqueous solution gives a red brown coloration on the addition of ferric chloride, whilst the substance itself also reacts with phenyl carbimide, phosphorus pentachloride, and benzoyl chloride. The two forms may thus be represented:—



the sodium salt corresponding to (II), the iso-nitroso configuration. The liquid form, although it gives rise to a sodium derivative, is not, strictly speaking, an acid, but is designated by Hantzsch as a pseudo-acid (ψ -acid), and before it yields a

sodium salt it undergoes intramolecular rearrangement, yielding the isonitroso or true acid form. Again, the sodium salt, on treatment with a mineral acid, yields first the true acid or isonitroso-form, which, however, is unstable and gradually passes into the true nitro-compound or ψ -acid. The investigations of Hantzsch show that the following criteria may be used for the recognition of ψ -acids:—

(i) The compound is a ψ -acid if it *gradually* neutralizes an alkali. The ψ -acid as such does not neutralize the base, but on transformation into the true acid neutralization takes place, and of necessity, if the transformation is slow, then the process of neutralization must also be gradual. Again, if it is found that on decomposition of a solution of the salts with an equivalent quantity of a mineral acid, the electrical conductivity of the solution is considerably greater at first than after the lapse of some time, it indicates that the acid is a ψ -acid, the explanation being that the iso-form is a true acid, and is, therefore, a conductor in aqueous solution, whilst the solution of the normal modification is a non-conductor.

(ii) If the compound is neutral or only feebly acid, and yields salts which are neutral or feebly basic, that is, salts which are not hydrolytically dissociated, then it is a ψ -acid, and the salts are derived from a more strongly acid isomeride. In such a case a neutral solution of the salt mixed with an equivalent quantity of an acid remains neutral.

(iii) If the compound gives a colourless solution in ionizing solvents, but yields coloured salts and coloured ions in alkaline solution, then it is a ψ -acid.

(iv) An abnormally large temperature coefficient in the conductivity or dissociation constant of a solution, is an indication of the presence of a ψ -acid.

(v) If a substance does not combine directly with water or alcohol, but yields a stable hydrate or alcoholate by indirect methods, then it is a ψ -acid.

(vi) If a substance does not form a salt by direct combination with dry ammonia in a non-dissociating solvent (*e.g.* anhydrous hydrocarbons), but does so in the presence of water, then the

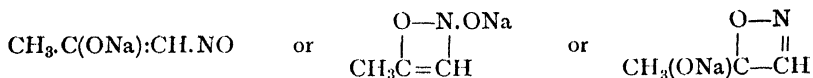
substance is a ψ -acid. The formation of a salt, however, does not prove that the compound in question is a true acid.

The method of characterization of ψ -acids by the ammonia reaction is applicable when the following conditions are fulfilled:—

- (a) The compound gives an ammonium salt in ionizing media.
- (b) The ammonium salt is insoluble in non-ionizing liquids.
- (c) The compound gives no precipitate of the ammonium salt on treatment with dry ammonia in the non-ionizing liquid.

As a rule it is merely necessary to see if the compound gives a precipitate of an ammonium salt in anhydrous ether solution, and if so, then it is a ψ -acid provided the salt is insoluble in benzene or chloroform. The method is of use for distinguishing between groups of isomeric and tautomeric substances and for detecting *ionization isomerism*.¹ The conclusion that all compounds which combine directly with ammonia, in benzene solution, are true acids, cannot be drawn, since a ψ -acid may undergo isomerism in the benzene solution, under the influence of the ammonia, and again, all enolic compounds yield ammonium salts in non-ionizing media.

Among the numerous compounds which behave as ψ -acids may be mentioned nitromethane and its mono and dibromo derivatives, phenyl-nitromethane (see above) and numerous other compounds, some typical examples of which are mentioned in the following context. *Isonitroso-acetone*, $\text{CH}_3\text{COCH:N.OH}$, is neutral to litmus and forms no compound with ammonia. The increase in conductivity of its sodium salt from dilution 32 to 1024 litres is only very little greater than that exhibited by salts of strong acids, and the sodium salt again is only very slightly hydrolyzed in aqueous solution. Hence the salt is perhaps to be considered as

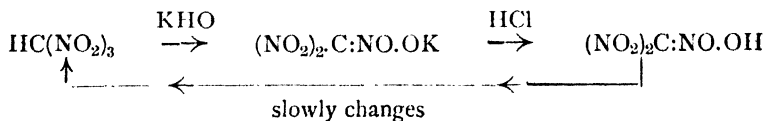


¹ When the salt-forming modification of a substance is not known in the free state, but only in solution (or as an ion in aqueous solution), Hantzsch describes the case as one of *ionization isomerism*.

236 MODERN RESEARCH IN ORGANIC CHEMISTRY

Quinone-oxime, $\text{HON:C}_6\text{H}_4\text{:O}$, is a ψ -acid, since it does not unite with ammonia, and the sodium salt shows the normal increase in conductivity, consequently this salt must be the salt of a strong acid. In aqueous solution quinone-oxime has an acid reaction and a large value for its dissociation (affinity) constant, and in very dilute aqueous solution possesses the same colour as equivalent solutions of the red sodium and green potassium salts. It would thus appear that the oxime undergoes partial transference in aqueous solution, and the case is one of ionization isomerism. On the other hand, the dioxime shows no appreciable conductivity, and the sodium salt is a true oxime salt, since it is largely hydrolyzed in aqueous solution.

Nitroform, $\text{CH}(\text{NO}_2)_3$, dissolves readily in solutions of caustic alkali, forming a yellow salt which does not undergo hydrolytic dissociation. On the addition of mineral acid to the solution a large electric conductivity is shown at first, but this gradually diminishes until it reaches the value due to that of the alkali ion and the mineral acid ion present in solution. The colour of the solution also disappears gradually, and the normal variety of nitroform may be extracted from the colourless solution.



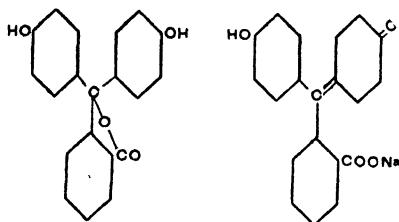
The *acid amides*, R.CONHX , are all ψ -acids, in the solid non-dissociated condition behaving as compounds R.CONHX , whereas their alkali salts possess the structure RC(OM):NX .¹ The true acids (isoamides) RC(OH):NX have not yet been obtained in the solid state. The tendency of these ψ -acids to form salts with true acids increases with the negative character of the group $\text{X}(\text{Cl}, \text{CN}, \text{NH}_2)$.

The *nitro-amines*, R.NH.NO_2 , are also ψ -acids and show a great tendency to undergo ionization isomerism.

The same idea may also be applied in the case of the phthaleins,

¹ M = metal.

thus in the case of phenolphthalein and its mono-sodium salt, which may be represented as



it is highly probable that the colourless free phenolphthalein is of the lactone type, whilst its highly-coloured sodium salt is quinonoid in structure, the free phenolphthalein thus behaving as a ψ -acid.

Similar considerations to those mentioned above may be extended to certain bases, and just as one can have ψ -acids, so the existence of ψ -bases may be assumed. These ψ -bases are neutral substances isomeric with the true ammonium hydroxides, and are capable, by the process of isomeric change, of passing into bases of the ammonium hydroxide type. Somewhat similar criteria are available for identifying such compounds, as were employed in the case of ψ -acids, the chief being:—

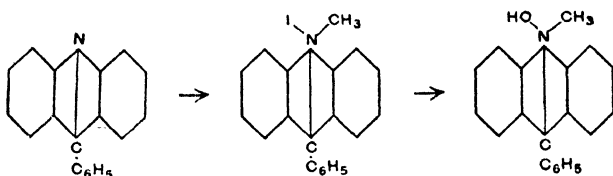
(i) The phenomenon of gradual neutralization, in which the conductivity of a mixture of a salt of the base and sodium hydroxide gradually decreases to that of the sodium salt produced, as the true base changes to the ψ -base.

(ii) Abnormal neutralization phenomena: where the velocity of change in (i) is too great to be observed, the neutral ammonium salt giving a neutral solution on the addition of one equivalent of alkali and the neutral ψ -base giving a neutral salt when mixed with one equivalent of acid.

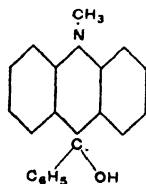
(iii) The reluctance of the ψ -base to combine with an anhydrous acid or with an acid anhydride.

(iv) The formation of abnormal ethers and anhydrides.

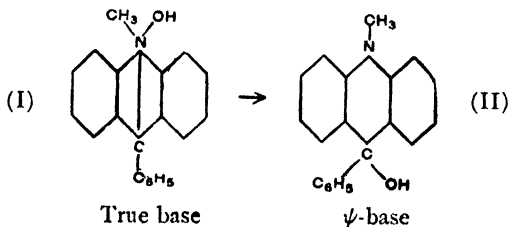
As examples of ψ -bases may be mentioned *methyl phenyl acridinium hydroxide*, which was obtained by Berntsen,



and was given the above constitution, corresponding to a quaternary ammonium base. The properties of the hydroxide do not, however, agree with the above structure, for such a compound should be a strong base, and should also dissolve in water and yield a strongly alkaline solution, whereas it is insoluble in water, and shows none of the properties associated with compounds of the type $R_4N.OH$. It is, on the other hand, soluble in hydrocarbon solvents, and behaves like a carbinol, so that Hantzsch considers it should be formulated as



the true base (I), which is at first liberated when its salts are decomposed by alkali passing into the ψ -base (II). This is practically a non-electrolyte, as is shown by the fact that when a solution of the hydrochloride of the base is mixed with an equivalent quantity of sodium hydroxide solution, the solution possesses at first a maximum conductivity, which gradually diminishes until it reaches the value for a solution of sodium chloride of the same concentration.



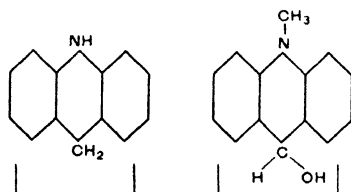
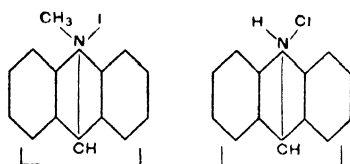
The values for the conductivity at 0° of a mixture of equal quantities of $\frac{1}{128}$ N. solutions of the base and sodium hydroxide are given by the numbers—

On mixing	178.1
At 1 min. after mixing	160.4
„ 30 „	„	„	.	.	.	101.8
After 18 hours	61.6

The equivalent conductivity (*i.e.* conductivity \div concentration) of sodium chloride at dilution $v = 256$ is 61.1.

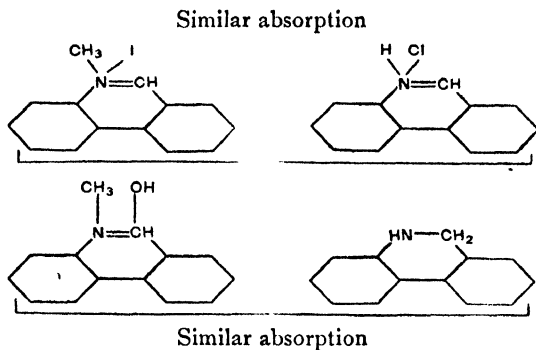
The above views of Hantzsch on the relation of quaternary ammonium salts to ψ -bases have received confirmation in the recent work of Tinkler, who has made spectroscopic examinations of acridine derivatives, and finds that acridine methiodide and acridine hychlorodide give practically identical absorption spectra, but that when caustic soda is added to an aqueous alcoholic solution of the methiodide, the absorption spectrum obtained closely resembles that of dihydroacridine.

Identical absorption spectra

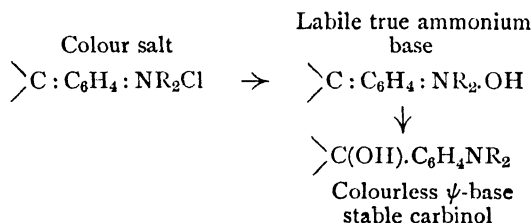


Identical absorption spectra, but different from other pair

Similar changes have been observed with methyl acridine derivatives and also with phenanthridine methiodide and its hydroxide.

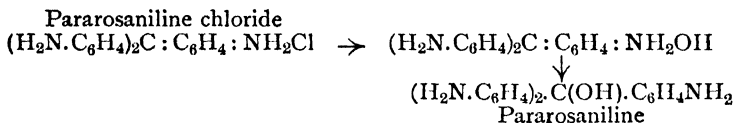


Several interesting examples of ψ -bases are found among the dye-stuffs of the triphenylmethane series. Crystal violet (hexamethyl-pararosaniline chloride) $[(\text{CH}_3)_2\text{N} \cdot \text{C}_6\text{H}_4]_2\text{C} : \text{C}_6\text{H}_4 : \text{N}(\text{CH}_3)_2\text{Cl}$ in solution, when mixed with an equivalent quantity of a base, at first still remains highly coloured, the solution being strongly alkaline, and conducting an electric current. After standing, however, for some hours the colour is gradually discharged, the alkalinity of the solution disappears, and it no longer conducts the electric current. The solution now contains the colour base which may be considered as a ψ -base of the carbinol type, the changes being represented:—

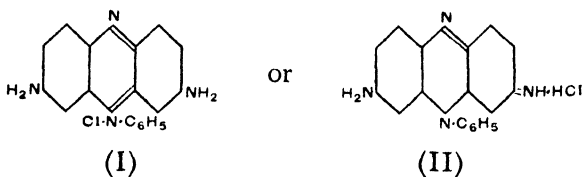


A similar condition appears to prevail among the triphenylmethane dyes generally, thus *pararosaniline chloride*, $\text{C}_{19}\text{H}_{18}\text{N}_3\text{Cl}$, on treatment with alkali, yields the colourless base $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$, which was recognized by E. and O. Fischer as being an ordinary carbinol base, and Rosenstiehl had suggested that the salts were consequently of the type $(\text{H}_2\text{N} \cdot \text{C}_6\text{H}_4)_3\text{C} \cdot \text{Cl}$, *i.e.* esters of a tertiary alcohol. This explanation does not, however, agree with the known facts, since on treatment with alkali the same phenomena

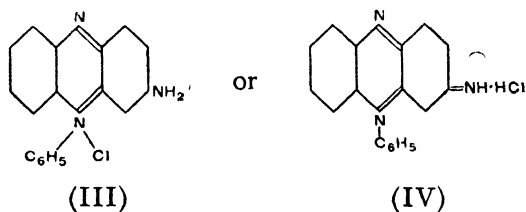
are observed as in the case of crystal violet, and a similar formulation of the colour salt true base and ψ -base must hold.



Considerable discussion has taken place as to the structure of the cyclic oxazine and thiazine dyestuffs, Hantzsch holding the view that they are paraquinonoid in structure and behave as quaternary ammonium salts, whilst Kehrman looks upon them as orthoquinonoid oxonium and thionium salts. Kehrman supports his views, as also in the case of the safranines, by the diazotizability of the amino-group, thus phenosafranin readily yields a chloride which may be either



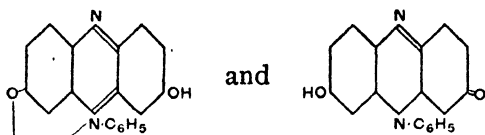
and this, when diazotized and boiled with alcohol, is converted into aposafranin, which may thus be



Since, however, aposafranin could be diazotized in the presence of concentrated sulphuric acid, and nitrogen eliminated from the product by boiling with alcohol (the addition of ferric chloride then salting out phenylphenazonium ferrichloride), Kehrman concluded that a free amino-group is present in aposafranin, which is consequently to be represented by (III), thus necessitating the chloride of phenosafranin being (I). The corresponding

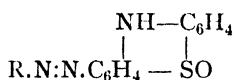
242 MODERN RESEARCH IN ORGANIC CHEMISTRY

formulae for hydroxyaposafranone, which had earlier been obtained by Nietzki and Otto, are

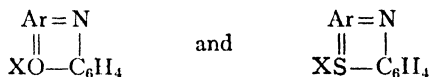


the former being favoured by Kehrmann. This would, however, lead to aposafranone being an internal salt of phenolic and quaternary ammonium functions, a conclusion in many respects at variance with facts, for such a compound should add on the elements of water and yield a strongly basic ammonium hydroxide, a result not realizable in practice.

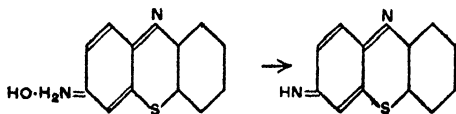
Since the azo-compounds obtained from the cyclic thiazine series are of the type



Hantzsch argues that the addition of water is a necessary preliminary to the possibility of diazotization, and that a quaternary ammonium salt type with paraquinonoid structure is present. He points out also that the salts of type

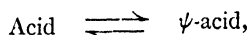


which Kehrmann views as the parent substances of Meldola's blue and methylene blue, are the salts of very weak bases, and are hydrolytically dissociated by water, whilst Meldola's blue and methylene blue are stable salts, the chlorides of Lauth's violet and Meldola's blue showing no more hydrolytic dissociation than does ammonium chloride. The addition of alkali brings about rapid and radical change in the base of Meldola's blue, whilst the hydroxyl base of Lauth's violet seems to have a transient existence, then passing into an anhydro-base,



methylene blue giving a more stable base, the addition of one equivalent of alkali only leading to a *gradual* decrease of electrical conductivity which is probably due to gradual absorption of carbon dioxide from the air, the base undergoing autocatalysis into methylene azure.

The theory developed by Hantzsch regarding the existence of ψ -acids and bases cannot be perhaps accepted in its entirety, for it necessitates the idea of ψ -acids and bases being characterized by the hydrolysis of their salts in aqueous solution giving abnormal values. Undoubtedly this relation is proved experimentally in a large number of cases, but it hardly accords with the relation expressed by the simple equilibrium equation—



and, as Kaufmann has pointed out, a consistent application of the theory of electrolytic dissociation to the problem leads to the conclusion that the hydrolysis of salts of the ψ -acid should be normal. v. Zawidski has assumed that the abnormal behaviour of ψ -acids is accounted for by the supposition that they may be amphoteric electrolytes.

BIBLIOGRAPHY

- V. Meyer, *Ber.* 1892, **25**, 2632 ; 1893, **26**, 1354, 1727 ; 1894, **27**, 502, 1592.
 Friedel, *Ber.* 1875, **8**, 777.
 Heyes, *Phil. Mag.* 1888, [5], **25**, 221.
 Meldola, *Phil. Mag.* 1889, [5], **26**, 403.
 Feist, *Ber.* 1892, **25**, 315, 340 ; *Ann.* 1890, **257**, 253.
 Collie and Tickle, *Jour. Chem. Soc.* 1899, **75**, 710.
 Walden, *Ber.* 1901, **34**, 4185.
 Baeyer, *Ber.* 1910, **43**, 2337.
 Bruhl, *Ber.* 1897, **30**, 162.
 Hewitt and Tervet, *Jour. Chem. Soc.* 1902, **81**, 663.
 Baeyer and Villiger, *Ber.* 1902, **35**, 1201.
 Archibald and M'Intosh, *Jour. Chem. Soc.* 1904, **85**, 919.
 Decker, *Ann.* 1906, **348**, 210.

244 MODERN RESEARCH IN ORGANIC CHEMISTRY

Perkin, *Jour. Chem. Soc.* 1908, **93**, 1085.

Baeyer, *Ber.* 1905, **38**, 570.

Silberrad, *Jour. Chem. Soc.* 1906, **89**, 1787.

Baker, *Jour. Chem. Soc.* 1907, **91**, 1490.

Hewitt and Fox, *Jour. Chem. Soc.* 1908, **93**, 333.

Hantzsch, *Ber.* 1899, **32**, 3066, 3109; 1900, **33**, 278; 1902, **35**, 210, 226,
877, 1001; 1906, **39**, 2098, 2478; 1907, **40**, 3798.

Tinkler, *Jour. Chem. Soc.* 1906, **89**, 856.

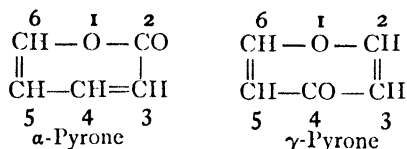
Kehrmann, *Ann.* 1902, **322**, 1. *Ber.* 1906, **39**, 914, 1403.

Hantzsch, *Ber.* 1906, **39**, 1365. •

CHAPTER VII

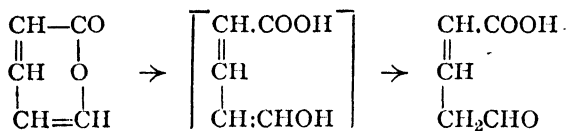
THE PYRONES

THE pyrones are a series of six-membered heterocyclic ring compounds which may be considered as the anhydrides of diolefine- δ -hydroxylactonic acids, or as the anhydrides of diolefine dihydroxy-ketones. The former are known as the α -pyrones, the latter the γ -pyrones, corresponding respectively to the formulæ—



the attached numerals indicating the positions assumed by substituents. In the pyrone series the oxygen ring member is readily replaced by the equivalent imino-group ($:\text{NH}$), when these compounds are digested with ammonia, and in this way the pyridones (hydroxy-pyridine derivatives) are obtained

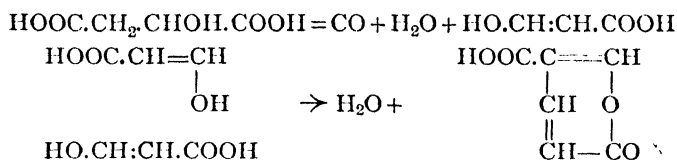
α -Pyrone, $\text{C}_5\text{H}_4\text{O}_2$, is obtained by the distillation of the mercury salt of coumalic acid (α -pyrone-5-carboxylic acid) and is a crystalline solid. It is readily decomposed by the action of caustic alkali, ring fission taking place in the 1:2 position with production of an unsaturated hydroxy-acid, which, however, rearranges itself to form the more stable formyl crotonic acid.



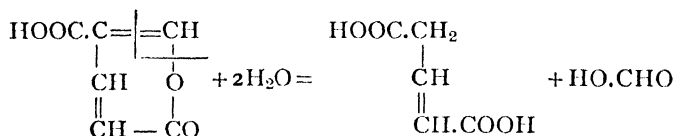
Coumalic acid is produced when malic acid is treated with fuming sulphuric acid to 100°C ., and it may be assumed in this reaction that the first stage of the change consists in the elimi-

246 MODERN RESEARCH IN ORGANIC CHEMISTRY

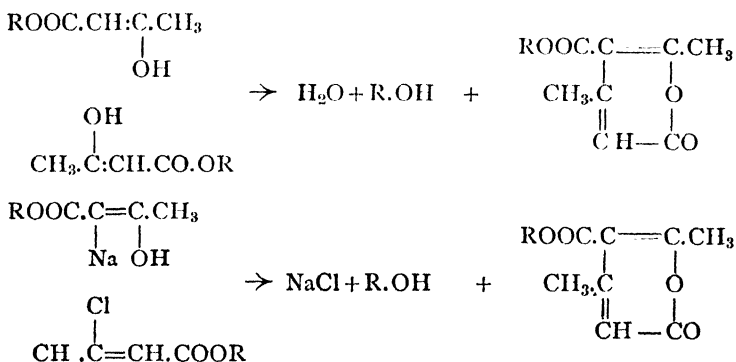
nation of carbon monoxide and of water from the malic acid, with the consequent production of hydroxy-methylene acetic acid, two molecules of this acid then reacting together to yield coumalic acid and water.



Coumalic acid is a crystalline solid and yields colourless crystalline salts. When boiled with baryta water it decomposes with formation of glutaconic and formic acids.



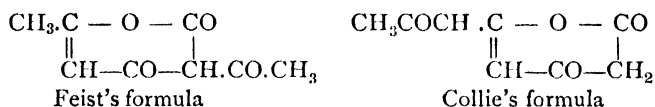
Dimethyl-coumalic acid (isodehydracetic acid), $\text{C}_8\text{H}_8\text{O}_4$, is an isomer of dehydracetic acid, and is obtained by the action of sulphuric acid on aceto-acetic ester, or by the condensation of sodium aceto-acetic ester with β -chloro-isocrotonic ester.



The free acid when heated to 240° C. loses carbon dioxide and is converted into dimethyl coumalin or mesitene lactone.

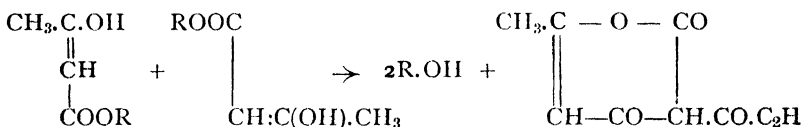
The most important of the α -pyrone derivatives, and certainly the one which has given rise to most discussion, is dehydracetic

acid, $C_8H_8O_4$, a compound first isolated in 1866 by Geuther, and which since then has been the subject of many investigations. Two alternative formulæ for the acid at present are in use, one due to Feist and the other to Collie. Each of these seems to answer fairly well with respect to the properties and reactions of the acid, and consequently a definite decision as to which is the more correct as yet seems impossible. The acid is thus represented as—

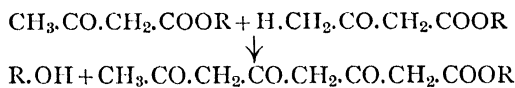


and is consequently a pyronone derivative. It is obtained by heating aceto-acetic ester alone, or with acetic anhydride at 200°C ., or by heating acetyl chloride with pyridine. It yields crystalline salts and is very reactive. On hydrolysis with cold alcoholic potash it reverts to aceto-acetic ester, whilst if a hot concentrated solution be used, the products of hydrolysis are acetone, and carbonate and acetate of potassium. These reactions may be explained as follows:—

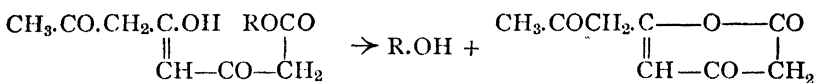
Synthesis (Feist)



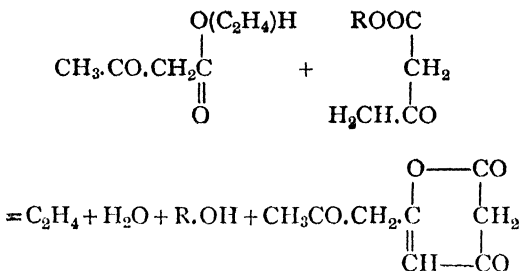
or (Collie)



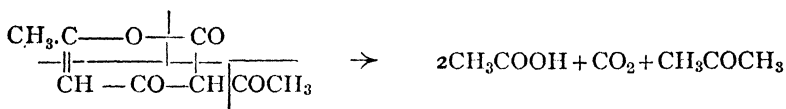
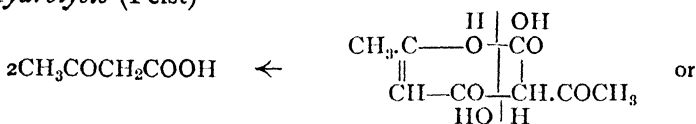
this ester now reacting in the enolic form and yielding the acid.



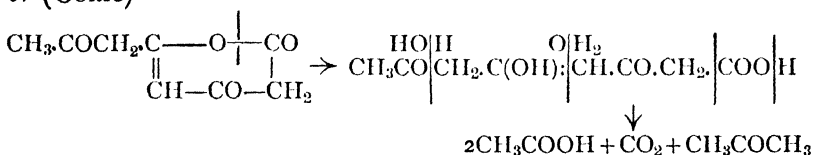
Since, however, a certain amount of ethylene is always simultaneously produced, it may be that this latter reaction takes the modified course—



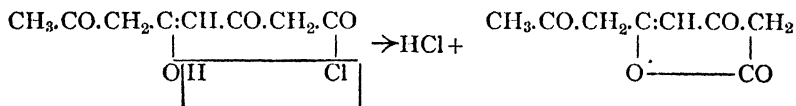
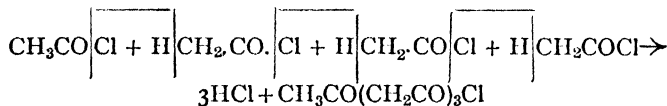
Hydrolysis (Feist)



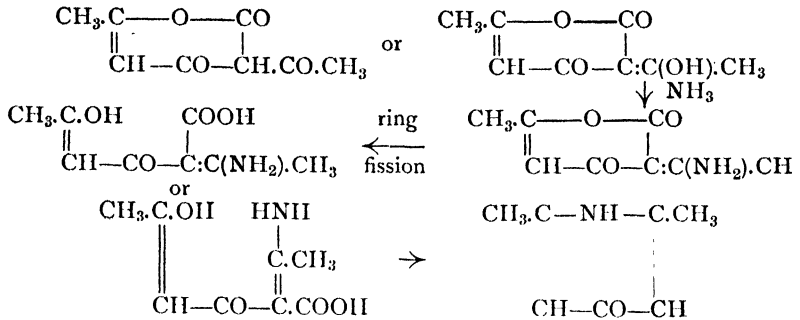
or (Collie)



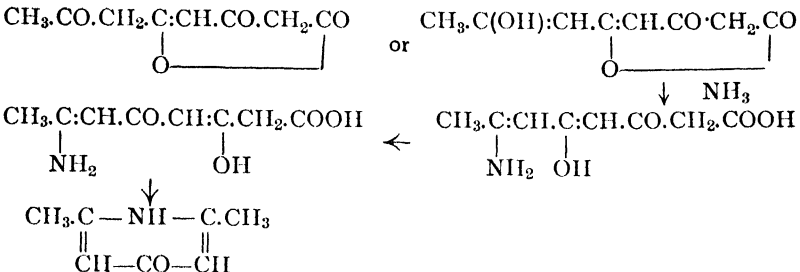
Collie's formula also explains the formation of dehydracetic acid from acetyl chloride, more readily than that of Feist.



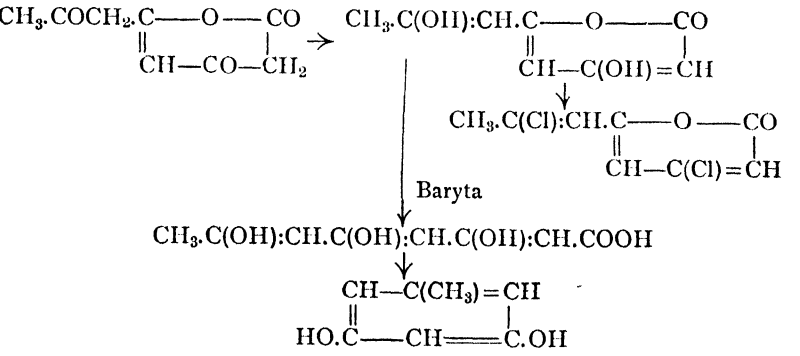
The acid reacts readily with ammonia to form pyridone derivatives, a result more easily explained on the Collie formula, although Feist has given a very ingenious interpretation to the reaction,



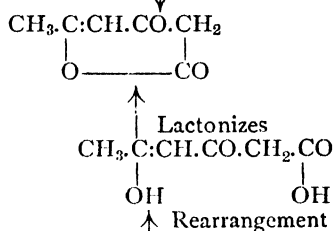
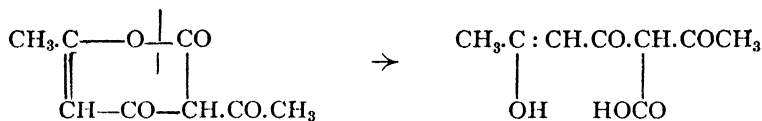
or (Collie)



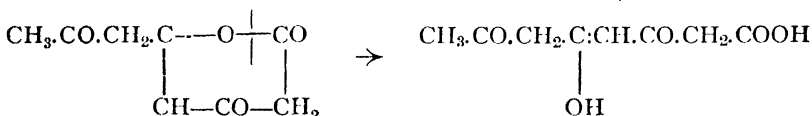
Dehydracetic acid on treatment with phosphorus pentachloride yields a dichloro-derivative, and on hydrolysis with caustic baryta yields orcinol, both reactions being readily explained by the Collie formula, but not by that of Feist.



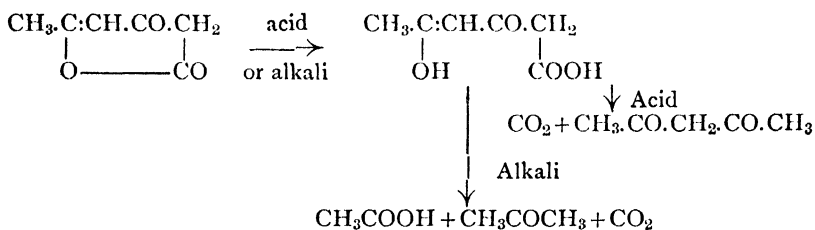
The production of triacetic lactone by heating dehydracetic acid with 90 per cent. sulphuric acid at 130° C. is readily explained by both formulæ.



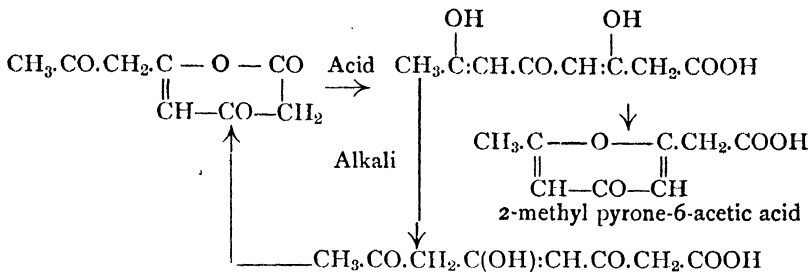
or



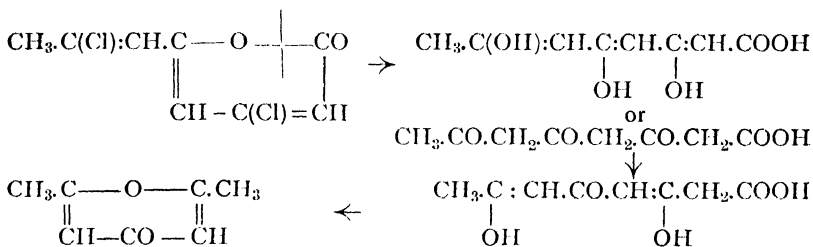
The triacetic lactone formed in this reaction, on treatment with excess of sulphuric acid is decomposed with production of acetyl acetone, whilst on hydrolysis by caustic alkali it yields acetone and alkali carbonate and acetate.



In 1907 Collie found that if the strength of the sulphuric acid used in the above reaction be reduced to 85 per cent., the yield of the triacetic lactone is diminished, but a compound, $\text{C}_8\text{H}_8\text{O}_4$, is obtained. This compound, when heated to 200°C . or with hydrochloric acid, decomposes into carbon dioxide and dimethylpyrone, and also when hydrolyzed with caustic baryta yields malonic and acetic acids. The solution of the sodium salt of this compound when boiled for some time decomposes with production of dehydracetic acid, and its fission product diacetyl acetone. These reactions are explained by Collie in the following manner:—

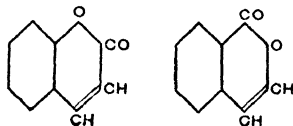


The formation of $\alpha\alpha$ -dimethyl- γ -pyrone by the action of sulphuric acid on the dichloro-derivative of dehydracetic acid, followed by the heating of the resultant product, may also be readily explained on Collie's formula—

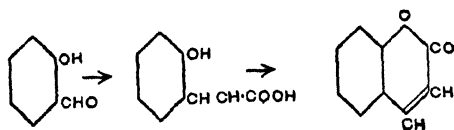


The formula for triacetic lactone given above has received confirmation at the hands of Tamburello and Carapelli, who have shown that it is converted by diazomethane into the corresponding methoxy-methyl pyrone.

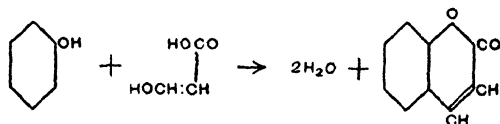
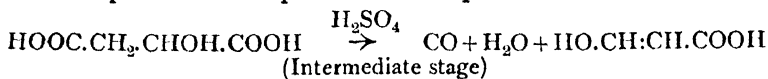
Two series of benzo- α -pyrones are known, and are designated respectively as the coumarins and the isocoumarins.



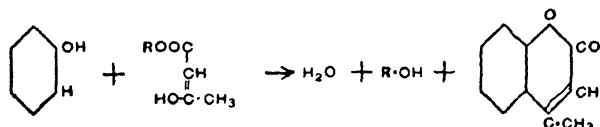
Coumarin, which is the odoriferous principle of the woodruff and of the tonka-bean, is prepared synthetically from salicylic aldehyde by the Perkin reaction,



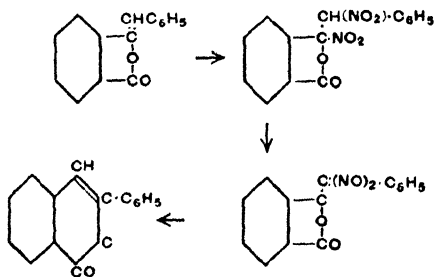
or, as von Pechmann has shown, by the condensation of malic acid with phenol in the presence of sulphuric acid.



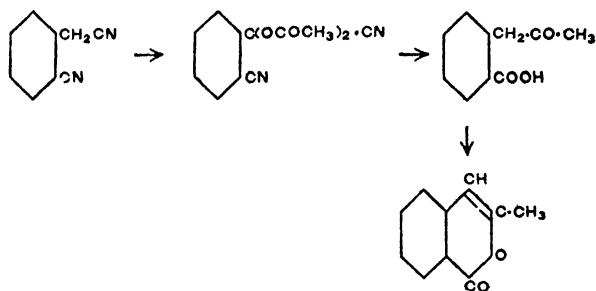
The homologous coumarins are similarly obtained by the condensation of phenols with aceto-acetic ester and substituted aceto-acetic esters, in the presence of sulphuric acid (v. Pechmann), or from the homologous (*o*)-hydroxyaldehydes by the Perkin reaction.



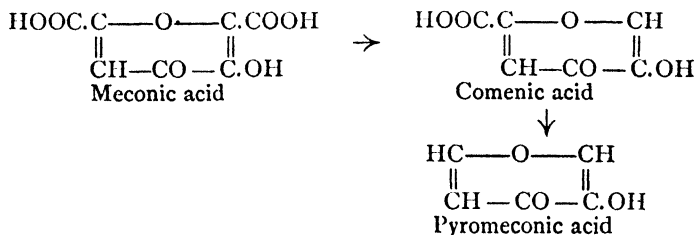
The isocoumarins have been prepared by Gabriel from the benzal or alkylidene phthalides. In this method of preparation the phthalides were converted into dinitro-derivatives either by the action of nitrous acid or by direct addition of nitrogen peroxide, and the nitro-derivatives so obtained were then heated, and finally reduced by hydriodic acid, when the isocoumarin was obtained.



As an alternative method of preparation the acid anhydrides or chlorides may be heated with (*o*)-cyanobenzyl cyanide, the resulting nitrile being then hydrolyzed with acids.

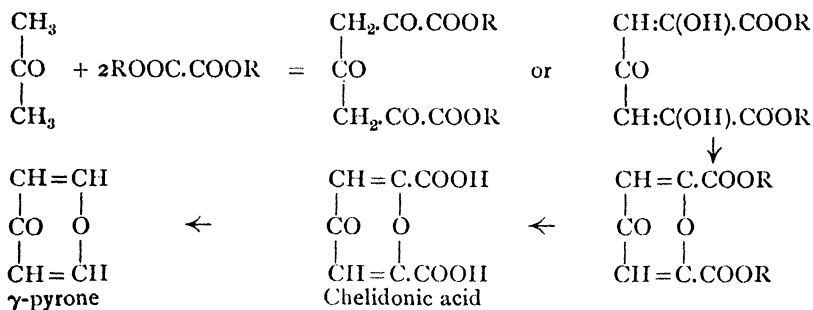


The γ -pyrones are the more important class of such compounds since many naturally occurring dyestuffs and other natural products are closely related to them. Ordinary opium readily yields meconic acid (3-hydroxy- γ -pyrone-2,6-dicarboxylic acid), and this acid when heated passes into comenic acid (3-hydroxyprone-6-carboxylic acid), and pyromeconic acid (3-hydroxy- γ -pyrone).

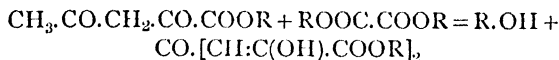


Chelidonic acid, $\text{C}_5\text{H}_4\text{O}_6$, is another naturally occurring pyrone derivative. It is found in the greater celandine (*chelidonium majus*), and has been synthesized from acetone and diethyl oxalate. These two compounds condense in the presence of sodium methoxide to form acetone dioxalic ester, which, when its alcoholic solution is boiled, immediately loses the elements of water and passes into the ethyl ester of chelidonic acid. Careful hydrolysis of this ester yields the free acid, and the latter, when heated, loses carbon dioxide and passes into the free γ -pyrone.

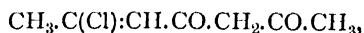
254 MODERN RESEARCH IN ORGANIC CHEMISTRY



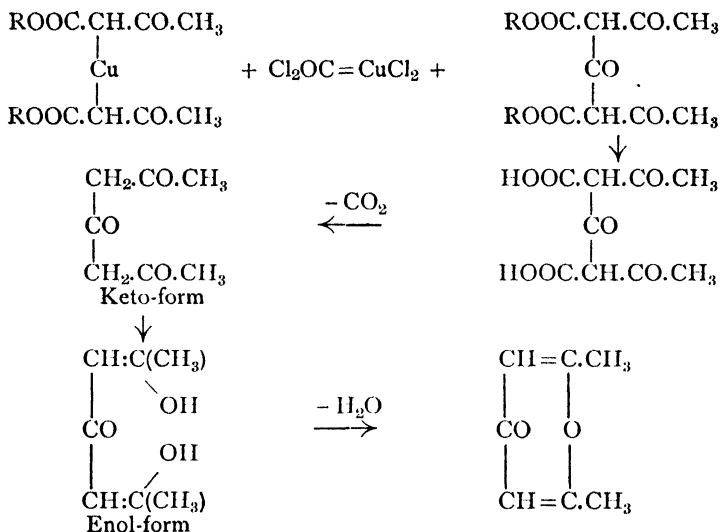
This acid yields colourless salts, but if it be warmed with an excess of alkali hydroxide, ring fission takes place, and the yellow salts of acetone-dioxalic acid (xantho-chelidonic acid) are produced. Xantho-chelidonic ester may also be synthesized by the condensation of oxalic ester with acetyl pyruvic ester in the presence of sodium ethoxide, the reaction taking place as shown.



The most important of the γ -pyrones is $\alpha\alpha$ -dimethyl- γ -pyrone, which, in the form of its hydrochloride, may be prepared by heating dehydracetic acid under pressure, followed by subsequent dehydration (over sulphuric acid) of the compound so formed. Feist concluded that the compound $\text{C}_7\text{H}_9\text{O}_2\text{Cl}$, formed in this manner, was a derivative of diacetyl-acetone and possessed the structure



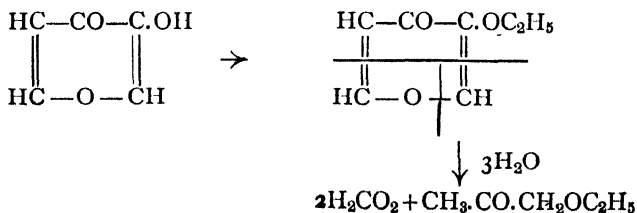
but Collie and Tiekle showed that such a formula does not agree with the reactions exhibited by it, since it gives no colour with ferric chloride solution, and again on dissolving in water shows the behaviour of a mixture of dimethyl pyrone and hydrochloric acid (see p. 225), hence it is the hydrochloride of $\alpha\alpha$ -dimethyl- γ -pyrone. It may also be prepared by the action of carbonyl chloride on the copper derivative of aceto-acetic ester, the resulting keto-ester being then hydrolyzed by sulphuric or hydrochloric acids.



Dimethyl- γ -pyrone is characterized by the well-defined salts it yields with mineral acids (see p. 226). On hydrolysis with hot baryta water it yields diacetyl acetone,

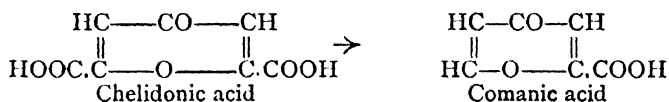


Numerous hydroxy-pyrones are known, and a certain amount of uncertainty as to the position of the hydroxyl group has arisen in various cases. An ingenious method has been devised by Peratoner for the determination of the position of the substituent in these cases, the *modus operandi* consisting in alkylating the hydroxy-compound by means of an aliphatic diazo-hydrocarbon and decomposing the resulting ether with baryta. In this way it is found that the ethyl ether of pyromeconic acid yields a formate and ethoxy-acetone, consequently pyromeconic acid must be 3-hydroxy- γ -pyrone.

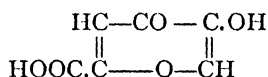


256 MODERN RESEARCH IN ORGANIC CHEMISTRY

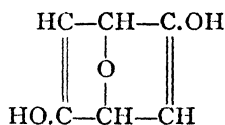
In the case of comenic acid the method will not distinguish between 3-hydroxypyrrone-2-carboxylic acid and 3-hydroxypyrrone 6-carboxylic acid, but a comparison of the dissociation constant of comenic acid and comanic acid (obtained by heating chelidonic acid)—



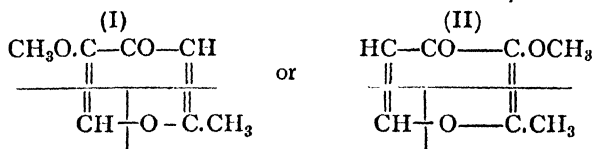
has shown that the latter is the stronger of the two. Since it has been shown that benzoic acid is a stronger acid than *p*-hydroxy benzoic acid, but a weaker acid than salicylic acid, it would appear by analogy, that in comenic acid the hydroxyl group should thus be in para-position to the carboxyl-group, that is, comenic acid should be 3-hydroxypyrrone-6-carboxylic acid.



The method has also been used for the determination of the structure of maltol, which had earlier been formulated as—



an unsatisfactory formula, since only mono-acyl derivatives are capable of preparation. Peratoner has found that on treatment with diazomethane it yields only a monomethyl ether, which on hydrolysis with baryta decomposes into formic and acetic acids, and acetyl carbinol methyl ether. This decomposition can be represented in the following manner :—

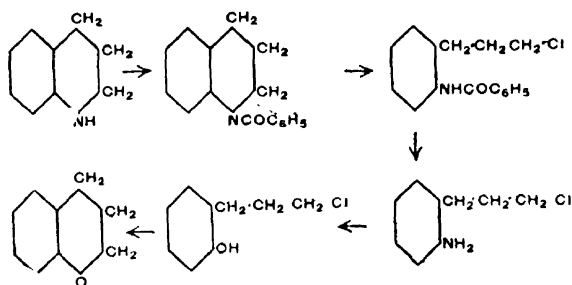


and of these formulæ (II) seems preferable, in that maltol differs

from its lower homologue (pyromeconic acid) in not reacting with amyl nitrite, diazonium salts or iodic acid.

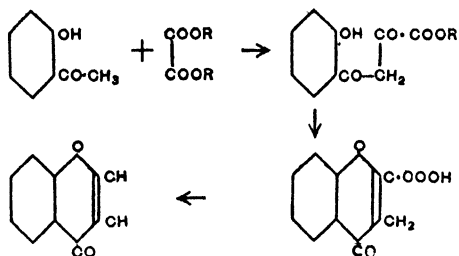
Numerous benzo- γ -pyrones and dibenzo- γ -pyrones are known, the former including the naturally occurring products chrysin, apigenin, luteolin, etc., for the elucidation of the constitution of which we are indebted principally to the labours of Herzig, A. G. Perkin, and Kostanecki and his pupils; while the dibenzo-pyrones include xanthone and its chief derivatives, which have been examined by Kostanecki and also by Graebe.

The parent substance of the benzo- γ -pyrone group is *chroman*, $C_9H_{10}O$, which has been synthesized by J. v. Braun and Steindorff from tetrahydroquinoline. This quinoline compound is benzoylated, and the resulting benzoyl compound by the action of phosphorus pentachloride is converted into (*o*)- γ -chloropropylbenzanilide. The benzoyl group is now eliminated by hydrolysis and the amino-group in the so-formed chloropropylaniline replaced by the hydroxyl group in the usual manner. The phenol when boiled in alkaline solution passes quantitatively into chroman.

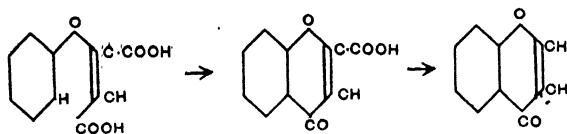


Chroman is thus obtained as a colourless strongly refractive liquid, boiling at $214-215^{\circ}C.$, and having an odour of peppermint.

The benzo- γ -pyrones are consequently to be considered as chromones, such compounds being capable of synthesis, as Kostanecki has shown, by the condensation of (*o*)-hydroxyacetophenones with oxalic ester in the presence of sodium, the β -diketone which is formed passing into the chromone when its alcoholic solution is heated with hydrochloric acid.



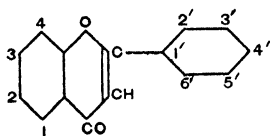
Benzo- γ -pyrone (chromone) has also been obtained by Ruhemann by the action of sulphuric acid on phenoxy-fumaric acid. In this reaction a benzo- γ -pyrone carboxylic acid is produced, and when heated in vacuo it loses carbon dioxide and is transformed into benzo- γ -pyrone.



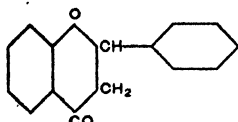
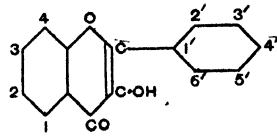
Chromone crystallizes in needles, melts at 59°C ., and dissolves in concentrated sulphuric acid with a yellow colour, the solution exhibiting a blue fluorescence.

The naturally occurring yellow dyestuffs of this series are derivatives of flavone or 2-phenylbenzo- γ -pyrone, and flavonol. In the following pages the scheme of nomenclature outlined below is used, the numbers indicating the position of substituents.

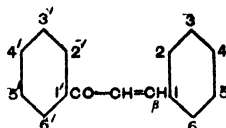
Flavone



Flavonol

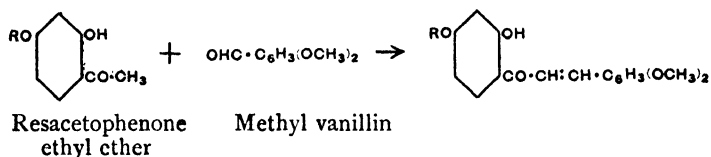


Flavanone

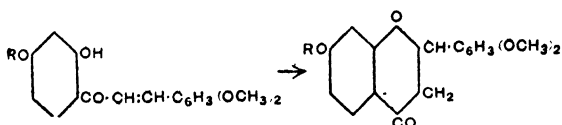


Chalcone

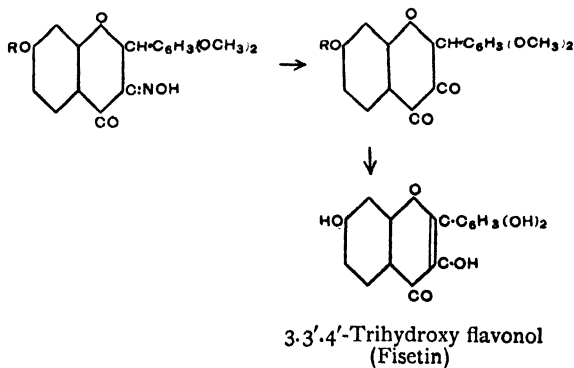
The chalcones are produced by the condensation of (*o*)-hydroxy-acetophenones and their derivatives, with aromatic aldehydes in the presence of the alkali hydroxides, thus :—



and when boiled with dilute sulphuric acid, pass, by ring closing, into the flavanones.



The flavanones are converted into flavonols by the action of amyl nitrite in acid solution, the isonitroso-compound first formed being decomposed by 10 per cent. sulphuric acid, and the resulting keto-compound finally reduced with hydriodic acid.

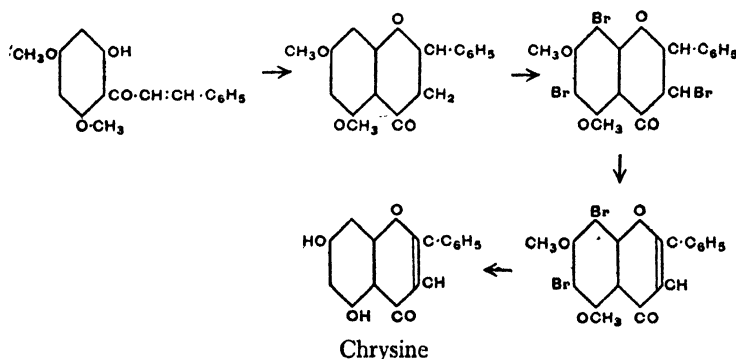


By similar processes the other members of the group are obtained, namely, chrysin, apigenin, luteolin, k ampferol, quercetin, galangin, and morin, the starting point in each case being indicated in the subjoined table.

NAME.	FORMULA.	STARTING POINT.
Chrysin	$C_{15}H_{10}O_4 = 1.3$ dihydroxy flavone	2'-Hydroxy-4'.6'.dimethoxy chalkone
Apigenine	$C_{15}H_{10}O_5 = 1.3.4$ trihydroxy flavone	2'-Hydroxy-4'.6'.4-trimethoxy chalkone
Luteoline	$C_{15}H_{10}O_6 = 1.3.3'.4$ tetrahydroxy flavone	2'-Hydroxy-4'.6'.3.4-tetramethoxy chalkone
Galangin	$C_{15}H_{10}O_5 = 1.3.$ dihydroxy flavonol	2'-Hydroxy-4'.6'.dimethoxy chalkone
Fisetin	$C_{15}H_{10}O_6 = 3.3'.4'$ trihydroxy flavonol	2'-Hydroxy-3.4.4'-trimethoxy chalkone
Kæmpferol	$C_{15}H_{10}O_6 = 1.3.4'$ trihydroxy flavonol	2'-Hydroxy-4.4'.6'-trimethoxy chalkone
Quercitol	$C_{15}H_{10}O_7 = 1.3.3'.4'$ tetrahydroxy flavonol	2'-Hydroxy-4'.6'.3.4-tetramethoxy chalkone
Morin	$C_{15}H_{10}O_7 = 1.3.2'.4'$ tetrahydroxy flavonol	2'-Hydroxy-4'.6'.2.4-tetramethoxy chalkone

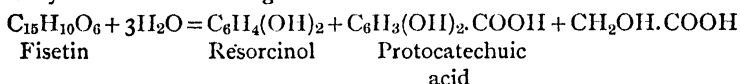
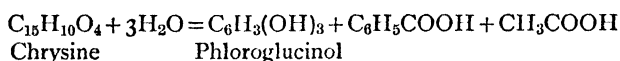
In the case of the first three compounds above mentioned (namely, chrysin, apigenine, and luteoline) the synthesis follows slightly different lines from that given with the others, the flavanone being brominated (whereby three bromine atoms are introduced) and hydrobromic acid then removed from the bromo-compound by means of alcoholic potash. The resulting dibromo-flavanone on reduction with hydriodic acid yields the hydroxy-flavone.

1.3 Dimethoxyflavanone

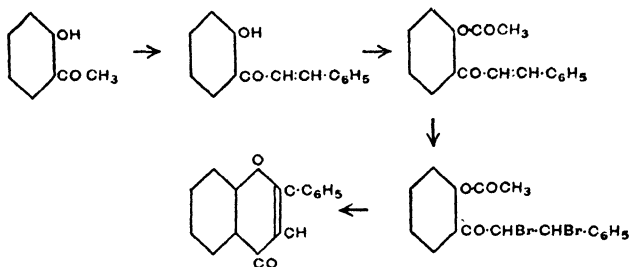


The reaction which supplied the clue rendering the synthesis of these compounds possible was their behaviour on fusion with

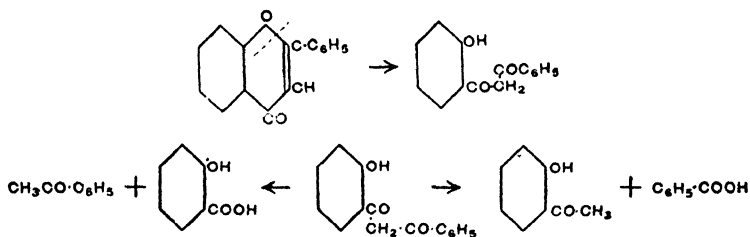
caustic alkali, whereby the polyhydric phenols were produced and generally an aromatic acid, examples being shown below.



Flavone itself was synthesized by Kostanecki from (*o*)-hydroxyacetophenone and benzaldehyde. These two compounds condense together in alkaline solutions to form (*o*)-hydroxybenzalacetophenone. The hydroxyl group of the ketone is protected by acetylation, the dibromo-addition product formed and finally converted into flavone by the action of alcoholic potash.



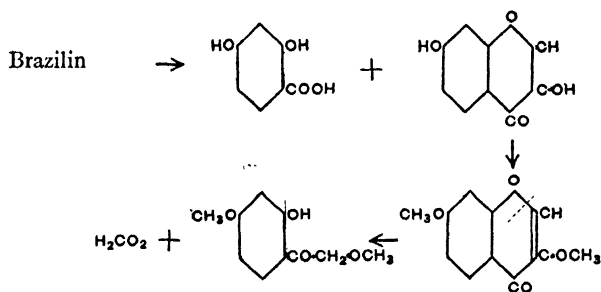
It dissolves in concentrated sulphuric acid, with a yellow colour and a weak blue fluorescence. The pyrone ring is readily broken by the action of the alkali hydroxides, the diketone first formed then undergoing further hydrolysis into (*o*)-hydroxyacetophenone and benzoic acid, together with salicylic acid and acetophenone.



Among other substances closely related to the benzo- γ -pyrone group may be mentioned brazilin, C₁₆H₁₄O₅, and hæmatoxylin,

262 MODERN RESEARCH IN ORGANIC CHEMISTRY

$C_{16}H_{14}O_6$, the colouring matters of Brazil wood and of logwood. Brazilin crystallizes in pale yellow prisms, and appears to have been first isolated by Chevreul in 1808. Somewhat later Kopp pointed out that it yielded resorcinol when distilled, or when fused with an alkali hydroxide. It contains four hydroxyl groups, since by the action of sodium methoxide it yields trimethyl-brazilin, a substance still containing a hydroxyl group, for, when heated in benzene solution at 120° C. with methyl iodide and sodium, it is further alkylated. These reactions show that three of the hydroxyl groups in brazilin possess phenolic properties, whilst the fourth is alcoholic in character. The oxidation of brazilin by drawing a current of air through its alkaline solution, gives an indication as to the structure of the molecule. In this reaction β -resorcylic acid and a dihydroxy-phenyl- γ -pyrone are obtained, the identity of the latter substance being confirmed by Feuerstein and Kostanecki, who showed that its dimethyl ether, on boiling with sodium ethoxide, yields fisetol dimethyl ether.



The constitution of brazilin has, however, been determined by W. H. Perkin in a series of investigations extending from 1901 to 1909, starting from the oxidation of trimethyl brazilin with potassium permanganate. In this oxidation, formic, acetic, and oxalic acids are produced, together with a series of acids of empirical formulæ.

$C_{19}H_{18}O_9$ = brazilinic acid.

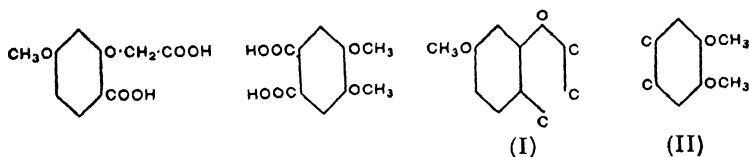
$C_{10}H_{10}O_6$ = 2-carboxy-5-methoxy-phenoxyacetic acid.

$C_{10}H_{10}O_6$ = (*m*)-hemipinic acid.

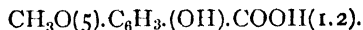
$C_{12}H_{12}O_6$ = brazilic acid.

The formation of the phenoxy-acetic acid and of (*m*)-hemipinic

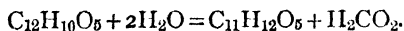
acid point to the presence of a resorcinol and a catechol nucleus in the molecule, and require the skeletal chains (I) and (II).



Perkin's earlier papers deal chiefly with the constitution of brazilic acid, from which the constitution of the brazilin itself is deduced. Brazilic acid, $C_{12}H_{12}O_6$, is a monobasic acid, but when boiled with baryta water yields a barium salt of composition $C_{12}H_{10}BaO_6$. The acid contains a methoxy-group (OCH_3) and a keto-group (CO), as shown by the Zeisel reaction, and by the formation of an oxime and a semi-carbazone. When fused with caustic alkali, it yields a water soluble acid, of which the aqueous solution gives an intense violet coloration on the addition of ferric chloride, a reaction pointing to the presence of a resorcylic nucleus. The carbonyl group is evidently in the γ -position, for the reduction of brazilic acid with sodium amalgam yields dihydrobrazilic acid, $C_{12}H_{14}O_6$, which, when liberated from its salts, immediately lactonizes. On treatment with concentrated sulphuric acid, brazilic acid passes into anhydrobrazilic acid, $C_{12}H_{10}O_6$, a monobasic acid which still contains the original methoxy-group and carbonyl group. The anhydro-acid is an unsaturated acid, since its solution in sodium carbonate at once decolorizes potassium permanganate, the product of oxidation being (*p*)-methoxy salicylic acid

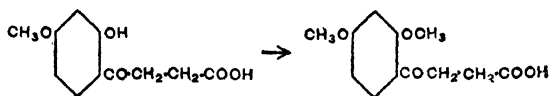


The anhydro-acid, on hydrolysis with caustic baryta, yields formic acid and a monobasic ketonic acid, $C_{11}H_{12}O_5$, which gives a violet coloration with ferric chloride.

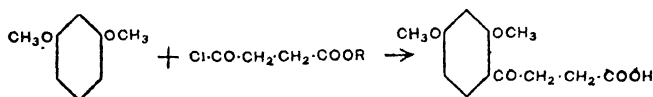


Since, however, anhydrobrazilic acid gives no coloration with ferric chloride, it is probable that the elimination of formic acid has been accompanied by the formation of a free hydroxyl-group in the benzene ring, a conclusion verified by the fact that the

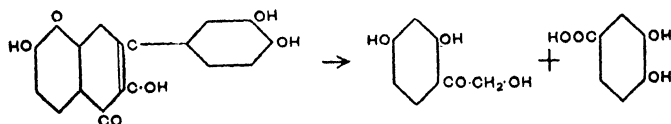
methyl ester of the acid on alkylation yields the methyl ester of an acid, $C_{12}H_{14}O_5$, which gives no coloration with ferric chloride, so that the hydroxyl group in the former acid becomes the methoxy group in the latter. The general reactions of the acid, $C_{11}H_{12}O_5$, taken in conjunction with the oxidation of anhydrobrazilic acid to (*p*)-methoxy-salicylic acid point to it being 6-hydroxy-4-methoxy-benzoyl propionic acid.



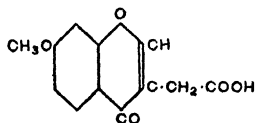
confirmation of which is found in the synthesis of the dimethoxy compound by the condensation of resorcinol dimethyl ether with the semi-chloride of succinic acid, in the presence of aluminium chloride.



The formation of the acid $C_{11}H_{12}O_5$, and of formic acid, by the action of caustic baryta on anhydrobrazilic acid, is a type of reaction frequently met with in the benzo- γ -pyrone series, *e.g.* with fisetin,

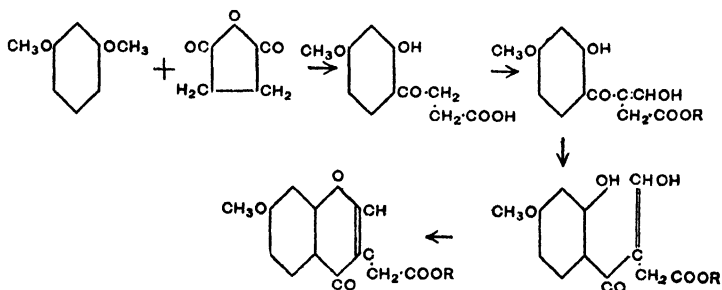


and by analogy it must be concluded that anhydrobrazilic acid is a γ -pyrone derivative of constitution.

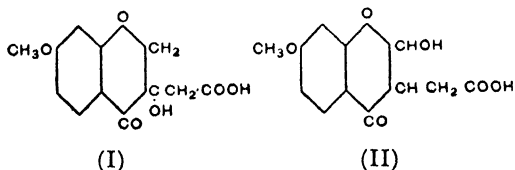


This structure has been confirmed by the synthesis of the acid from resorcinol dimethyl ether and succinyl chloride, which condense together in the presence of aluminium chloride (no solvent

being required) to form the acid $C_{11}H_{12}O_5$. The methyl ester of this acid, on treatment with ethyl formate in the presence of sodium, then yields a hydroxy-methylene derivative which passes by loss of water into anhydrobrazilic acid.

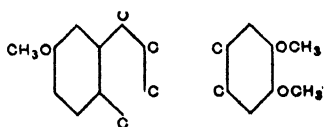


These results lead to brazilic acid being either

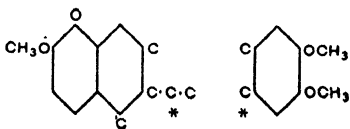


and of these only (II) could give a γ -lactone, but as brazilic acid is stable even when boiled with hydrochloric acid it must be (I).

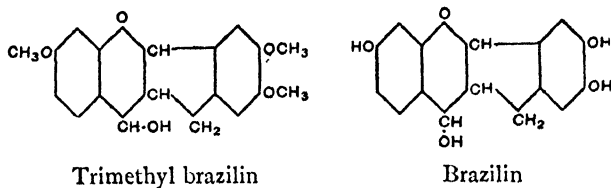
Now, since the groupings



contain twenty carbon atoms and brazilin only contains nineteen, there must be one carbon atom in common, and this seems to be the one marked below

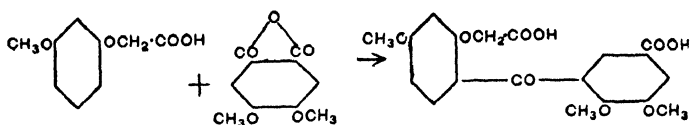


so that trimethyl brazilin and brazilin should apparently be represented as

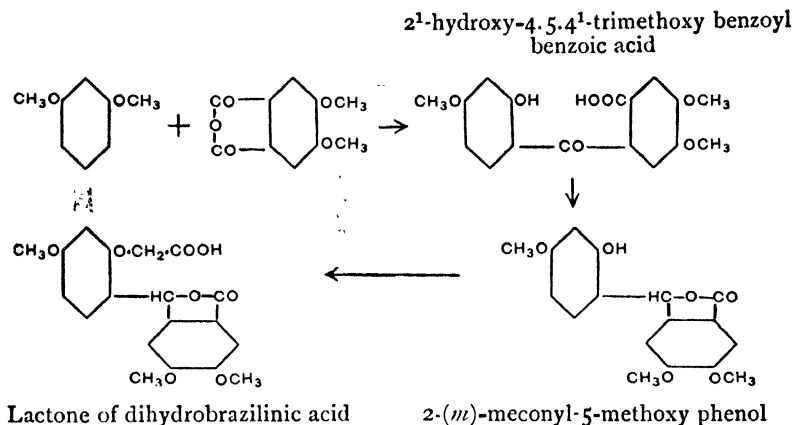


in order to account for the formation of brazilic acid, and of the presence of the three phenolic hydroxyl groups, the fourth being alcoholic in character.

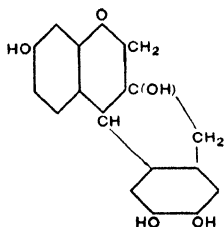
In some respects the above formula did not seem satisfactory as a representation of brazilin, and further work was undertaken on brazilinic acid, which is formed in considerable quantity when trimethyl brazilin is oxidized with potassium permanganate. This acid, $C_{19}H_{18}O_9$, is dibasic, contains three methoxy groups, and on reduction with sodium amalgam yields a dihydro acid, which immediately lactonizes. The constitution of these acids was finally determined by their synthesis, brazilinic acid being formed in somewhat small yield by the condensation of (*m*)-hemipinic anhydride with the ethyl ester of (*m*)-methoxy phenoxy acetic acid in the presence of aluminium chloride.



The lactone of dihydrobrazilinic acid arises in a similar fashion from (*m*)-hemipinic anhydride and resorcinol dimethyl ether, the pyrone derivative first formed being reduced by sodium amalgam, and the reduction product finally condensed with monochloroacetic ester in the presence of alkali.

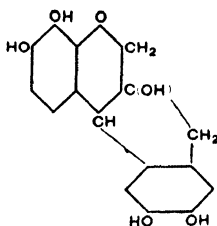


These syntheses require a slight alteration in the formula of brazilin, which must now consequently be written as



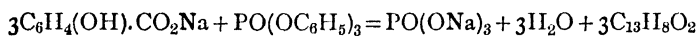
a configuration that allows for the formation of the four acids obtained when trimethyl brazilin is oxidized.

Hæmatoxylin is very similar to brazilin, yielding on fusion with alkali, pyrogallol. It contains five hydroxyl groups, one of which is alcoholic in character. Its tetramethyl derivative on oxidation yields among other products (*m*)-hemipinic acid, which points to the presence of a catechol nucleus, and thus the only point of difference between hæmatoxylin and brazilin seems to be that the former contains a pyrogallol and a catechol nucleus, whilst the latter contains a resorcinol and a catechol nucleus. Proceeding on lines similar to those used in the case of brazilin, hæmatoxylin must be represented by the following formula :—

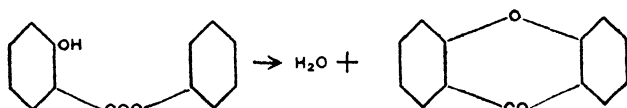


A similar series of synthetical reactions were carried out as in the case of brazilin, the lactone of dihydrohæmatoxylinic acid being prepared by the condensation of (*m*)-hemipinic anhydride with pyrogallol trimethyl ether.

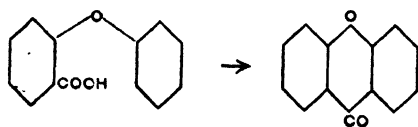
The simplest of the dibenzo- γ -pyrones is xanthone, $C_{18}H_8O_2$, which was first obtained by Kolbe from the action of phosphorus oxychloride on sodium salicylate. It may also be obtained by the oxidation of xanthene with chromic acid, by distilling sodium salicylate with phenyl phosphate



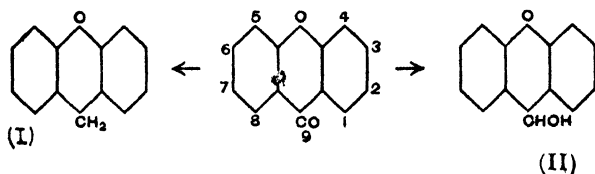
by the long continued boiling of salol,



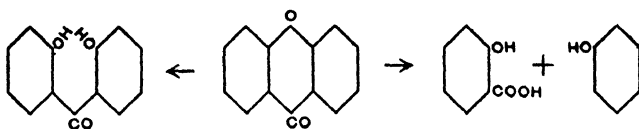
and by the dehydration of phenyl salicylic acid,



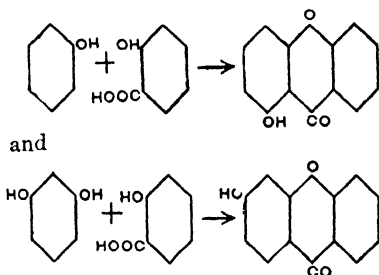
It is a crystalline solid. When distilled over zinc dust it passes into xanthene I (diphenylene methane oxide), whilst a less drastic reduction by means of zinc dust in the presence of an alcoholic solution of sodium hydroxide yields xanthidrol (II).



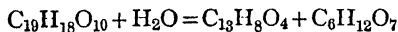
The position taken by substituents is indicated by the attached numbers in the xanthone formula. When heated with alcoholic potassium hydroxide at 180° C. it yields (*o*)-dihydroxybenzophenone, whilst an alkali fusion decomposes it into salicylic acid and phenol



Numerous hydroxy-xanthenes are known and are obtained by the condensation of (*o*)-hydroxy-carboxylic acids (*e.g.* salicylic acid, etc.) with phenols; thus from resorcinol the 1-hydroxy and 3-hydroxy-xanthenes are obtained, whilst quinol yields 2-hydroxy-xanthone, and catechol, 4-hydroxy-xanthone.



The most important of the dihydroxy-xanthenes is the 1.7 compound or euxanthone which is obtained from Indian Yellow or Purree. Purree is obtained from the urine of cows which have been fed on mango leaves, and Graebe showed that it contains euxanthic acid (in the form of magnesium salt), $C_{19}H_{18}O_{11}$. This acid on hydrolysis yields euxanthone and glucuronic acid.

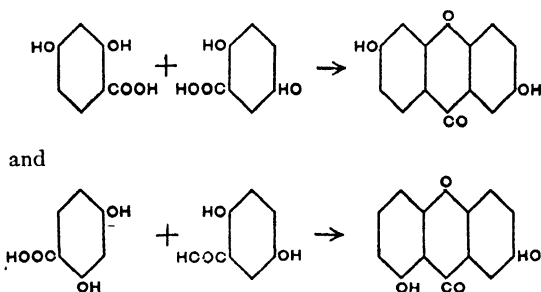


An examination of purree by Graebe showed that it contained,

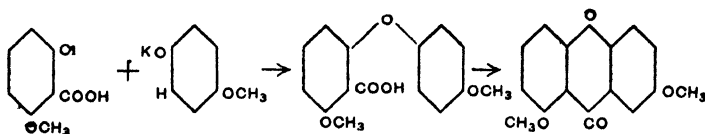
Euxanthic acid, . . .	51%
Silica and alumina, . . .	1.5
Magnesium, . . .	4.2
Calcium, . . .	3.4
Water and volatile matter,	39.0

the euxanthic acid and euxanthonone being separated by rubbing it with dilute hydrochloric acid until the mass became bright yellow. The mass was then well washed and the free acid extracted by means of ammonium carbonate, whilst the residual euxanthonone was extracted by sodium hydroxide and reprecipitated by the addition of acid.

Euxanthonone was afterwards synthesized (by Graebe) by the condensation of β -resorcylic acid with quinol carboxylic acid, but this synthesis does not fix the position of the hydroxyl groups since there are two possibilities for the course of the reaction, namely,



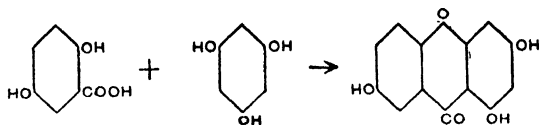
The constitution has, however, been definitely settled by Ullmann and Panchaud, who have shown that 2-chloro-6-methoxybenzoic acid condenses with quinol monomethyl ether in the presence of copper powder to 2-phenoxy-6-methoxy benzoic acid, which, when heated with concentrated sulphuric acid, yields euxanthonone dimethyl ether.



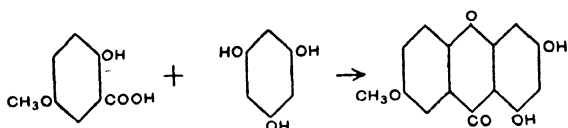
Euxanthonone crystallizes in yellow needles and dissolves in solutions of the alkali hydroxides with a yellow colour.

Gentisin, $C_{14}H_{10}O_5$, and gentisein, $C_{13}H_8O_6$, which are found in the root of the gentian (*Gentiana luteola*) are trihydroxyxanthonone derivatives. On alkali fusion, gentisin yields phloroglucinol, acetic acid, and quinol carboxylic acid. On methylation both

yield the same dimethyl ether, and so apparently gentisin is the monomethyl ether of gentisein. Kostanecki and Tambor have prepared gentisein synthetically by the condensation of phloroglucinol with quinol carboxylic acid in the presence of acetic anhydride.

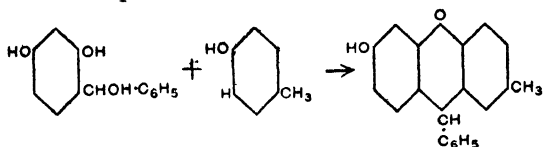


whilst gentisin is obtained by a similar reaction, using the monomethyl ether of quinol carboxylic acid.

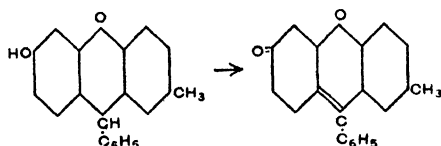


It is worth noting here that these compounds only yield dialkyl derivatives and not trialkyl compounds, for Kostanecki has shown that hydroxyxanthenes with a hydroxyl group in the ortho-position to the CO group do not alkylate on this hydroxyl group.

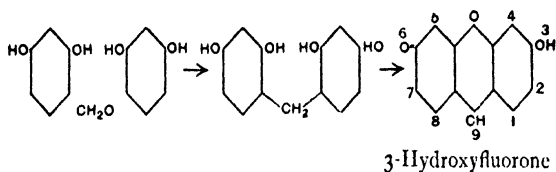
Xanthene, C₁₃H₁₀O, the parent substance of the group, is not only obtained by the reduction of xanthone and of euxanthone, but is also produced when phenol is condensed with (*o*)-cresol in the presence of aluminium chloride. It is readily oxidized by chromic acid to xanthone. Various hydroxyxanthenes have been obtained recently by the condensation of dihydroxybenzhydrols with phenols in the presence of zinc chloride.



They are colourless solids which rapidly oxidize on exposure, becoming converted into the *fluorones*.

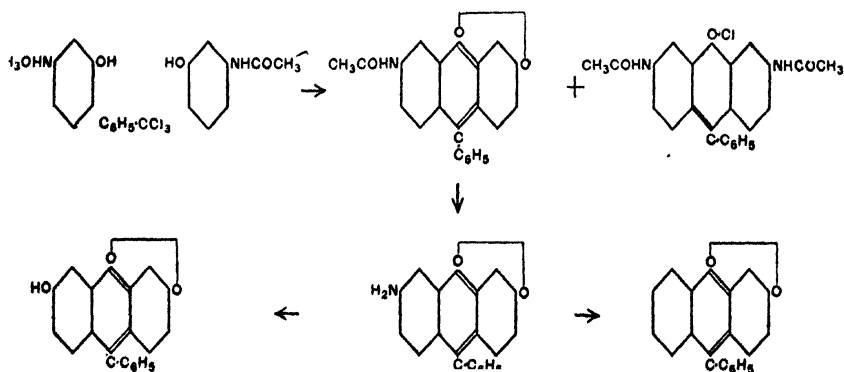


Compounds of the fluorone type were apparently first obtained by Möhlau and Koch in 1894 by the condensation of two molecular proportions of resorcinol with one molecular proportion of an aliphatic aldehyde in the presence of dilute (1:5) sulphuric acid, the resulting diphenylmethane derivative being then oxidized by heating with sulphuric acid. The hydroxyfluorones thus obtained were considered from their method of preparation to possess a para-quinonoid structure.



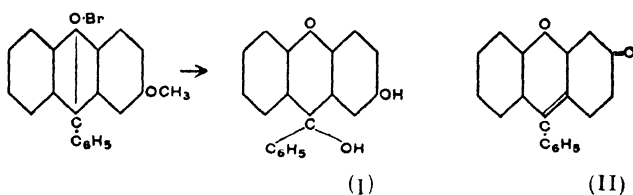
In a somewhat similar manner, by using substituted phloroglucinols and hydroxyquinols in the presence of hydroxyaldehydes, numerous fluorone derivatives are obtained.

Kehrmann has recently prepared phenylfluorone and hydroxyphenylfluorone starting from acetyl-*m*-aminophenol and benzotrichloride, which, when heated together in nitrobenzene solution at 160° C., yield diacetylosamine chloride and acetylaminophenylfluorone. The acetylaminofluorone is hydrolyzed and the amino-group diazotized, when hydroxyphenyl fluorone or phenylfluorone is produced, accordingly as the diazo-solution is boiled alone or with alcohol, thus :—

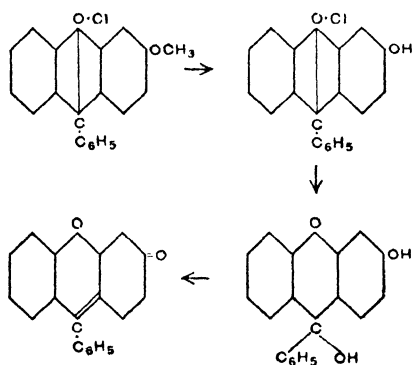


and in accordance with his well-known views, Kehrmann ascribes to these compounds the betaine type of orthoquinonoid structure.

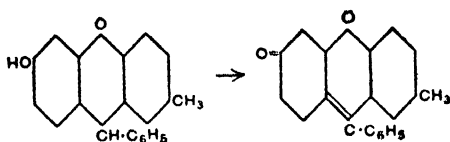
This view of structure is combated by Decker, who has tried to prepare the analogue of phenyl fluorone from quinolphthalein by hydrolysis of 2-methoxy-9-phenylxanthonium bromide, but the only product obtained was a colourless carbinol base (I), namely, 2-hydroxy-9-phenylxanthen-9-ol, a reaction which shows that there is a fundamental difference between the two series, and hence phenyl fluorone must be represented by the formula (II)—



Again, Decker found that 3-methoxy-9-phenylxanthonium chloride, when heated with hydrochloric acid under pressure, yielded the corresponding hydroxy-compound, which was converted by sodium hydroxide into phenyl fluorone, the properties of the latter bearing no resemblance to those of a phenol-betaine, which should be soluble in water.



Pope and Howard have also prepared fluorones by the oxidation of hydroxyxanthenes in alkaline solution, with a current of air,



and find that the phenyl methyl fluorone obtained in this way is quite insoluble in water and in solutions of the alkali hydroxides, even when boiled; hence they conclude that the phenol-betaine formula of Kehrman is untenable, and that (in agreement with Decker) the fluorones are paraquinonoid in structure.

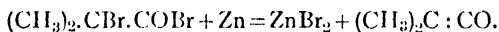
BIBLIOGRAPHY

- Feist, *Ber.* 1892, **25**, 315, 340; *Ann.* 1890, **257**, 253.
 Collie, *Jour. Chem. Soc.* 1891, **59**, 179; 1893, **63**, 122; 1900, **77**, 971.
 Tamburello and Carapelli, *Gazz.* 1907, **37** (i), 561.
 Pechmann, *Ber.* 1899, **32**, 3681, 3690, 3696; 1901, **34**, 354, 378, 421, 660.
 Gabriel, *Ber.* 1894, **27**, 827.
 Peratoner, *Gazz.* 1906, **36** (i), 1, 21, 33.
 Herzig, *Monats.* 1891, **12**, 161, 172, 177; 1892, **13**, 411; 1893, **14**, 39, 53;
 1894, **15**, 139, 683; 1895, **16**, 312, 906; 1896, **17**, 421; 1897, **18**, 700;
 1898, **19**, 738; 1901, **22**, 207.
 Perkin, *Jour. Chem. Soc.* 1896, **69**, 206, 799; 1897, **71**, 805; 1900, **77**, 1314;
 1902, **81**, 203, 469, 1174, etc.
 Kostanecki. Only the most important papers of this worker are given in the following list. From those given, references may be obtained to the earlier work.
Ber. 1895, **28**, 2302; 1899, **32**, 2260; 1900, **33**, 330, 3410; 1904, **37**,
 784, 1402, 2096, 2625, 2803, 3167; 1905, **38**, 3587; 1906, **39**, 425;
 1907, **40**, 3669.
 Perkin, *Jour. Chem. Soc.* 1901, **79**, 1401; 1902, **81**, 221, 1008, 1057; 1907,
91, 1073; 1909, **95**, 381.
 Graebe, *Ann.* 1889, **254**, 265; 1901, **318**, 345.
 Ullmann, *Ber.* 1905, **38**, 2111; *Ann.* 1906, **350**, 108.
 Kostanecki, *Ber.* 1894, **27**, 1993.
 Möhlau and Koch, *Ber.* 1894, **27**, 2887.
 Kehrman, *Ber.* 1908, **41**, 3440.
 Decker, *Ber.* 1909, **42**, 578.
 Pope and Howard, *Jour. Chem. Soc.* 1910, **97**, 1023.

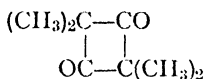
CHAPTER VIII

KETENS, OZONIDES, TRIPHENYLMETHYL

KETENS—The ketens are a series of unsaturated compounds containing the grouping $C:CO$, and may be considered as internal anhydrides of acetic acid and its substitution derivatives. The first member of the series was isolated by Staudinger in 1905, by the action of zinc upon a solution of α -bromoisobutyryl bromide in acetic acid.



This dimethyl keten is a yellowish liquid that is stable at $-20^\circ C.$, but at ordinary temperatures rapidly polymerizes to a compound which is probably a tetramethyl cyclobutane-dione.

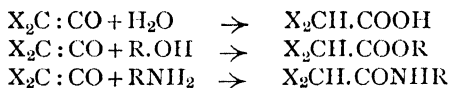


The ketens are usually prepared by the action of zinc filings on a solution of an α -halogen substituted acid chloride or bromide, in ether or ethyl acetate. In an examination of the relative merits of acid chlorides and bromides as starting-points for the preparation of ketens, Staudinger has found that α -bromo-acid bromides give the best results, but that if these are not available, then it is found to be preferable to employ an α -bromo-chloride rather than α -chloro-bromide, since the chlorine atom in the α -position is bound more tightly to the carbon atom than is the bromine atom in the α -position. In the case of diphenyl α -chloro-acetyl chloride it is found that this will readily react with zinc, although chloro-acetyl chloride will not, and the difference is explained by the assumption of the weakening effect of the two phenyl groups adjacent to the chlorine atom. Staudinger has tried the effect of replacing the metal zinc in these preparations by magnesium,

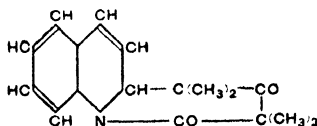
276 MODERN RESEARCH IN ORGANIC CHEMISTRY

but although with bromo-acetyl bromide a good yield is apparent at first, so much hydrobromic acid is liberated towards the end of the reaction that the keten cannot be isolated.

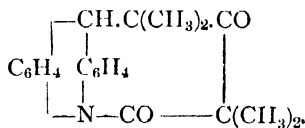
The ketens are characterized by their additive reactions, combining readily with water to form acids, with alcohols to form esters, and with primary amines to form amides.



Two classes of ketens have been recognized, namely, the *keto-ketens*, $X_2C : CO$, which comprise the dialkyl or diaryl ketens, and the *aldo-ketens* $X.CH : CO$. The former are coloured compounds which readily undergo autoxidation, form keten bases on the addition of pyridine and quinoline, and combine with substances containing the $C : N$ and $C : O$ groupings, to form addition compounds. It is found that the Schiff's bases combine with two molecules of the keten, the combination taking place through the $C : N$ linking, and on this account the quinoline derivative of dimethyl keten is considered to be



whilst the addition product with acridine possibly results by the fission of the para-linkage, the base having the annexed formula—

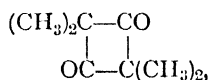


The products from the keto-ketens and Schiff's bases have apparently not yet been isolated in a pure condition, but are in all probability to be represented thus:—

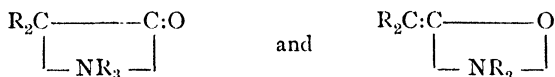


On the other hand, the aldo-ketens are colourless compounds which are not capable of autoxidation, are readily polymerized by pyridine and quinoline, and are inert towards substances containing the C : N and C : O groupings.

Wedekind has shown that the addition of a solution of isobutyryl chloride in carbon bisulphide to trimethylamine or other fatty tertiary amine in the same solvent, yields dimethyl keten, which at once polymerises to 1,3-diketotetramethylcyclobutane,



whilst an addition product of composition $(\text{CH}_3)_2\text{C}:\text{CO}:\text{NR}_3$ is simultaneously formed. These latter products, which Wedekind designates as "ketenium" compounds, are obtained in larger yield if more of the tertiary amine be added as the reaction progresses. In the case of dimethyl keten and triethylamine, the dimethyl keten triethylium, $(\text{CH}_3)_2\text{C}:\text{CO}:\text{N}(\text{C}_2\text{H}_5)_3$, is isolated as a yellow oil of boiling-point 192°C ., and possessing an odour like that of menthol. The compounds of this type differ from Staudinger's keten bases (1) in their very great stability, since they are not attacked by boiling dilute acid or alkali, or even by water at 160°C ., whereas Staudinger's bases are decomposed by alkali; (2) in the relative proportion in which the constituent compounds unite to form the bases. Their reactions, as far as yet studied, apparently point to a cyclic structure, and the following formulæ have been proposed:—

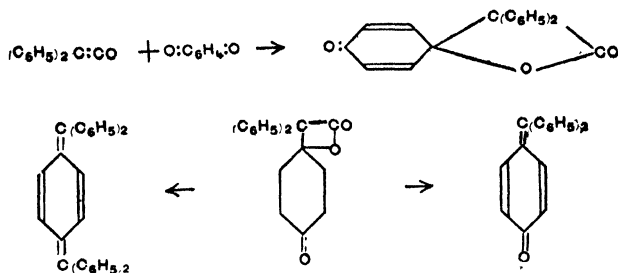


but it is as yet impossible to decide between the two alternatives.

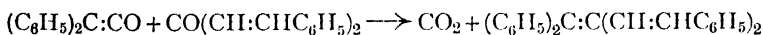
Diethyl keten, $(\text{C}_2\text{H}_5)_2\text{C}:\text{CO}$, is obtained by heating diethylmalonic anhydride, whilst diphenyl keten, $(\text{C}_6\text{H}_5)_2\text{C}:\text{CO}$, is prepared by the action of zinc on diphenyl-chloroacetyl chloride. The latter compound is an orange-red liquid which rapidly becomes viscid on exposure to air; it does not, however, polymerize. It

278 MODERN RESEARCH IN ORGANIC CHEMISTRY

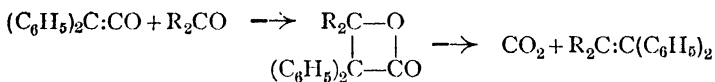
combines with benzoquinone, the resulting addition product being readily decomposed by heat.



The addition product of diphenyl ketene and dibenzylidene acetone is not stable, it loses carbon dioxide spontaneously, yielding 1,5-diphenyl-3-diphenylmethylene-1,4-pentadiene, a substance related to the fulvenes, but possessing less colour.



This appears, from some recent work of Staudinger's, to be a fairly general reaction, since experiments conducted with the quinoline derivative of diphenyl ketene show that when heated with various carbonyl derivatives at 130°C . for 1.5 hours, reaction takes place in two stages, the first consisting in the formation of a β -lactone, which then splits up into carbon dioxide and an olefine derivative—



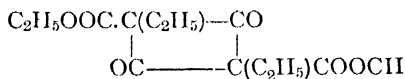
It is assumed that the second reaction proceeds with an incomparably greater velocity than the first. Among other results obtained it is shown that the reactivity of the keto-group is least when it is attached to an NR_2 or OR group (*i.e.* in carboxylic derivatives), more reactive when attached to H , CH_3 or C_6H_5 , and most reactive when unsaturated groups (*e.g.* cyano, and cinnamyl groups) are present. The following table shows the percentage amount of ketone entering into reaction with various carbonyl compounds:—

Carbonyl Cpd.	%.	Carbonyl Cpd.	%.
R'.CO.CH:CHC ₆ H ₅	82.3	R'.CO.OCOCII:CHC ₆ H ₅	5.3
R'.COCN	76.3	R'.CO.OC ₂ H ₅	5.4
R'.COH	65.9	R'.CON(C ₆ H ₅) ₂	0.0
R'.COC ₆ H ₅	42.5	R''.COCH:CH.CH:CHC ₆ H ₅	85.7
R'.COCH ₃	32.8	R''CO.C ₆ H ₅	55.6
R'.COCl	5.5	R''.COCH ₃	20.7

(where R' = C₆H₅CH:CH - ; R'' = C₆H₅CH:CH.CH:CH -)

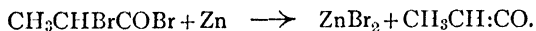
Among other keto-ketens may be mentioned ethyl ethylketen carboxylate, $OC:C \begin{matrix} \nearrow COOC_2H_5 \\ \searrow C_2H_5 \end{matrix}$, which is obtained by the action

of zinc on ethyl bromoethylmalonate chloride, and differs greatly from the other disubstituted ketens in being colourless and incapable of forming additive compounds. It rapidly polymerizes to 1.3-diethylcyclobutane-2.4-dione-1.3-dicarboxylate,



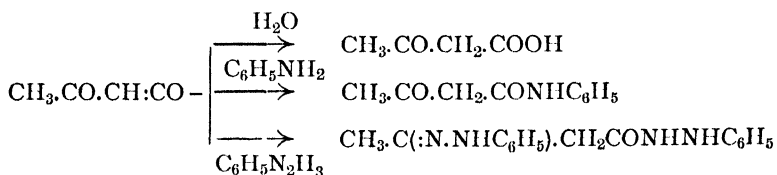
which, when heated to 180-200° C., depolymerizes and passes into the unimolecular keten.

Aldo-ketens may be prepared by methods similar to those used for the keto-ketens, thus methyl keten results from the action of zinc upon α-bromopropionyl bromide dissolved in ethyl acetate—

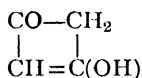


The parent substance of the group, keten itself, CH₂:CO (which may be regarded as an internal anhydride of acetic acid) was first obtained in 1907 by Wilsmore, among the gaseous products formed when a platinum wire is electrically heated under the surface of acetic anhydride; and subsequently by Staudinger, from the decomposition of bromo-acetyl bromide by means of zinc, the products of reaction being separated by fractional distillation. At ordinary temperature it is a colourless gas which may be condensed to a liquid (b.p. - 56°), and finally to a solid (m.p. - 151°).¹ It possesses a pungent odour, and its vapour

attacks the mucous membrane violently. Tertiary bases induce polymerization of keten, a similar condition arising if it be allowed to stand for some time, when a brown-coloured liquid is obtained. From this liquid Wilsmore isolated a compound which he considers to be acetyl keten, $\text{CH}_3\text{CO}\cdot\text{CH}:\text{CO}$, as it dissolves in water to form acetoacetic ester, reacts with aniline to form anilido-acetoacetic ester, and with phenyl hydrazine to form the hydrazone of phenyl hydrazido-acetoacetic acid, whilst caustic baryta converts it into an acetate.

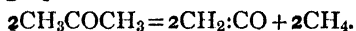


Thus acetyl keten shows to acetoacetic ester the relation of keten to acetic acid, and on this account is, according to Wilsmore, to be formulated as shown. On the other hand Staudinger is opposed to this open chain structure on account of the general chemical inertness of acetyl keten, and considers that all ketens form bimolecular polymerides, which are cyclobutane derivatives, acetyl keten being consequently formulated as a Δ^1 -cyclobuten-1-ol-3-one.

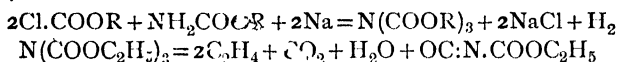


As regards the formula of keten itself, an alternative is suggested in $\text{CH}:\text{C}(\text{OH})$, but this seems to be negatived by the fact that the usual reagents employed for detecting hydroxyl groups (potassium, sodium, phenyl carbimide) have no action on it, hence the hydroxyl group is not present. The somewhat recently

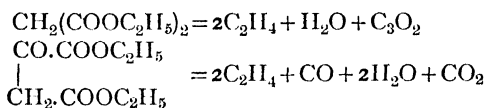
¹ Schmidlin and Bergmann (*Ber.* 1910, **43**, 2821) have recently shown that keten is stable at moderately high temperature, and can be obtained by passing the vapour of acetone through a hard glass tube filled with porous earthenware and heated to 500-600° C. The yield of keten obtained in this manner is about 14 per cent., and the decomposition of the acetone may be represented by the following equation:—



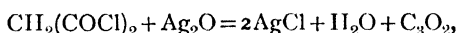
isolated carbon suboxide, C_3O_2 , may be included among the ketens. This compound was first obtained in 1906 by Diels and Wolff as a sequel to the earlier work of Diels on the behaviour of nitrogen tricarboxylic ester with phosphorus pentoxide. This nitrogen carboxylic ester is formed by the interaction of chlorocarbonic ester with urethane, in the presence of sodium, and, when heated with phosphorus pentoxide, decomposes into ethylene, carbon dioxide, water, and ethyl carbimide carbonate.



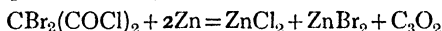
This decomposition led to the investigation of the action of phosphorus pentoxide on other esters, and it was found that malonic ester and oxalacetic ester both yielded ethylene and the new oxide of carbon.



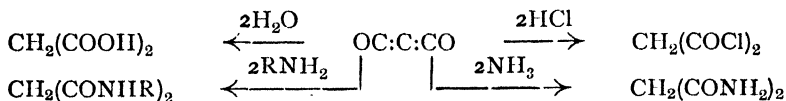
At a later date Staudinger showed that it could be obtained in small yield by the action of silver oxide on malonyl chloride,



and in good yield by the action of zinc on dibromo-malonyl chloride (*cf.* prep. of ketens),

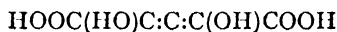


It is a mobile refractive liquid which boils at $7^\circ C.$ and possesses a smell resembling that of a mustard oil. It may be solidified by cooling, the solid melting at -107 to $-108^\circ C.$ It burns with a smoky blue flame, to form carbon dioxide. In its general behaviour it appears to be an internal anhydride of malonic acid, since it combines with water to yield malonic acid, with hydrochloric acid to malonyl chloride, with primary amines to amides of malonic acid, and with ammonia to malonamide.



Carbon suboxide has little or no tendency to combine with

aldehydes, hydrogen cyanide, etc., but forms addition products with formic and acetic acids, the former behaving as if it were a dihydroxy-diolefine carboxylic acid of structure.

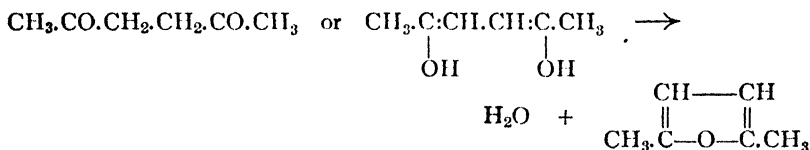


The addition product formed with acetic acid decomposes, when heated, into acetic anhydride, and a syrup which passes into malonic acid on treatment with water. This latter reaction seems to point to the syrupy liquid as being a polymerized form of carbon suboxide. Liquid carbon suboxide decomposes at ordinary temperature, a dark red solid, soluble in water, being gradually formed. This substance approximates in composition to the original liquid. The decomposition is instantaneous at 100°C ., carbon monoxide being evolved and a dark product remaining, which contains less oxygen than carbon suboxide.

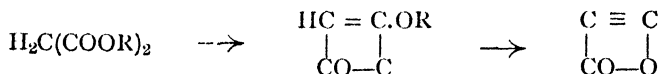
The molecular formula, C_3O_2 , has been established by combustion with copper oxide, by molecular weight determination according to Hofmann's vapour density method, and by explosion with oxygen and measurement of the amount of carbon dioxide formed. These results, taken in conjunction with the reactions of the oxide, have led Diels to formulate it as



Michael, on the other hand, considers such a formula improbable, and points out that when the elimination of water occurs, with the possibility of ring formation, the change usually follows an unsymmetric course, as, for example, in acetonylacetone, where dehydration leads to the formation of dimethylfuran, and *not* to a dimethyl-diacetylene.



Following this idea, Michael considers that the oxide should be represented as the lactone of β -hydroxypropionic acid, and explains its formation thus:—

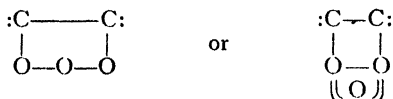


Diels, however, considers that his formula is the more correct for the following reasons—(1) the low boiling-point of the oxide, (2) the similarity of the oxide to the metallic carbonyls, (3) the high values of its molecular refraction and dispersion, (4) that it combines with four atomic proportions of bromine, (5) that water converts it into malonic acid, and (6) the improbability of the existence of a β -lactone containing the grouping $-\text{C} : \text{C}-$.

Finally, it may be pointed out that Staudinger's preparation of the oxide, by the general method employed for the formation of ketens, seems definitely to prove its keten structure, and consequently to disprove Michael's formula.

Ozonides—The use of ozone as an oxidizing agent has been known for some time, but it was left for Harries to show that it could be used for the preparation of complex aldehydes, and for the determination of the constitution of various unsaturated acids and hydrocarbons. In the preparation of ozonides, the substance to be examined is dissolved in a non-dissociating solvent, such as chloroform, and a current of ozonized oxygen, mixed with carbon dioxide, is passed into the solution at a low temperature. By working under these conditions the danger of accidents is lessened, the risk of explosions is minimized, and, of course, any volatile products are removed by the current of gas. The most important results were obtained with compounds containing an ethylenic linkage, such substances uniting with one molecule of ozone to form ozonides, which are usually thick oils or syrups of suffocating odour, and often of explosive character.

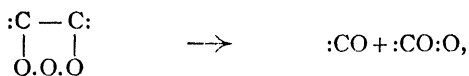
These ozonides are formulated either as containing the grouping—



and in general behaviour somewhat resemble the peroxides, in that they liberate iodine from potassium iodide and bleach both potassium permanganate and indigo. They are decomposed by

284 MODERN RESEARCH IN ORGANIC CHEMISTRY

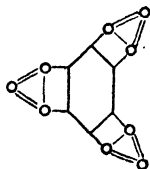
water, usually into aldehydes and ketones and peroxides of these, or hydrogen peroxide, the point of fission being the position of the ethylenic linkage in the original unsaturated compound, hence their use as aids in the determination of constitution. The typical decomposition is thus represented—



an example of which is seen in the case of the hydrocarbons of type $\text{R.C}(\text{CH}_3)\text{:CHR}$, the ozonide on decomposition by water yielding an aldehyde and a ketone peroxide.



The method has been applied to the determination of the constitution of the so-called ozobenzene, a white amorphous mass produced by the action of ozone on benzene. This explodes violently when brought into contact with hot water, but Harries and Wein showed that if it were very carefully warmed with water, it decomposed with production of glyoxal (OHC.CHO), and is consequently to be regarded as benzene oxonide.

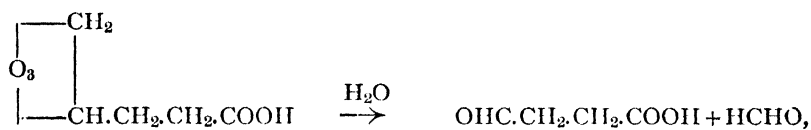


It is found that substances containing a carbonyl group (*e.g.* aldehydes, ketones, and monobasic acids) react under the above conditions in such a manner that they combine with four atoms of oxygen, and yield compounds which are termed ozonide-peroxides. These ozonide-peroxides are also decomposed by water, the decomposition resulting in the production of aldehydes and ketones (or their peroxides) as shown above, the excess oxygen being liberated in the form of hydrogen peroxide. Thus mesityl oxide ozonide peroxide yields bimolecular acetone peroxide, methyl glyoxal, and hydrogen peroxide,

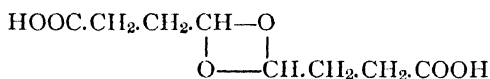
288 MODERN RESEARCH IN ORGANIC CHEMISTRY

The acetone peroxide which is simultaneously formed is removed and the residual liquid concentrated under reduced pressure and finally dried *in vacuo*, when a glassy mass, consisting of a hydrate of mesoxalic dialdehyde, is obtained. This mass, when heated over phosphorus pentoxide at 65° C., yields a yellow compound possessing the composition of the anhydrous dialdehyde, but is probably a polymeride.

The semialdehyde of succinic acid is formed by the decomposition of allylacetic acid ozonide,

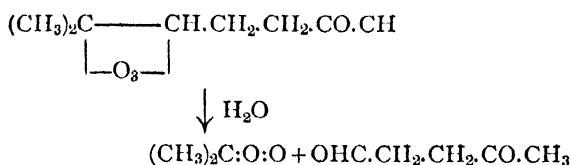


formic acid and succinic acid being simultaneously produced. The semi-aldehyde is an easily oxidizable oil, which on keeping, solidifies to a white crystalline mass of melting-point 147°. Molecular weight determinations show the oil to be a unimolecular compound, whilst the crystalline solid is bimolecular. Since the bimolecular compound is very stable towards oxidizing agents, Harries is of the opinion that condensation has taken place between the two carbonyl groups, and the compound is to be represented as—



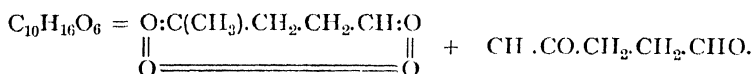
The crystalline variety passes back into the oily form when distilled at 134-136° C. (14 mm.).

Laevulinic aldehyde is obtained from the ozonide of methylheptenone,

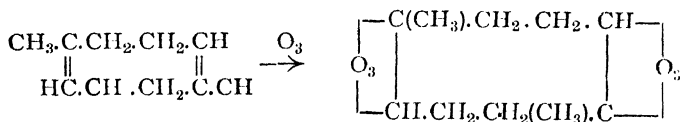


It is readily soluble in water, and reduces Fehling's solution in the cold. It does not polymerize, a fact which distinguishes it

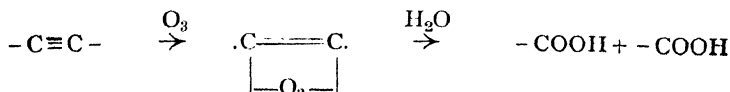
from succinic aldehyde, which contains the carbonyl groups in the same relative positions. It is also obtained from the ozonide of Para caoutchouc, which was obtained by Harries as a white vitreous explosive solid of molecular composition, $C_{10}H_{16}O_6$. This ozonide, on treatment with water and subsequent distillation in steam, yields laevulinic aldehyde and its peroxide, together with some laevulinic acid. The reactions may be thus represented—



A similar result is obtained by use of the hydrocarbon, $C_{10}H_{16}$, which is obtained by the decomposition of gutta-percha, except that the yield of the aldehyde is diminished whilst that of the acid is increased. From these results Harries concludes that the parent hydrocarbons in the caoutchouc and the gutta-percha are identical, but that the ozonides are probably stereo-isomers, and that the reacting molecule is a 1.5-dimethylcyclo-octadiene.



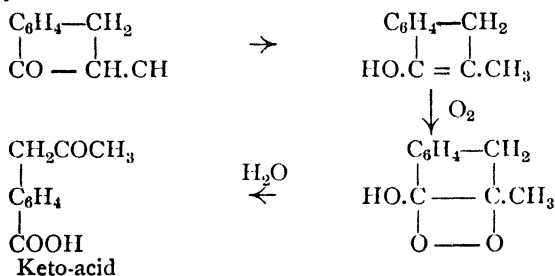
Molinari has tried to use ozone to distinguish between compounds containing an ethylenic linkage, and those containing an acetylenic linkage, for according to his results the latter class do not combine with ozone. Harries, however, considers that the results obtained and the conclusions drawn are incorrect, since certain compounds containing $C \equiv$ combine with ozone, more rapidly than compounds containing a $C =$ grouping, these ozonides on decomposition by water yielding acids—



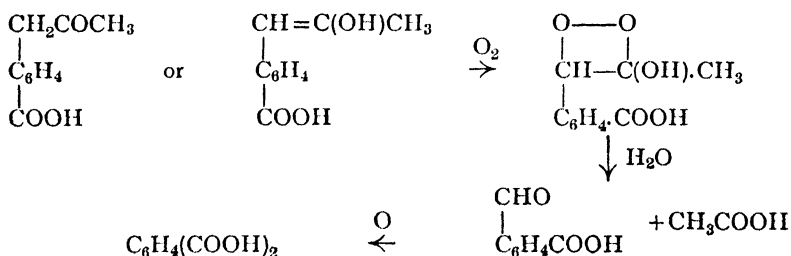
whilst it is also shown that both stearolic acid and phenylpropionic acid form ozonides. This difference between the two observers may be explained, according to Harries, by the fact that Molinari

uses ozonized air, whilst Harries himself uses the presumably more energetic ozonized oxygen.

An interesting case of the behaviour of atmospheric oxygen in a manner analogous to ozone has been observed by Perkin and Salway, who found that β -methylhydrindone on exposure to atmospheric oxygen became converted into phthalic acid and benzylmethylketone-(*o*)-carboxylic acid. In this reaction it appears to be necessary to assume that the ketone is first transformed into the enolic form, which then forms an additive product with one molecule of oxygen, this product being broken down by the action of water thus—

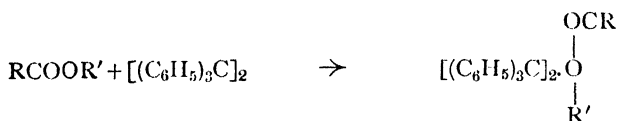


The keto-acid also assumes the enolic condition and gives the same series of transformations, resulting in the production of phthalic acid.

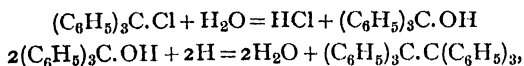


Triphenylmethyl.—In 1900 Gomberg, by the action of zinc on a solution of triphenylmethyl chloride in benzene, in absence of air, obtained a white crystalline solid, analysis of which yielded data corresponding to the empirical formula, $\text{C}_{19}\text{H}_{15}$. Molecular weight determinations by the cryoscopic method showed, however, that the substance corresponded to $\text{C}_{38}\text{H}_{30}$, that is $(\text{C}_{19}\text{H}_{15})_2$, or bimolecular triphenylmethyl, $[(\text{C}_6\text{H}_5)_3\text{C}]_2$, the first recorded exist-

ence of a compound containing carbon in the tervalent condition. The compound itself shows a characteristic unsaturated behaviour, in that it unites with the halogens, whilst it combines vigorously with oxygen to form a peroxide, $C_{38}H_{30}O_2$, which by the action of concentrated sulphuric acid is converted into triphenyl carbinol $(C_6H_5)_3C.OH$. It had been suggested that the bimolecular form might be hexaphenylethane, but Gomberg, in his earlier papers, considered this was improbable, since his compound had properties quite distinct from the ethane derivative as obtained by Ullmann and Borsum, and moreover was converted into it by the action of hydrochloric acid. The crystalline solid dissolves readily in organic solvents yielding yellow solutions, and Gomberg attributes this phenomenon to the presence of the free triphenyl methyl $[C_{19}H_{15}$ or $(C_6H_5)_3C -]$ ion, which possesses the properties of a univalent metal, confirmation of the latter fact being given in the ability of the halide derivatives to form perbromides and periodides. At a somewhat later date Gomberg showed that his new compound, which he concluded was the bimolecular form of triphenylmethyl, formed a series of additive compounds with hydrocarbons and esters, the latter being formulated as oxonium salts.



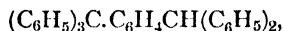
Ullmann and Borsum in 1902, with the idea that triphenylmethyl might be identical with hexaphenylethane, attempted to synthesize the latter compound by the action of zinc on triphenyl methyl chloride dissolved in glacial acetic acid, using zinc chloride as a condensing agent. They consider that the small amount of water in the glacial acetic acid converts the chloride into the carbinol, which is then reduced by the hydrogen liberated by the action of the zinc on the acid, thus—



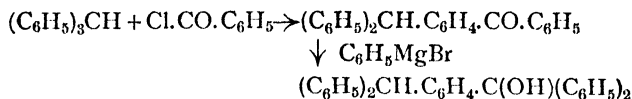
and since the compound so obtained was a stable substance, with

properties distinct from triphenylmethyl, they concluded that the identity of triphenylmethyl with hexaphenylethane was disproved.

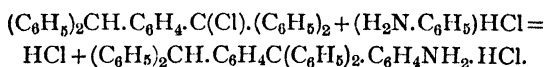
A further investigation on Ullmann's compound was, however, carried out in 1904 by Tschitschibabin, who found that it was not hexaphenylethane, but was in all probability an isomer, of constitution



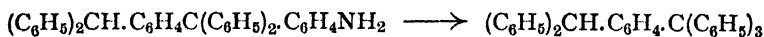
that is a (*p*)-benzhydryl tetraphenyl methane. This conclusion was arrived at by showing that the substance in question contained a methane hydrogen atom, since it yields a monobromo-derivative when brominated in carbon bisulphide solution in presence of sunlight, and the bromo-compound can be converted into the carbinol by the action of water in the presence of pyridine. The correctness of this view was shown in 1908, when Tschitschibabin synthesized Ullmann's compound from triphenyl methane and benzoyl chloride. These two substances, when condensed by the Friedel and Craft method, yield (*p*)-benzoyl triphenyl methane, which by the action of magnesium phenyl bromide and subsequent hydrolysis is converted into the tertiary alcohol (*p*)-benzhydryl triphenyl carbinol.



The hydroxyl group is then replaced by chlorine in the usual manner, and the chloro-derivative heated in boiling glacial acetic acid solution with aniline hydrochloride.

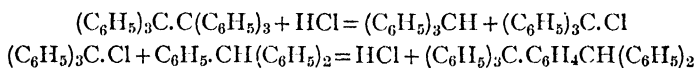


The amino-compound is diazotized and nitrogen eliminated in the usual manner, when Ullmann's compound is produced.

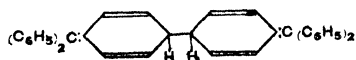


Thus it would seem that the probability of triphenylmethyl being hexaphenylethane had not been disproved by Ullmann's work. Gomberg had rejected the hexaphenylethane hypothesis on the

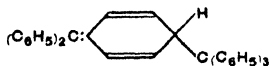
grounds that both the tetra- and pentaphenylethanes were stable substances, and there seemed to be no reason why hexaphenylethane should be different from the other two, whereas triphenylmethyl is very reactive. Tschitschibabin has, however, pointed out that the remarkable activity of triphenylmethyl is not inconsistent with the structure of hexaphenylethane, since the presence of many electronegative groups in a compound leads to an increased activity of the compound, and he draws attention to the fact that the researches of Engler and others have shown that many substances react with atmospheric oxygen to form peroxides, as the first product of oxidation. The formation of Ullmann's compound from triphenylmethyl is assumed by Tschitschibabin to be due to an intermediate decomposition into triphenylmethane and triphenylmethyl chloride, which then react one with the other, with elimination of hydrochloric acid and production of (*p*)-benzhydryltetraphenylmethane.



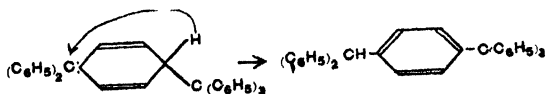
In 1905 Jacobson suggested a possible constitution, based on one given earlier by Heintschel, the latter investigator having proposed a di-quinonoid structure,



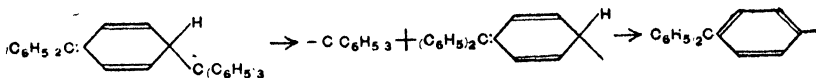
the difference being that Jacobson would make triphenylmethyl a combination of one quinonoid group with one non-quinonoid complex, thus:—



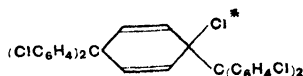
He argues that compounds of such type show a marked tendency to pass back into the aromatic condition, and shows that by the shifting of one hydrogen atom, such a compound would yield Ullmann and Borsum's hydrocarbon.



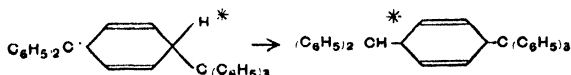
Again, he points out that if the aromatic group $(C_6H_5)_3C$ should detach itself, a quinonoid complex would remain, which could rearrange itself to the aromatic form by a shifting of linkages, and such a substance would thus act as triphenylmethyl.



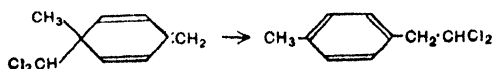
Gomberg has criticized this view, and points out that if it were correct then the parahalogen derivatives of the type—



should be capable of losing the chlorine atom marked * when acted upon by silver or zinc, and consequently give a compound formed by the linking up of two molecules of the original compound. This is not the case, for the derivatives obtained are considered to possess the same structure as triphenylmethyl, since they all give peroxides under similar conditions. This structure, however, cannot be $(ClC_6H_4)_3C-$, for such a configuration would require all these chlorine atoms to be of the same value, which is not the case, since the chlorine attached to one phenyl group is removable, showing that one phenyl group possesses functions different from the other two. Auwers has also pointed out the improbability of such a formula as Jacobson's, for he thinks that such a compound would be so unstable that it would rearrange itself as indicated in the following scheme:—



and as an argument in favour of this change mentions the case of methyl-dichloromethyl quinomethane, which spontaneously rearranges itself to (*p*)-methyl dichloroethyl benzene.



Since the heavy $-CHCl_2$ group wanders in this case into the

para-position, Auwers considers that the hydrogen atom indicated in Jacobson's formula would also do the same. Tschitschibabin also thinks that a quinonoid configuration is improbable, for Baeyer's work would seem to negative the quinonoid structure for the haloid derivatives; and since triphenyl methyl and its haloid derivatives are closely related, it would be hardly necessary to assume that the hydrocarbon itself possessed a quinonoid configuration. He also shows that the solid form is relatively stable, and may be retained for months in contact with dry air. This seems to render it necessary to regard it as being hexaphenylethane, or else to assume that a substance having a free valency is capable of existing in a condition of relative stability in the solid form, although in solutions in which its valencies are all neutralized in the normal manner it exhibits an enormous reactivity.

There seems at present to be strong presumptive evidence that the solid form is hexaphenylethane, but since the solid is colourless, whilst solutions of the hydrocarbon are yellow, it would appear that a different constitution is required for the dissolved hydrocarbon. No definite conclusions have as yet been reached regarding the solutions, but the following views have been suggested:—

1. The colour is due to ionization.
2. The solution contains $(C_6H_5)_2C : C_6H_4 : \left\langle \begin{array}{c} H \\ C(C_6H_5)_3 \end{array} \right.$, which partly dissociates into a quinonoid cation, and a benzenoid anion.
3. The solution contains a quinonoid compound of the type indicated by Jacobson.

Finally, it may be mentioned that Schmidlin has suggested that triphenylmethyl is an equilibrium mixture of the two forms $(C_6H_5)_3C-$, and $(C_6H_5)_3C.C(C_6H_5)_3$, and has devised the following means of showing the relative proportions of the two forms. The yellow solution on shaking with air becomes colourless owing to the formation of the peroxide. The peroxide is insoluble in ether, so that an ether solution is shaken up with air, and after it becomes colourless the precipitate is filtered off, and the filtrate

296 MODERN RESEARCH IN ORGANIC CHEMISTRY

now shaken again with excess of air and the precipitate again filtered. According to Schmidlin, the two precipitates will approximate to the proportions of the coloured and colourless varieties present in the original solution, and an experiment showed that the ratio was roughly one to ten.

Thus the question of constitution remains at present, but no doubt further investigations will be made, and the structure of this interesting compound will be finally settled in the near future.

BIBLIOGRAPHY

- Ketens** Staudinger, *Ber.* 1905, **38**, 1735; 1906, **39**, 968, 3062; 1907, **40**, 1145, 1149; 1908, **41**, 594, 906, 1355, 1493, 2208, 4461; 1909, **42**, 4213, 4249, 4908; *Ann.* 1910, **374**, 1.
- Wilsmore, *J. Chem. Soc.* 1907, **91**, 1938; 1908, **93**, 946; 1910, **97**, 1968, 1978; *Nature*, 1907, **75**, 510.
- Michael, *Ber.* 1906, **39**, 1915.
- Diels, *Ber.* 1906, **39**, 689; 1907, **40**, 355.
- Ozonides** Molinari, *Ber.* 1906, **39**, 2735; 1907, **40**, 4154.
- Harries, *Ber.* 1905, **38**, 1195, 3985; 1906, **39**, 2844, 2846, 3728; 1907, **40**, 165, 2823, 4905; 1908, **41**, 38, 2187, 3098, 3552; 1909, **42**, 159, 446, 3305; 1910, **43**, 1432; *Ann.* 1905, **343**, 311; ¹ 1910, **374**, 288.¹
- Triphenylmethyl.** Gomberg, *Ber.* 1900, **33**, 3150; 1901, **34**, 2726; 1902, **35**, 1822, 2397, 3914; 1903, **36**, 376; 1907, **37**, 1626, 2033, 3538; 1905, **38**, 1333, 2447; 1906, **39**, 1461, 2957, 3274; 1907, **40**, 1847; *J. Amer. Chem. Soc.* 1901, **23**, 496; 1902, **24**, 597; *Ann.* 1909, **370**, 142.
- Tschitschibabin, *Ber.* 1904, **37**, 4709; 1905, **38**, 771; 1907, **40**, 3056, 3965; 1909, **42**, 3469.
- Jacobson, *Ber.* 1905, **38**, 196.
- Heintschel, *Ber.* 1903, **36**, 320.
- Schmidlin, *Ber.* 1906, **39**, 628, 4183; 1907, **40**, 2316; 1908, **41**, 423, 426, 2471.
- Baeyer, *Ber.* 1907, **40**, 691.
- Wieland, *Ber.* 1909, **42**, 3020.

¹ These two papers contain general resumé of the work on ozonides.

CHAPTER IX

THE GRIGNARD REACTION

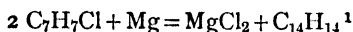
THE use of organo-metallic compounds as synthetic reagents has, of course, been known for many years, but it appears to have been Barbier (in 1899) who pointed out that magnesium might be employed in the Saytzeff reaction, in place of zinc. In the following year Grignard published a general method for the preparation of alcohols and hydrocarbons by the condensation of magnesium alkyl or aryl halides in conjunction with various organic compounds.

Magnesium methyl iodide and magnesium dimethyl have, of course, been long known, but Grignard observed that in the presence of anhydrous ether, magnesium combines at ordinary temperature with alkyl or aryl iodides, with the appearance of brisk boiling, to form compounds of the type RMgX , which are soluble in an excess of ether. These compounds contain one molecule of ether, are not inflammable, and are very reactive.

In the preparation of the reagent, it is necessary to see that all the materials used are pure and dry, and it is found that the solution of the magnesium takes place more or less rapidly according to the nature of the halide compound used, and to the quantity of ether employed. The beginning of the reaction is frequently accelerated by the addition of a trace of iodine, or, as Baeyer found, by "activating" the magnesium, by warming it with about one-half its weight of iodine, so as to form a certain amount of magnesium iodide, care being taken to avoid melting of the mixture. It is probable that the formulation of the reagent as RMgX (R = aliphyl or aryl radical, X = halogen) only represents the last stage in a series of reactions, and although such a type of compound is generally produced, it is found that secondary reactions occasionally take place, leading to the production of

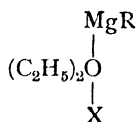
298 MODERN RESEARCH IN ORGANIC CHEMISTRY

hydrocarbons. This latter change is found to occur to a greater extent as the group R increases in complexity, benzyl chloride, for example, reacting with magnesium to yield more or less dibenzyl.¹

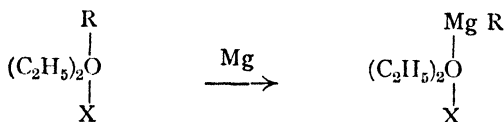


Experiment has shown that other solvents may be used in place of ethyl ether; thus Tschelinzeff found that it could be replaced by benzene, to which a small quantity of ether or anisole had been added, whilst benzene and xylene could be used alone provided a high enough temperature were employed. Methyl amyl ether, amyl phenyl ether, dimethylaniline, and other tertiary amines have also been used by various investigators.

Various views are held regarding the constitution of the complex formed between the magnesium organo-halide compounds and the ether, Baeyer and Villiger being of the opinion that an oxonium salt of type—

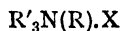


is produced, whilst, according to Tschelinzeff, the ether appears to act as a catalyst, anyhow at low temperatures, for he finds that if an inert solvent, such as benzene, be employed, a trace of ether added to the solution leads to the formation of the organo-magnesium halide. The change is represented thus:—



¹ In a recent communication to the Chemical Society, Kipping has pointed out that it is not really necessary to prepare the Grignard reagent first, and then bring it in contact with the other component of the reaction, but that equally good results may be obtained by mixing all the reaction substances together immediately. This method of procedure seems to diminish the amount of bye-products (*e.g.* dibenzyl, diphenyl, etc.) obtained, but it is also found that by working in this manner, no reaction can be obtained when acetone is one constituent of the mixture.

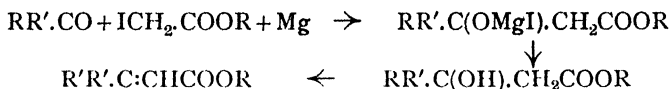
In the case of the inert solvent, it is found that anisole gives an even better result than ether, whilst a tertiary amine can also be used as catalyst, the intermediate stage being the production of a quinquevalent nitrogen compound, such as—



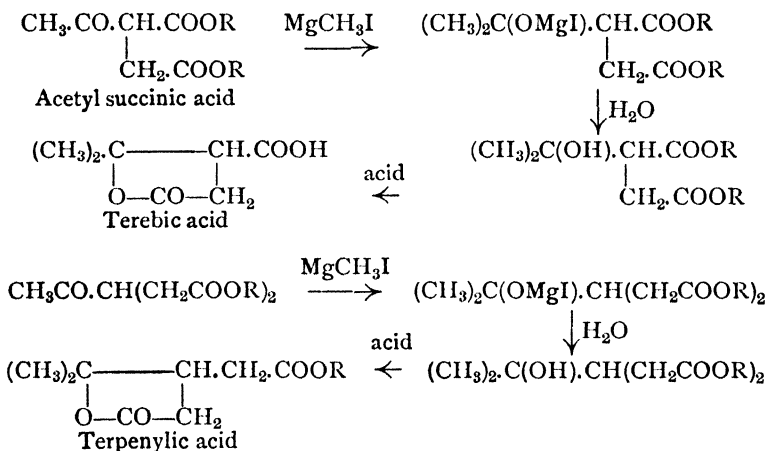
Blaise, who carried out some of the earlier work on the reaction, was also of the opinion that an oxonium salt was formed, and concluded that the basic character of the quadrivalent oxygen in such compounds increased with the increasing complexity of the alkyl groups, since the ethyl ether may be readily replaced by di-amyl ether in such compounds, but less readily by methyl amyl ether, or again it may be replaced by the more acidic phenyl ethyl ether. Finally, Tschelinzeff has prepared the compounds $RMgX.(C_2H_5)_2O$, and finds that two molecules of ether are combined with one of the organo-magnesium halide, the formation of such compounds being evident from the fact that on the addition of ether to a benzene solution of propyl iodide or isoamyl iodide containing magnesium, equal quantities of heat are evolved for each addition of the first two molecular proportions of ether added, the subsequent addition of ether causing little effect in this direction.

In the case of unsaturated alkyl halides it has been found that the reaction proceeds in a different manner, the product obtained being only slightly soluble in ether and containing two hydrocarbon residues combined with one atom of magnesium; thus, for example, with allyl iodide, the substance formed seems to possess the constitution $C_3H_5I.MgI.C_3H_5$. The products of this type are very unstable and do not react readily with aldehydes and ketones. As regards the method of procedure where the Grignard reaction is used, the magnesium is added in the form of wire, filings, or turnings, to the dry ether, and the halide compound usually dropped in through a tap-funnel. To complete the solution of the magnesium it is occasionally necessary to heat the ether. When the reaction is finished the contents of the vessel are cooled and the halide added, a vigorous reaction generally

302 MODERN RESEARCH IN ORGANIC CHEMISTRY

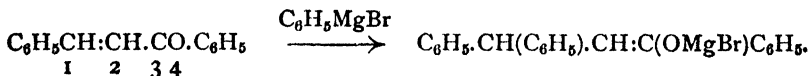


Ketonic acids of the type of acetyl-succinic acid and acetyl-glutaric acid have been used by Simonsen, the products obtained with magnesium methyl iodide being terebic and terpenylic acids, the synthesis of which, in this manner, has definitely determined their structure. It must, of course, be understood that the acids in such a reaction are used in the form of esters in order to prevent reaction between the carboxyl group and the reagent—

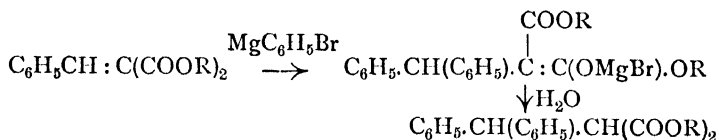


Kohler and his students have examined the behaviour of the Grignard reagent with unsaturated aldehydes and ketones containing the grouping $-C:C:O.R$, and have shown that the reactions depended on the nature of the atoms or groups associated with the ethylene carbon atom or carbonyl group. The nature of the addition appears to be determined by the following rules:—

1. In aldehydes ($R = H$) and ketones ($R = CH_3$), the organo-magnesium compound reacts normally with the carbonyl group.
2. In ketones ($R = C_6H_5$), addition products are formed in the 1:4 position, thus with cinnamyl phenyl ketone—



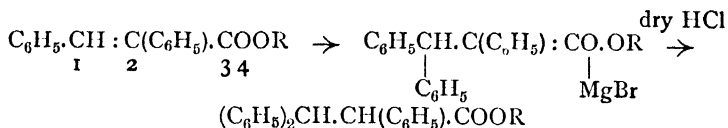
3. With unsaturated esters (R=OR) either addition takes place as in (2) above, or the -OR group is replaced by an alkyl group, the former reaction taking place with aromatic and the latter with aliphatic magnesium compounds ; for example, ethyl benzylidene malonate, when heated with magnesium phenyl bromide for a short time yields an addition product which is decomposed by water to form the substituted, ester shown.



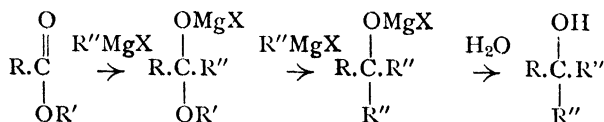
This ester, on acidification and boiling with water, loses carbon dioxide, and is converted into $\beta\beta$ -diphenylpropionic acid.



The methyl ester of α -phenyl cinnamic acid reacts in a similar manner.



Esters react readily with the reagent, the normal course of the reaction resulting in the production of a tertiary alcohol, the various stages of the process being shown in the following scheme:—



Many of the tertiary carbinols formed in this way are unstable, and lose water readily, passing into unsaturated compounds. This latter reaction takes place very readily if the carbinol be heated with acetic anhydride.

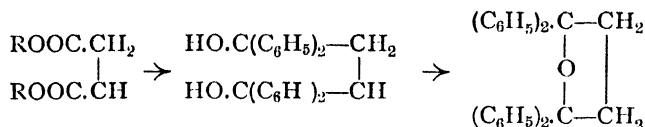
If formic ester be used in the above reaction, a secondary alcohol results, since it merely means the replacement of the radical R by a hydrogen atom. By using formic ester (3 mols.)

304 MODERN RESEARCH IN ORGANIC CHEMISTRY

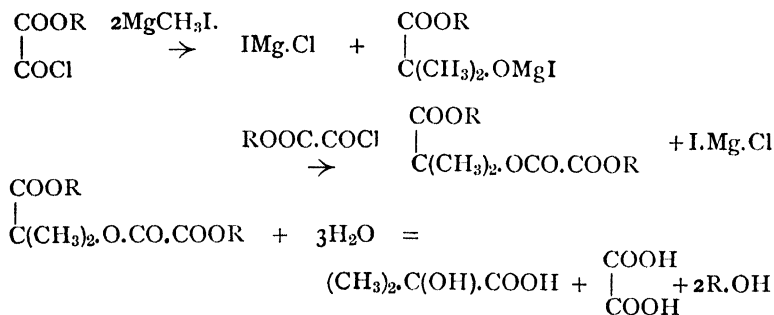
dissolved in dry ether cooled to -50°C ., and adding well-cooled magnesium phenyl bromide (1 mol.), Gattermann found that the reaction led to the formation of benzaldehyde.



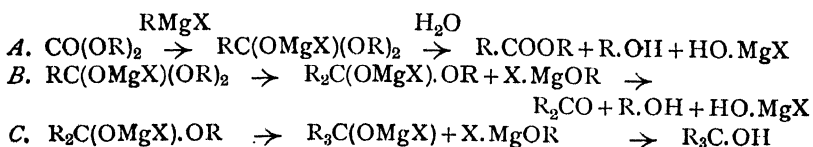
Valeur, by application of magnesium phenyl halides to ethyl succinate, obtained tetraphenylbutane di-ol, which on heating with acetic acid passed in tetraphenyl tetrahydrofuran, by ring closing between the two hydroxyl groups.



Grignard himself has obtained substituted glycollic acids by the action of magnesium methyl iodide on chloro-oxalic ester, adding the chloro-compound (1 mol.) to the magnesium organo-halide. By working in this manner the group $-\text{COCl}$ is alone attacked.

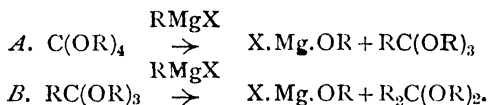


The esters of carbonic acid readily react with the reagent, the possible changes being represented by the following equations, as was shown by Tschitschabin.

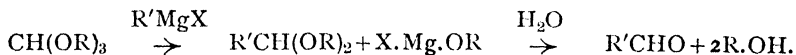


Hydrolysis of the addition products gives rise to esters, ketones,

and tertiary alcohols. The chief reaction is as shown in (A) and, provided the experiment is carefully carried out, may be stopped at that stage. The same investigator has shown that ortho-carbonic ester reacts in a similar manner, yielding as principal product the esters of an ortho-acid—

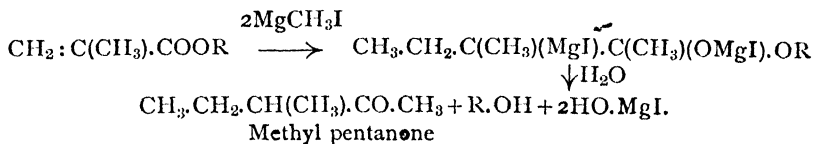


He also found that orthoformic ester reacts with the reagent, but that the action was only completed when the solvent ether was distilled off. In this way an acetal is formed, and may be converted into an aldehyde by hydrolysis with acid—



Bodroux also found that a good yield of benzaldehyde could be obtained by prolonged boiling of magnesium phenyl bromide with orthoformic ester, and subsequent hydrolysis of the acetal.

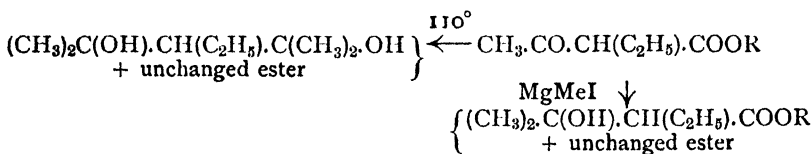
Blaise has used unsaturated esters of the type of methacrylic ester, and finds that one molecule of the organo-magnesium halide adds on to the ethylene linkage, whilst another molecule reacts with the —COOR group in the normal manner. Hydrolysis of the product yields a saturated ketone—



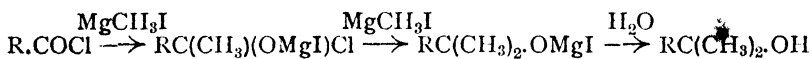
Ketonic acids, such as aceto-acetic ester, in which the possibility of a keto-enolic tautomerism exists, show an interesting behaviour with the reagent, in that, so far as they are enolic they decompose it, and as far as they are ketonic they react normally. Thus aceto-acetic ester reacts with magnesium methyl iodide to give a little methane and a product which, on decomposition with water, yields magnesium iodide and unchanged ester. If, however, the enolic formation be inhibited, as in ethyl aceto-acetic ester, then a normal type of reaction takes place, the

306 MODERN RESEARCH IN ORGANIC CHEMISTRY

keto-group reacting, or, if an elevated temperature be employed, both the $>CO$ and $-COOR$ groups taking part in the change.



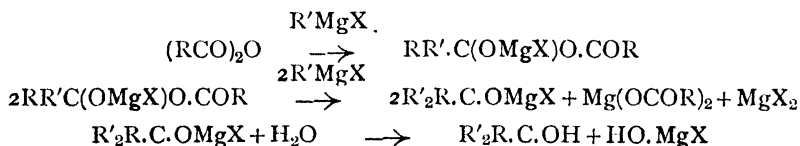
Acid chlorides and acid anhydrides react in a manner analogous to the esters, yielding tertiary alcohols—



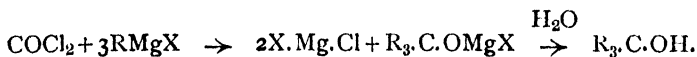
In this reaction the possibility of ketone formation also exists—



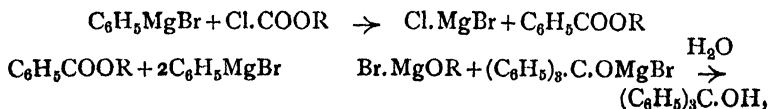
but where such a change happens the yield of ketone is usually small, the reaction proceeding further (as shown above) to the production of the tertiary alcohol. With acid anhydrides the stages of the change are possibly as shown in the subjoined scheme:—



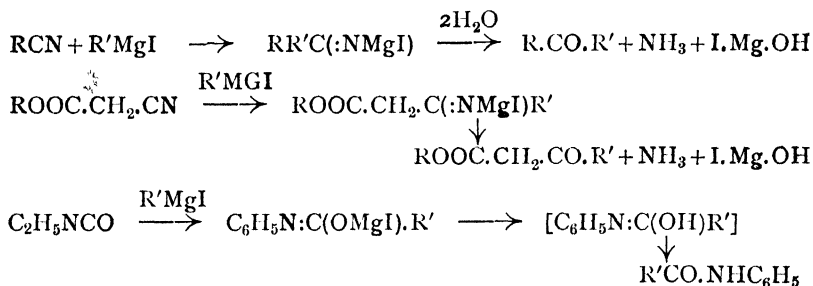
Carbonyl chloride similarly yields tertiary alcohols—



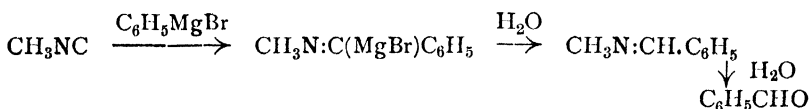
Houben found that if a solution of magnesium phenyl bromide in ether, be added to chlorocarbonic ester, the chief product of the reaction was ethyl benzoate, but if the ester be added to the organo-magnesium halide, then the chief product was triphenyl-carbinol, the following equations explaining the reaction in the two cases:—



the benzoic ester undergoing normal ester reaction with the reagent. Numerous applications of the reagent have been made to nitrogen compounds, one of the earliest workers in this field being the French chemist Blaise, who showed that nitriles, α -cyano-acid esters, and phenyl carbimide readily react. Ketones are obtained in this way from the nitriles, the reaction proceeding best in the aromatic series; β -ketonic acids result from the cyano-acids, and anilides from the carbimides.



Sachs and Loevy have shown that mustard oils behave in the same way as the carbimides, giving thio-anilides, $\text{RCS}\cdot\text{NHC}_6\text{H}_5$, whilst from the isonitriles they were able to obtain aldehydes.



Sand and Singer, by using magnesium phenyl bromide and nitric oxide, have prepared nitroso- β -phenylhydroxylamine—

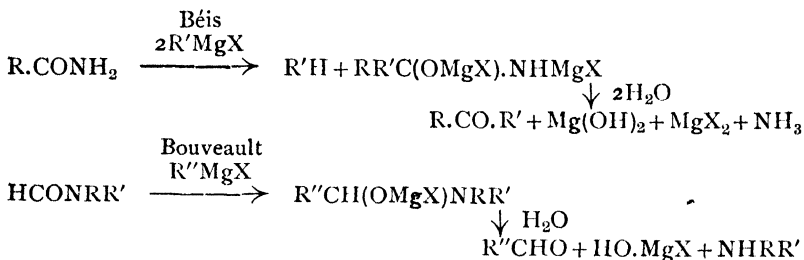


and Wieland extended the reaction to nitrogen peroxide, hoping to get nitroxylic acids, $\text{R}\cdot\text{NOOH}$. Since, however, only β -substituted hydroxylamines were obtained, it seems apparent that the nitrogen peroxide must undergo reduction at some stage of the process.

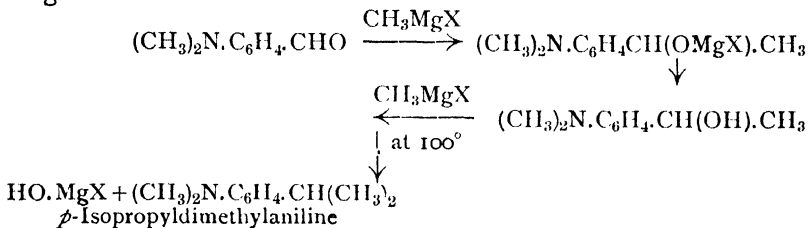
Béis has used acid amides, and has found that on long boiling with an excess of the reagent they yield products from which ketones may be obtained by hydrolysis. This type of reaction has been carried further by Bouveault, who showed that substituted

308 MODERN RESEARCH IN ORGANIC CHEMISTRY

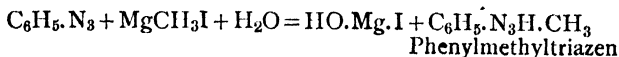
formamides could be in a similar manner made to yield aldehydes.



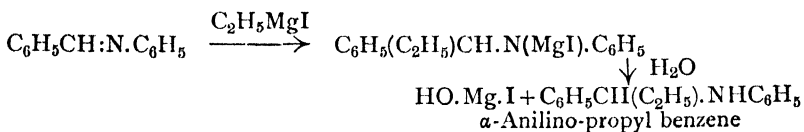
Various basic nitrogen compounds have been used by different observers, Sachs in 1905 showing that, with (*p*)-dimethylamino-benzaldehyde, the aldehydic oxygen atom could be replaced by two alkyl groups, when the product first obtained from the aldehyde and the reagent was heated at 100° C. with an excess of the reagent.



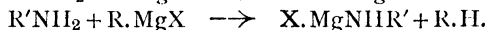
An important synthetical preparation of diazo-amines (triazens) has been devised by Dimroth, who has shown that mixed aromatic-aliphatic triazens can be obtained by the action of the reagent on organic azoimides, phenyl methyl triazen, for example, being prepared by adding phenyl azoimide to magnesium methyl iodide, and then bringing the mixture into aqueous ammonia and ammonium chloride at 0° C.



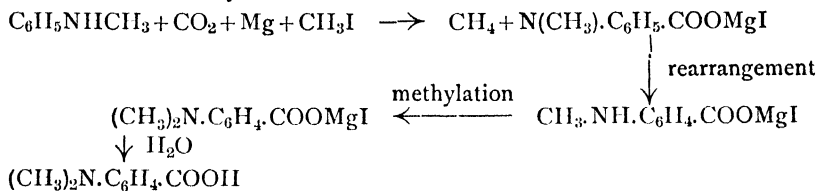
At a somewhat later date, the simple aliphatic diazoaminomethane or dimethyltriazen was similarly prepared from methylazoimide and magnesium methyl iodide. M. Busch has found that unsaturated alkylidene amines form addition compounds, which are decomposed by acid with production of anilino-benzenes.



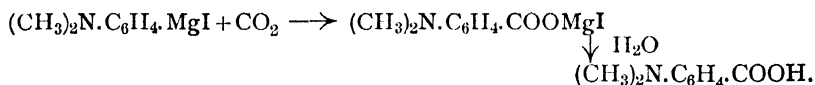
Amines containing available hydrogen react with the reagent in the same manner as simple hydroxylic compounds, yielding hydrocarbons.



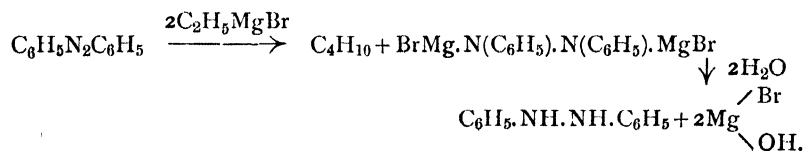
Houben has recently shown that methylaniline, when heated in dimethylaniline solution in a stream of carbon dioxide with magnesium and methyl iodide, yields (*p*)-dimethylaminobenzoic acid, the dimethylaniline probably acting as a methylating agent of the mono-methyl acid first formed.



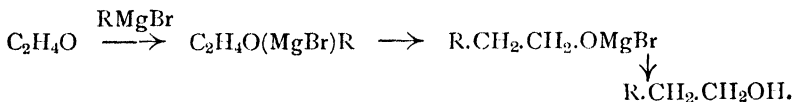
He further suggests that perhaps the first step in the reaction consists in the formation of a complex $\text{IMg.C}_6\text{H}_4\text{N(CH}_3)_2$, from the interaction of the dimethyl aniline and magnesium methyl iodide, and this then reacts in the normal manner with the carbon dioxide—



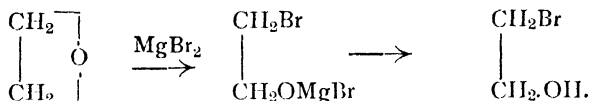
Occasionally the reagent acts as a reducing substance, Franzen having found that azobenzene reacts with magnesium ethyl bromide to yield butane and a compound from which, by hydrolysis, he obtained hydrazobenzene—



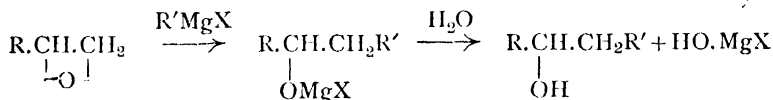
In the case of ethylene oxide and magnesium alkyl bromides, Blaise found that an oxonium salt was first produced. This salt, on removal of the solvent, isomerizes rapidly to the corresponding hydroxylic derivative, from which the alcohol may be prepared in the usual manner—



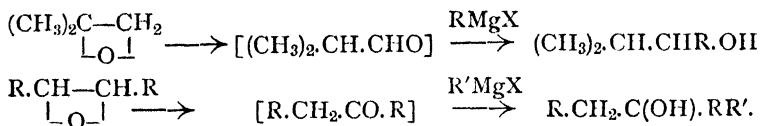
If, however, the addition product be subjected to the action of water, it decomposes, and the regenerated ethylene oxide, reacting with the magnesium bromide, simultaneously produced, yields a glycol bromohydrin derivative—



The simple homologues of ethylene oxide yield secondary alcohols,

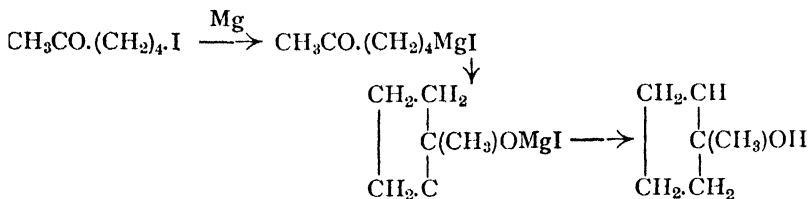


but the α -dialkyl derivatives react abnormally, the unsymmetrical members of the series behaving as if they first isomerized to aldehydes, and the symmetrical as though to ketones, reaction then taking place in the normal manner, the final products obtained being secondary and tertiary alcohols.

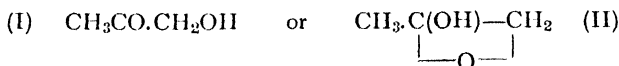


An interesting reaction was discovered by Zelinsky in 1902, when he found that the product of the action of magnesium on acetyl-(*n*)-butyl iodide, on decomposition with acetic acid, yielded 1-methyl cyclopentane-ol-1, probably due to rearrangement of the magnesium organo-halide compound first formed.

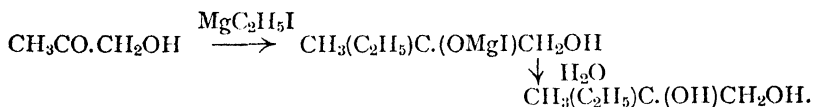
312 MODERN RESEARCH IN ORGANIC CHEMISTRY



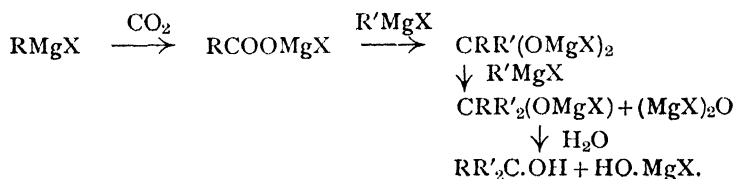
Kling has used the reagent to determine the constitution of acetol (acetyl carbinol), $\text{C}_3\text{H}_6\text{O}_2$, which may be represented as,



and consequently should behave towards the reagent either as a keto-compound or as an ethylene oxide. By using the acetyl derivative and magnesium ethyl iodide an amylene glycol was obtained, which shows that acetol must be represented by (I)—



Tertiary alcohols may be prepared from the addition product of the reagent and carbon dioxide. After removal of excess of the carbon dioxide the product is brought into contact with a further quantity of the reagent in the cold, and the resulting product heated for some time on the water bath and then decomposed by acid—

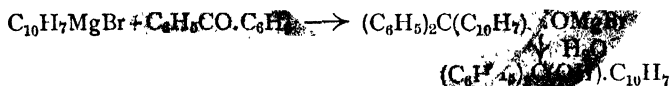


Werner has produced aromatic hydrocarbons by the action of dimethyl-sulphate on the reagent, paraxylene resulting when magnesium tolyl bromide is thus treated—

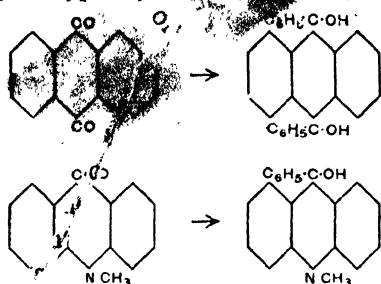


Mention may also be made of the extension of the reaction to the compounds of the naphthalene, anthracene, and acridine

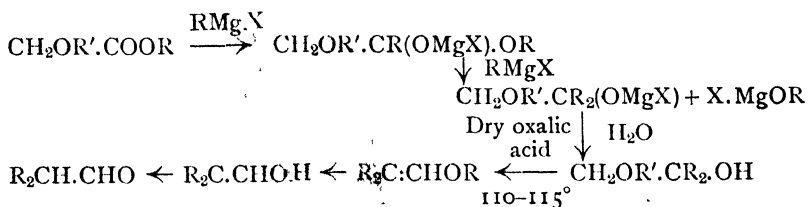
series, β -naphthyl magnesium bromide reacting in the normal way with aromatic ketone



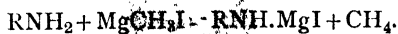
Anthraquinone with magnesium phenyl bromide yields γ -dihydroxy- γ -diphenyldihydroanthracene. N-methyl acridone similarly yields hydroxyphenyl N-methyl dihydroacridine.



Behr has prepared substituted aldehydes from the ethers of glycols, these ethers resulting from the action of the reagent on such compounds as the ethyl ester of ethoxy-acetic acid. They are then converted into the aldehydes by heating with dry oxalic acid at 110° - 115° C.



Sudborough has pointed out that the reaction between the reagent and a primary amine is, in the cold, quantitative, one molecule of methane being liberated for each molecule of magnesium methyl iodide used, thus—

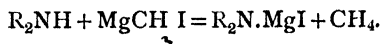


When heated, a second molecule of methane is liberated, the reaction perhaps occurring as shown in the following equation:—



314 MODERN RESEARCH IN ORGANIC CHEMISTRY

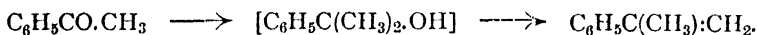
With secondary amines, only one molecule of methane is liberated, whilst tertiary amines do not enter into reaction.



Hence it is suggested that this reaction might be used for the characterization and estimation of amines.

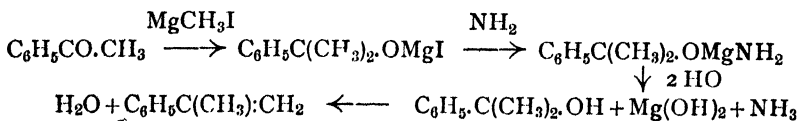
Perhaps the most important synthetic use made as yet with the Grignard reaction is that which led Perkin to prepare members of the terpene series, for details of which see Chapter II.

As thus far shown in the previous pages, the Grignard reaction has been used for the preparation in most cases of saturated compounds, but Klages has shown that by a modification of the conditions of reaction, unsaturated compounds can be obtained directly, in the aromatic series. Using an aromatic ketone, magnesium, and an alkyl iodide in equimolecular proportions, the normal course of the reaction is to yield a tertiary alcohol, but if the proportion of magnesium and alkyl iodide be doubled, and the whole reaction mixture heated for several hours, it is found that an unsaturated hydrocarbon is formed. Acetophenone, for example, under these conditions, yields β -allyl benzene when condensed with magnesium methyl iodide, presumably owing to the dehydration of the intermediately formed carbinol—



This appears to be a general reaction in the aromatic series, except when two ortho-substituents are present in the aromatic compound. Acetyl mesitylene, for example, is such a compound, and here, although the normal addition product is formed with the reagent, on decomposition with acid it yields unchanged acetyl mesitylene.

The magnesium alkyl iodides of the ketones were also found to react with dry ammonia to form derivatives which on decomposition by water yielded alkyl styrenes.



316 MODERN RESEARCH IN ORGANIC CHEMISTRY

Grignard and Tissier, *C.R.* 1901, **132**, 558, 835, 683; 1903, **136**, 815.

Tiffeneau, *C.R.* 1903, **137**, 573.

Simonsen, *Jour. Chem. Soc.* 1907, **91**, 184.

Kohler, *Amer. Chem. Jour.* 1905, **34**, 132.

Gattermann, *Ber.* 1903, **36**, 4152.

Valeur, *C.R.* 1903, **136**, 694.

Grignard, *C.R.* 1903, **136**, 1200; 1902, **134**, 849.

Tschitschibabin, *Ber.* 1904, **37**, 186; 1905, **38**, 561.

Bodroux, *C.R.* 1904, **138**, 72.

Blaise, *C.R.* 1901, **133**, 1217; 1902, **134**, 551.

Houben, *Ber.* 1903, **36**, 3087.

Sachs and Loevy, *Ber.* 1904, **37**, 874.

Sand and Singer, *Ann.* 1903, **329**, 190.

Wieland, *Ber.* 1903, **36**, 2315.

Béis, *C.R.* 1903, **137**, 575.

Sachs, *Ber.* 1905, **38**, 517.

Dimroth, *Ber.* 1905, **38**, 670.

Busch, *Ber.* 1905, **38**, 1761.

Houben, *Ber.* 1909, **42**, 3729, 4815.

Franzen, *Ber.* 1905, **38**, 2716.

Zelinsky, *Ber.* 1902, **35**, 2684.

Kling, *C.R.* 1903, **137**, 756.

Werner, *Ber.* 1903, **36**, 2116, 3618.

Behal, *C.R.* 1904, **138**, 89.

Sudborough, *Proc. Chem. Soc.* 1904, **20** 165.

Perkin, see Chap. II. p. 53.

Kluges, *Ber.* 1902, **35**, 2633, 3506

M'Kenzie, *B.A. Reports*, 1907, p. 273.

INDEX OF AUTHORS

- | | |
|---|---|
| <p style="text-align: center;">A</p> <p>Antonaz, 194
Archibald, 229
Armstrong, 203
Aschan, 11
Auwers, 57, 62, 294</p> | <p>Dimroth, 308
Dobbie, 181
Dodge, 45
Doebner, 36, 131</p> |
| <p style="text-align: center;">B</p> <p>v. Babo, 130
Baeyer, 2, 4, 12, 15, 51, 58, 69, 77, 84,
86, 104, 211, 226, 229, 231, 297
Baker, 231
Baly, 213, 215
Barbier, 40, 46, 48, 71, 297
Baum, 135
Beckmann, 71
Béhal, 313
Behrend, 109
Béis, 307
Blaise, 299, 305, 307
Blanc, 4, 5, 19, 24, 25, 26, 94
Bodroux, 305
Bouveault, 4, 26, 27, 40, 46, 48, 71, 88,
307
v. Braun, 257
Bredt, 21, 26, 90, 92, 94
Brühl, 228
Buchner, 9, 33
Busch, 308</p> | <p style="text-align: center;">E</p> <p>Einhorn, 71, 150
Étard, 136, 137</p> |
| <p style="text-align: center;">C</p> <p>Carapelli, 251
Ciamician, 31
Collie, 225, 247, 250, 254
Conrad, 79</p> | <p style="text-align: center;">F</p> <p>Feist, 225, 247
Fischer, E., 106, 111, 113, 115, 240
Fittig, 79, 105, 131, 142
Fox, 232
Franzen, 309
Freund, A., 1, 11
Freund, M., 167, 170
Friedel, 223
Fritsch, 173</p> |
| <p style="text-align: center;">D</p> <p>Decker, 230, 273
Dieckmann, 4
Diels, 281</p> | <p style="text-align: center;">G</p> <p>Gabriel, 252
Gadamer, 179
Gardner, 19
Gattermann, 304
Genequand, 130
Gomberg, 232, 290, 294
Graebe, 269
Green, 206
Grignard, 297, 301, 310
Grimaux, 162</p> |
| | <p style="text-align: center;">H</p> <p>Haller, 19, 24, 71, 89, 91
Hantzsch, 17, 129, 208, 233, 238, 241
Harries, 27, 41, 47, 56, 73, 283, 289
Hartley, 103
Heintschel, 293</p> |

318 MODERN RESEARCH IN ORGANIC CHEMISTRY

Helle, 68
 Herzig, 257
 Hesse, 72
 Hessenland, 57
 Hewitt, 212, 217, 218, 228, 230, 231, 232
 Heyes, 224
 Hill, 111
 Hofmann, 132
 Horbaczewski, 109
 Houben, 307, 309, 310

I

Ipatiew, 40
 Isay, 122

J

Jacobson, 293
 Jahns, 128, 129

K

Kauffmann, 200, 202, 210, 243
 Kehrmann, 233, 241, 242, 272
 Kipping, 298
 Klages, 71, 314
 Kling, 312
 Knoevenagel, 5
 Knorr, 162, 165, 166, 167
 Koch, 272
 Koenigs, 125, 193
 Koetz, 72
 Kohler, 302
 Komppa, 19, 21, 22, 94
 Kondakow, 65
 Kostanecki, 257, 261, 271
 Krüger, 48

L

Ladenburg, 131, 133, 141, 143
 Lagodzinski, 157
 Lapworth, 21, 93
 Lauder, 181
 Leuchs, 184, 188
 Levallois, 88
 Liebermann, 16, 177, 203
 Liebig, 101
 Loevy, 307
 Losanitsch, 191
 Lossen, 141
 Lowry, 91

M

M'Intosh, 229
 Marckwald, 27
 Marsh, 19
 Martine, 71
 Marx, 207
 Matthiessen, 162
 Medicus, 105
 Meldola, 224
 Merling, 144
 Meyer, R., 207
 Meyer, V., 222
 Michael, 9, 282
 Mitchell, 217
 Möhlau, 272
 Molinari, 285, 289
 Moureau, 315

N

Nietzki, 205

P

v. Pechmann, 252
 Peratoner, 255, 256
 Perkin, A. G., 206, 230
 Perkin, W. H., 8, 12, 23, 30, 52, 54, 66,
 73, 96, 159, 173, 175, 184, 186, 262
 Pictet, 130, 135, 140, 153, 155, 179
 Pinner, 137
 Pope, F. G., 273
 Pschorr, 162, 163, 168, 169

R

Rabe, 190, 195
 Remsen, 131
 Roeder, 27, 73
 Rohde, 194
 Rossin, 171
 Rugheimer, 131, 141
 Ruhemann, 258

S

Sabatier, 3
 Sachs, 307, 308
 Salm, 208
 Salway, 159
 Sand, 307
 Schmidlin, 280, 295
 Schmidt, 45

Scholtz, 131
 Schotten, 135
 Semmler, 15, 50, 61, 62, 68, 78, 80, 87
 Senderens, 3
 Silber, 31
 Silberrad, 208, 231
 Simonsen, 85, 302
 Singer, 307
 Skraup, 136, 191
 Staudinger, 275, 279, 281
 Stephan, 68
 Sudborough, 313

T

Tafel, 123, 184, 185
 Tamburello, 251
 Thiele, 27
 Thorpe, J. F., 93
 Tickle, 225, 254
 Tiemann, 15, 26, 45, 47, 48, 61, 76
 Tiffeneau, 301
 Tilden, 50
 Tinkler, 239
 Traube, 119
 Tschelinzeff, 298
 Tschitschibabin, 292, 293, 304
 Tschugaeff, 3, 81, 96

U

Ullmann, 270, 291, 293

V

Valeur, 304
 Villiger, 229
 Vongerichten, 162
 Vörländer, 5
 Vortmann, 136.

W

Wagner, 4, 51, 84
 Walden, 227
 Wallach, 6, 7, 29, 30, 54, 60, 62, 63,
 69, 74, 83, 95, 96
 Wedekind, 277
 Wegscheider, 157
 Werner, 228, 312
 Wieland, 307
 Willstätter, 13, 33, 144, 146, 149, 150,
 151
 Wilsmore, 279
 Wislicenus, 3, 4, 28
 Witt, 200
 Wöhler, 101
 Wohl, 129, 191
 Wolfenstein, 134
 Würster, 142

Z

Zelinsky, 10, 311
 Zincke, 17

INDEX OF SUBJECTS

A

Absorption spectra, 213
Acetoacetic ester, 214
Acetyl keten, 280
Acetyl-methylmorphol quinone, 164
Acti-compounds, 209
Acridinium salts, 239
Aldo-ketens, 276, 279
Alkaloids, 125
Allantoic acid, 104
Allantoin, 104
Allanturic acid, 104
Alloxan, 101
Alloxanic acid, 102
Alloxantin, 102, 103
Aminothymol, 75
Anhydroberberilic acid, 174
Anhydrobrazilic acid, 263
Anhydroecgonine, 149
Apigenine, 259
Apocaffeine, 107
Apocamphoric acid, 19
Apomorphine, 162
Apophyllenic acid, 158
Aposafuranine, 241
Arecaidine, 128
Atrolactic acid, 142
Atropic acid, 141
Atropine, 141
Auxochromes, 201, 202
Azo-compounds, 232

B

Balbiano's acid, 20, 93
Barbituric acid, 101
Benzhydryltetraphenylmethane, 292
Benzo- γ -pyrones, 257
Berberal, 176
Berberilic acid, 174, 176
Berberinal, 179
Berberine, 152, 173
Borneol, 96
Bornyl chloride, 95
Brazilic acid, 263
Barzilin, 261

Brazilinic acid, 266
Brucine, 189

C

Caffeidine, 106
Caffeine, 106, 113, 114, 115
Caffolin, 107, 108, 120
Caffuric acid, 107
Camphanic acid, 21
Camphene, 86, 95, 97
Camphenilone, 87
Campholene, 19, 26
Campholic acid, 18, 26
Campholenic acid, 26, 96
Campholide, 19
Campholytic acid, 95
Camphononic acid, 22
Camphor, 89
Camphoramidic acid, 92
Camphoric acid, 19, 20, 22, 23, 91
Camphoronic acid, 19, 22, 92
Camphorophorone, 27
Carbon suboxide, 281
Carbonium salts, 211, 232
Caronic acid, 11
Carvacrylamine, 75
Carvenone, 70
Carvestrene, 53
Carvone, 68, 74
Carvotanacetone, 64
Carvothujone, 64
Carvoximes, 60
Chalkone, 258
Characteristics of ψ -acids, 234
Characteristics of ψ -bases, 237
Chelidonic acid, 253
Chlorocaffeine, 115
Chlorotheobromine, 115
Chlorotheophylline, 113
Chroman, 257
Chromone, 258
Chromophores, 201
Chrysin, 259
Cincholeupone, 192
Cincholeuponic acid, 190
Cinchonine, 190

Cinchonic acid, 190
 Cinchoninone, 191, 195
 Cinchotennine, 190
 Cinchotoxine, 193, 194
 Cineol, 67
 Cineolic acid, 67
 Citral, 39, 41, 42
 Citronellal, 45
 Citrylidene-cyanacetic acid, 44
 Cocaine, 141, 148
 Codeine, 152, 162, 165
 Codeinone, 165
 Coeroxonium salts, 230
 Comenic acid, 253, 256
 Coniine, 132
 Conylene, 134
 Conyrrine, 132
 Corydaldine, 181, 182
 Corydaline, 152, 180
 Corydic acid, 181
 Corydalic acid, 181
 Cotarnic acid, 158
 Cotarnine, 158, 159
 Cotarnone, 158
 Coumalic acid, 245
 Coumarins, 251
 Cyclobutanes, 13
 Cyclocitral, 44
 Cycloheptanes, 33
 Cyclohexanes, 28
 Cyclohexanone, 28
 Cyclohexenones, 30
 Cyclopentanes, 17
 Cyclopropanes, 11

D

Dehydracetic acid, 246
 Dehydrocorydaline, 181
 Dehydrostrychnoline, 187
 Desoxystrychnine, 184, 187
 Desoxyxanthine, 123
 Diacetyl, 216
 Dialuric acid, 102
 Dibromocotinine, 138, 139
 Dibromoticonine, 138, 140
 Diethyl keten, 277
 Dihydrobrazilinic acid, 266
 Dihydrocarveol, 76
 Dihydrofencholenamide, 88
 Dihydroxyphenanthrene, 163
 Di-iodopurine, 112
 Dimethoxyphenanthrene, 163
 Dimethyl adipic acid $\alpha\alpha$, 43
 Dimethyl adipic acid $\beta\beta$, 43
 Dimethyl coumalic acid, 246
 Dimethyl keten, 273

Dimethyl lævulinic acid, 26, 79
 Dimethyl morphol, 163
 Dimethyl oxyethylamine, 163
 Dimethyl pyrone, 225, 254
 Dimethyl strychnine, 185
 Dimethyl tricarballic acid, 15
 Dimethyl uric acids, 118
 Dinitrostrychol, 185
 Diosphenol, 32
 Dipentene, 53, 60
 Diphenyl iodonium hydroxide, 223
 Dipyriddyis, 137

E

Ecgonine, 149
 Electro-reduction (Purines), 123
 Epicamphor, 96
 Ethyl pyruvate, 215
 Ethylene ozonide, 287
 Euxanthone, 269
 Extraction of alkaloids, 126

F

Fenchene, 88
 Fisetin, 260
 Flavanone, 258
 Flavone, 261
 Fluoran salts, 228
 Fluorenone, 201
 Fluorescence, 212
 Fluorones, 271
 Fulgenic acids, 219
 Fulvenes, 27, 220

G

Galangin, 259
 Geranial, 39
 Geranic acid, 41
 Geraniol, 44
 Gentisein, 270
 Gentisin, 270
 Geric acid, 42
 Glyoxal, 287
 Grignard reaction, 297
 Guanine, 106, 116, 120

H

Hæmatoxylin, 267
 Hemipinic acid, 156
 Hemiterpenes, 39
 Hexamethylene, 1

322 MODERN RESEARCH IN ORGANIC CHEMISTRY

Hexaphenylethane, 291
 Hofmann's methylation process, 128
 Homocamphoric acid, 24, 91
 Homocamphoronic acid, 21
 Homoterpenylic acid, 61
 Hydrastic acid, 171
 Hydrastine, 152, 170
 Hydrastinic acid, 170, 172
 Hydrastinine, 170, 172
 Hydrocaffuric acid, 107
 Hydrocotarnine, 156
 Hydroecgonidine, 149
 Hydrohydrastinine, 170, 172
 Hydroxyaposafranone, 242
 Hydroxy-caffeine, 106, 113, 114
 Hydroxy-phenylfluorone, 272
 Hydroxyxanthenes, 273
 Hypocaffeine, 107
 Hypoxanthine, 119

I

Iminodipropionacetal, 191
 Indian yellow, 269
 Ionone, 43
 Iodosobenzene, 222
 Irene, 48
 Irone, 48
 Isoadenine, 123
 Isobarbituric acid, 110
 Isoberberal, 177
 Isoborneol, 97
 Isocamphoronic acid, 14
 socoumarins, 252
 Isolehydracetic acid, 246
 Isodialuric acid, 110
 Isogeronic acid, 42
 Isoketocamphoric acid, 14
 Isolaurulene, 24
 Isolauronic acid, 25
 Isonitroso-acetone, 235
 Isonitrosocinchotoxine, 194
 Iso-oximes, 6
 Isophenylacetic acids, 34
 Isopulegol, 56
 Isopulegone, 73
 Isorropesis, 215
 Isothujene, 81
 Isothujone 80

K

Kaempterol, 259
 Ketens, 274, 279
 Ketenium compounds, 277
 Keto-hexahydrobenzoic acid, 52

Ketoisocamphoronic acid, 15
 Keto-ketens, 276

L

Lævulinic aldehyde, 287
 Laudanosine, 152, 154
 Lauth's Violet, 242
 Limonene, 60
 Linalool, 45
 Luteoline, 259

M

Maltol, 256
 Mayer's Solution, 126
 Meconic acid, 253
 Meconine, 156
 Meldola's Blue, 242
 Mentane, 52
 Menthene, 30, 55
 Menthol, 65
 Menthone, 71
 Menthone iso-oxime, 73
 Meroquinene, 190, 192
 Mesityl oxide ozonide, 284
 Mesoxalic dialdehyde, 287
 Metahempinic acid, 153, 171
 Metanicothine, 138
 Methebenine, 168
 Methyl adipic acid, 72
 Methyl cincholeuponic acid, 191
 Methyl cinchotoxine, 193
 Methyl cyclohexanone, 29, 54
 Methyl guanine, 116
 Methyl heptenone, 40
 Methyl hydantoin, 107
 Methyl morphimethine, 163
 Methyl morphol, 164
 Methyl purine, 122
 Methyl strychnine, 185
 Methyl uracil, 110
 Methyl uric acid, 111
 Monocyclic terpenes, 50
 Morin, 259
 Morphine, 152, 162
 Morphenol, 164
 Morphol, 163
 Morphol quinone, 163
 Morpholine, 165
 Murexide, 103

N

Narcotine, 152, 156

Nicotine, 135
 Nitro-amines, 216, 236
 Nitroform, 236
 Nitrolamines, 60
 Nitrophenols, 208, 217
 Nopinene, 95
 Nopinone, 86
 Nornarceine, 196
 Nor-oxyhydrastinine, 175
 Norpinic acid, 14

O

Oleic acid ozonide, 285
 Olefine terpenes, 39
 Opianic acid, 156
 Ortho-terpenes, 51
 Oxamino-oximes, 31
 Oxazines, 241
 Oxonium Salts, 226
 Oxyhydrastinine, 170
 Oxymentholic acid, 72
 Oxyterpenylic acid, 77
 Ozobenzene, 284
 Ozonides, 283

P

Papaverine, 152
 Parabanic acid, 102
 Pararosaniline chloride, 240
 Paraxanthine, 115, 117
 Pentamethylene, 1
 Phellandrene- α , 56, 62
 Phellandrene- β , 62
 Phenolphthalein, 205
 Phenylfluorone, 271
 Phenylmethyl fluorone, 274
 Phenylnitromethane, 233
 Picric acid, 126
 Pimelic acid, 145
 Pinene, 14, 83
 Pinene- β , 86
 Pinene glycol, 84
 Pinic acid, 14
 Pinonic acid, 13
 Pinol, 84
 Pinoyl formic acid, 13
 Piperic acid, 130
 Piperine, 130
 Piperonylic acid, 130
 Polymethylenes, 1
 Polyterpenes, 39
 Pseudo-acids, 233
 Pseudo-bases, 237
 Pseudo-ionone, 43

Pseudo-meconine, 176
 Pseudo-morphine, 162
 Pseudo-opianic acid, 176
 Pseudo-pelletierine, 36
 Pseudo-phenylacetic acid, 34
 Pseudo-terpenes, 51
 Pseudo-uric acid, 104
 Pulegone, 73
 Pulegone dioxime, 74
 Pulegone hydroxylamine, 74
 Purine, 111
 Purone, 123
 Pyranol salts, 230
 Pyridyl methyl ketone, 138
 Pyrimidine syntheses, 120
 Pyromeconic acid, 253
 Pyrones, 245
 Pyruvic aldehyde, 287

Q

Quadrivalent oxygen, 224
 Quercitol, 259
 Quinine, 190
 Quinone, 195
 Quinone oxime, 236
 Quinonoid theory, 203

R

Rhodinal, 45, 46
 Rhodinol, 47

S

Sabinene, 78, 81
 Sabinene ketone, 82
 Sabinol, 82
 Sabinol acetic ester, 62
 Salt formation, 222
 Sarcine, 119
 Sedanolic acid, 31
 Sedanolid, 31
 Sedanonic acid, 31
 Semicyclic hydrocarbons, 7
 Sesquiterpenes, 39
 Sobrerol, 85
 Sonnenschein's reagent, 126
 Spannungs Theorie, 2
 Strychnic acid, 184
 Strychnidine, 185
 Strychnine, 183, 189
 Strychninolic acid, 188
 Strychninolone, 188
 Strychninonic acid, 188

324 MODERN RESEARCH IN ORGANIC CHEMISTRY

Strychnoline, 185, 188
 Suberone, 146, 151
 Succinic acid semialdehyde, 288

T

Tanacetogen dicarboxylic acids, 79
 Terebic acid, 68
 Terpenes, 39
 Terpenylic acid, 61, 85
 Terpin, 66
 Terpin hydrate, 66
 Terpinene, 57, 61
 Terpinenol, 69, 70
 Terpeneol, 44, 53, 61, 68
 Terpinolene, 58
 Tertiary menthol, 30, 66
 Tetramethylene, 1, 13
 Thebaine, 152, 167
 Thebaol, 168
 Thebaol quinone, 169
 Thebenine, 168
 Theobromine, 106, 117, 118, 120
 Theophylline, 113, 115, 117, 120
 Thiazines, 241
 Thuja ketonic acids, 78, 79
 Thujene, 78, 81
 Thujone, 78
 Thujyl alcohol, 78
 Triacetic lactone, 249
 Trichloropurine, 112

Trigonelline, 129
 Trimethyl brazilin, 262, 266
 Trimethylene, 1, 11
 Triphenylmethyl, 290
 Tropic acid, 141
 Tropidine, 143
 Tropilidine, 34, 143, 144, 147
 Tropiline, 142
 Tropine, 143, 146
 Tropinic acid, 144, 145
 Tropinone, 145
 Truxillic acid, 16
 Truxilline, 16

U

Uramil, 102
 Ureides, 101
 Uric acid, 101, 105, 109, 120

X

Xanthene, 268, 271
 Xanthenols, 233
 Xanthine, 106, 112, 115, 116, 120
 Xanthidrol, 228, 268
 Xanthochelidonic ester, 254
 Xanthogenic esters, 3
 Xanthone, 268

Messrs. Methuen's . Complete Educational Catalogue

CONTENTS

	PAGE
CIVICS	3
COMMERCE	3
DIVINITY	4
DOMESTIC SCIENCE	5
ENGLISH	6
FRENCH	10
GENERAL INFORMATION	13
GEOGRAPHY	14
GERMAN	15
GREEK	17
HISTORY	18
LATIN	26
MATHEMATICS	30
SCIENCE	32
TECHNOLOGY	42
<hr/>	
SERIES OF EDUCATIONAL WORKS	43

MESSRS. METHUEN WILL BE GLAD TO SEND THEIR
COMPLETE ILLUSTRATED CATALOGUE OR PAR-
TICULARS OF THEIR BOOKS ON ANY SUBJECT TO
ANY ADDRESS, POST FREE, ON APPLICATION

METHUEN & CO. LTD., 36 ESSEX STREET, W.C.

LONDON

JANUARY 1914

NOTE

MESSRS. METHUEN will be happy to consider applications for Specimen Copies of any of the books in this list from Heads of Schools. Specimen Copies of many of their School Books are supplied gratis, but a charge must be made in all cases for volumes of Examination Papers and the higher priced books. Specimen Copies of Keys are not given. In writing please state the probable number of copies required if the book be adopted.

A copy of any book in this List can be seen at Messrs. Methuen's offices, 36 Essex Street, Strand, W.C., and most of them may be consulted at the Library of The Teachers' Guild, 74 Gower Street, W.C., at the Library of the College of Preceptors, Bloomsbury Square, W.C., and the Teachers' Libraries at the Universities.

MESSRS. METHUEN'S EDUCATIONAL BOOKS

CIVICS

Home and State: An Introduction to the Study of Economics and Civics. By SUSAN CUNNINGTON, Wiston's School, Brighton, Author of "The Story of Arithmetic," etc. Crown 8vo, 2s. 6d.

This book is for the Upper Forms in schools, and gives in simple language an account of the fundamental principles which underlie our modern economic and political conditions. Throughout, the present has been connected with the past, by noting the beginnings of corporate life and effort, and by tracing the development of political institutions.

The desirability of cultivating an intelligent patriotism is acknowledged by all, and there is a growing recognition that this can best be done, as in this book, by training in the young a conception of the value and meaning of civic and social responsibility.

The Rights and Duties of the English Citizen. By H. E. MALDEN, M.A. Eighth Edition. Crown 8vo, 1s. 6d.

A reader describing in outline the Imperial and Local Government of England.

A London Reader for Young Citizens. By F. W. G. FOAT, D.Litt., M.A., Lecturer in History and English at the City of London College, Assistant Master at the City of London School. With 4 Illustrations in Colour, 8 Maps, and 17 other Illustrations. Crown 8vo, 1s. 6d.

In fifty short sections, each forming a complete "lesson," the story of London is told. The treatment is that of the interesting class-lecture, not that of the formal history.

COMMERCE

The Economics of Commerce. By H. de B. GIBBINS, Litt.D., M.A. Second Edition, Revised. Crown 8vo, 1s. 6d. [*Commercial Series.*]

This book presents in a simple, popular, and elementary way the main economic principles which underlie modern commerce.

Commercial Law. By W. DOUGLAS EDWARDS. Second Edition, Revised. Crown 8vo, 2s. [*Commercial Series.*]

A comprehensive outline of the Commercial Law of England adapted for students. As far as possible technical phraseology has been avoided, and the book has not been burdened with legal decisions.

1 Primer of Business. By S. JACKSON, M.A. Fourth Edition, Revised and Enlarged. Crown 8vo, 1s. 6d. [*Commercial Series.*]

A sketch in a readable yet exact form of the salient points in the theory and practice of Modern Commerce. In addition to such fundamental subjects as Exchanges, Banking, and Insurance, it contains some account of Office-work, Book-keeping, Correspondence with Examples, and in particular, the best devices for sorting papers, docketing letters, reckoning dates, etc., are fully explained.

1d Testament History for Use in Schools. By the Rev. W. F. BURNSIDE, M.A., Headmaster of St. Edmund's School, Canterbury. Sixth Edition. Crown 8vo, 3s. 6d.

A Fifth Form textbook written in the belief that it is possible with all reverence to tradition to make the Old Testament a real living force in religious education.

An Entrance Guide to Professions and Business. By H. JONES. With a Preface by H. de B. GIBBINS, D.Litt., M.A. Crown 8vo. 1s. 6d. [*Commercial Series.*]

This book deals with three professions and a large number of trades, and shows the qualities necessary to success in each, the age at which it is best to begin, the conditions of preparation, and the cost of all that is preliminary to the boy's earning his own living.

Précis Writing and Office Correspondence. By E. E. WHITFIELD, M.A. Third Edition. Crown 8vo, 2s. [*Commercial Series.*]

The subjects dealt with here are Business Correspondence in General, Circulars and Advertisements, Sale and Purchase, Carrying Trade, Transmission of Money, Précis, Civil Service Précis, Commercial Précis, Application of Précis to Journalism, Application of Précis to Foreign Languages.

Commercial Examination Papers. By H. de B. GIBBINS, Litt.D., M.A. Crown 8vo, 1s. 6d. [*Commercial Series.*]

A volume of Examination Papers on Commercial Geography, Commercial History, Book-keeping, Business and Office Work, Commercial French, and Commercial German.

For other books on Commerce, see also under "French," "German," "Geography," "History," "Mathematics."

DIVINITY

The First Book of Kings. Edited by A. E. RUBIE, D.D., Headmaster of Eltham College. With 4 Maps. Crown 8vo, 2s. [*Junior School Books.*]

The Gospel according to St. Matthew. Edited by E. W. SOUTH, M.A. With 3 Maps. Crown 8vo, 1s. 6d. [*Junior School Books.*]

The Gospel according to St. Mark. Edited by A. E. RUBIE, D.D. With 3 Maps. Second Edition. Cr. 8vo, 1s. 6d. [*Junior School Books.*]

The Gospel according to St. Luke. Edited by W. WILLIAMSON, B.A. With 3 Maps. Crown 8vo, 2s. [*Junior School Books.*]

The Acts of the Apostles. Edited by A. E. RUBIE, D.D. With 3 Maps. Second Edition. Crown 8vo, 2s. [*Junior School Books.*]

These editions are designed primarily for those preparing for junior examinations such as the Junior Locals, and those of the Joint Board. At the same time they will also prove useful for those preparing for higher examinations, such as the Higher Certificate. The editors have tried to make the introduction and notes as stimulating as possible, and to avoid mere "cram."

The Boys' Prayer Book. Compiled by ALEX. DEVINE, Headmaster of Clayesmore School, Pangbourne. Medium 16mo, 1s. 6d. net.

A collection of prayers, prefaced by appropriate texts for almost all the necessities of school life.

Junior Scripture Examination Papers: Old Testament. By Rev. S. A. P. KERMODE and Rev. W. WILLIAMSON. Fcap. 8vo, 1s. net. [*Junior Examination Series.*]

A Primer of the Bible. By W. H. BENNETT, M.A., Professor of Old Testament Exegesis at New and Hackney Colleges, London. With a concise Bibliography. Fifth Edition. Crown 8vo, 2s. 6d.

This Primer sketches the history of the books which make up the Bible in the light of recent criticism. It gives an account of their character, origin, and composition, as far as possible in chronological order, with special reference to their relations to one another, and to the history of Israel and the Church.

Stories from the Old Testament. By E. M. WILMOT-BUXTON, F.R.Hist.S. Second Edition. Crown 8vo, 1s. 6d. [*Beginner's Books.*]

These stories have been told in the simple and dignified words of the Bible, with brief explanations where necessary, and selected so as to show the continuity of the Divine dealings with the Hebrew people in preparation for the revelation of the New Testament.

An attempt has been made to avoid the chief difficulty met with in teaching the Old Testament to children, by basing these stories on the firm foundation of spiritual rather than literal inspiration. It is hoped that by showing that they are concerned rather with *values* than with supernatural history, they may never have to be unlearned or unduly modified in later years.

Stories from the New Testament. By E. M. WILMOT-BUXTON, F.R.Hist.S. Crown 8vo, 1s. 6d. [*Beginner's Books.*]

Arranged in the form of consecutive stories, with brief explanations and connecting links where necessary, this volume forms a complete life of Christ, together with an account of the Early Church and the life of St. Paul. The stories are told almost entirely in the words of the Bible, and form a companion volume to "Stories from the Old Testament," by the same author.

The Student's Prayer Book. The Text of Morning and Evening Prayer and Litany. By W. H. FLECKER, M.A., D.C.L., Headmaster of the Dean Close School, Cheltenham. With Notes. Crown 8vo, 2s. 6d.

An edition arranged for the Local Examinations. The Notes are at the foot of the page, and so arranged that they are on the same page as the text to which they refer, thus avoiding the necessity of constantly turning over the pages.

An English Church History for Children. By MARY E. SHIPLEY. With a Preface by WILLIAM E. COLLINS, D.D., late Bishop of Gibraltar. Three Volumes, crown 8vo, 2s. 6d. net each.

Vol. I., A.D. 597-1066, with 12 Illustrations and 3 Maps. Second Edition.

Vol. II., A.D. 1066-1500, with 12 Illustrations and 1 Map.

Vol. III., A.D. 1500-1911, with a Map and 12 Illustrations.

"This instructive little book is very well written, and furnished with a good index, and rendered attractive by beautiful illustrations."—*Record.*

DOMESTIC SCIENCE

Millinery, Theoretical and Practical. By CLARE HILL. With numerous Diagrams. Sixth Edition. Crown 8vo, 2s.

[*Textbooks of Technology.*]

A treatise, concise and simple, containing all required for the City and Guilds of London Examination, and providing a suitable course for evening classes.

Instruction in Cookery. By A. P. THOMPSON, Instructress to the London County Council. With 10 Illustrations. Crown 8vo, 2s. 6d.

[*Textbooks of Technology.*]

The most suitable form of syllabus and the best practical examples for demonstration are discussed at some length.

How to make a Dress. By J. A. E. WOOD. With numerous Diagrams. Fifth Edition. Crown 8vo, 1s. 6d.

[*Textbooks of Technology.*]

A short textbook based on the syllabus of the City and Guilds of London Institute Examination.

ENGLISH

Grammar, Dictation, and Composition

A First Course in English. By W. S. BEARD. Crown 8vo, 1s. 6d.
[*Beginner's Books.*]

This book is a working class-book in English for the Lower Forms of Secondary Schools and pupils in Primary Schools. First, it provides, side by side, a progressive course in analysis and elementary composition; the use of words and their relation to each other in sentences. The exercises for practice are very numerous, varied, and carefully graduated; many exercises are adapted for oral composition. Second, it provides a textbook of the leading principles of grammar—accidence and elementary syntax—which will enable young pupils to apply these principles intelligently, step by step, to practical work in analysis and parsing. The book is specially suitable as an introductory course to "A Junior English Grammar," by W. Williamson. Sets of Examination Questions are included which will furnish useful preparation for the Oxford and Cambridge Preliminary and the College of Preceptors Examinations; also for pupils in Primary Schools preparing for County Council Scholarships.

A Junior English Grammar. By W. WILLIAMSON, B.A. With numerous passages for Parsing and Analysis, and a chapter on Essay Writing. Fifth Edition. Crown 8vo, 2s. [*Junior School Books.*]

In this book the author, while following the lines usually adopted, restates many of the Definitions, reducing their number as far as possible. He endeavours to simplify the classification of the parts of speech, and pays considerable attention to the Gerund. To give freshness and a sense of reality to the subject, the examples in illustration of rules are taken from the everyday life of young people.

Junior English. By F. J. RAHTZ, M.A., B.Sc., Senior Lecturer at Merchant Venturers' Technical College, Bristol. Ninth Edition. Crown 8vo, 1s. 6d.

This book is intended for the Lower Forms of Secondary Schools. It deals with Grammar, the Construction of Phrase and Sentence, Analysis, Parsing, Expansion, Condensation, Composition, and Paraphrasing, and many other Exercises in the use of English. The Questions and Exercises are numerous and varied.

Higher English. By F. J. RAHTZ, M.A., B.Sc. Eighth Edition. Crown 8vo, 3s. 6d.

This book provides a much-needed course in the study of modern English, suitable for pupils in the Upper Forms of Secondary Schools. Examination Papers set recently at London University are added.

English Composition. By F. J. RAHTZ, M.A., B.Sc. Crown 8vo, 1s. 6d.

This work is intended for pupils of Secondary Schools and private students. It supplies a progressive course in English composition, embracing not only essays and letters but also other important and useful work in writing English. Numerous and varied exercises are appended to each chapter, while questions and shorter exercises, many of which may be used orally, are introduced in the text. The importance of connecting the student's composition with his reading has been borne in mind throughout.

English Composition from Models. By C. ROONEY, B.A., LL.B. Crown 8vo, 2s. 6d.

This book is an attempt to apply the Direct Method to the teaching of English Composition. The models range from Bacon to Stevenson, and the extracts, which have been carefully selected, are calculated to interest senior

students. Emphasis is laid on the fact that to write we must read, and that to read with profit we must be interested. "All literary skill is based upon imitation." The book deals in an interesting way with certain inherent difficulties, and has useful hints as to how the literary taste of young people may be developed and guided. It is the work of a practical teacher.

A Class-Book of Easy Dictation and Spelling. Selected by W. WILLIAMSON, B.A. Tenth Edition. Fcap. 8vo, 1s.

[*Beginner's Books.*

This book contains many interesting passages from English classics chosen on account of the large number of everyday words which they contain.

A Class-Book of Dictation Passages. Selected by W. WILLIAMSON, B.A. Eighteenth Edition. Crown 8vo, 1s. 6d. [*Junior School Books.*

160 passages chosen from a wide field of modern literature on account of the large number of words they contain.

Junior English Examination Papers. By W. WILLIAMSON, B.A. Second Edition. Fcap. 8vo, 1s. [*Junior Examination Series.*

This book contains Seventy-two Papers of Ten Questions each, and will be found to meet the requirements of all the Examinations in English usually taken in Schools up to the "Senior Locals."

Literature

English Literature for Schools. By E. E. FIRTH, History Mistress at the High School, Croydon, Author of "A First History of Greece." With 4 Maps. Crown 8vo, 2s. 6d. [*Junior School Books.*

This excellent Introduction to English Literature has five special features:—(1) By comparison the style and importance of the various writers are shown. (2) Many illustrations of their works help the reader to a knowledge of the great writers. (3) Difficulties are explained by footnotes. (4) Short summaries of the chief historical events are given with explanations of the political, social, and religious tendencies of the times. Thus the reader realises that all great writers are representative of their generation. (5) Useful Maps have been included, which show the local environment of the great writers.

At the end of each chapter are to be found summaries, sets of questions, and also suggestions for further reading.

A Short Story of English Literature. By EMMA S. MELLOWS. Crown 8vo, 3s. 6d.

The story of the beginning and growth of English literature told in a very simple form for schools and the home. In addition to describing the literature and writers, some space is given to describing the character of the age under consideration.

English Literature. By F. J. RAHTZ, M.A., B.Sc. Crown 8vo, 2s. 6d.

This work is suitable for pupils in the Upper Forms of Secondary Schools, and also for older students. Its aim is to review in a general but critical manner the groundwork of English Literature. Special attention has therefore been paid to the course of the development of our literature; the general characteristics of each period and the external influences bearing upon it are carefully explained. The work and style of the greater authors are discussed in some detail, and brief illustrative extracts from their works are given; lesser authors are treated in due proportion. Questions, many of which are suggestive and require further thought and study, are appended to each chapter.

The book will be found useful for such examinations as the Cambridge Senior Local and London Matriculation, and will form an excellent foundation for more advanced examinations.

Selections from English Literature. Vol. I. (1350-1700). By F. J. RAHTZ, M.A., B.Sc. Crown 8vo, 2s.

It is important for the student to have a first hand acquaintance with the authors themselves beyond what may be obtained from the brief extracts given in the English Literature above described. For this purpose two volumes of Selections, uniform with the "English Literature," have been prepared. The present volume covers the period from 1350 to 1700. Extracts are given from prose, poetry, and the drama. In dealing with verse, complete poems have been given where space would permit; and in the case of the drama, prose, and longer poems, the extracts are such as should be intelligible by themselves or with the aid of brief prefatory notes. As a rule, the space devoted to an author is in proportion to his importance.

Selections from English Literature. Vol. II. (1700-1900). By H. N. ASMAN, M.A., B.D., Second Master of Owen's School, Islington. Crown 8vo, 2s.

This is the second of two volumes of selections that have been prepared for use with "English Literature," by F. J. Rahtz, M.A., B.Sc.

The period covered is 1700 to the present day. The extracts from prose, poetry, and drama have been chosen to illustrate the various aspects of the work of the leading authors, and the general development of the literature of the period. Care has been taken that the selections should all be thoroughly worth studying.

The Story of Milton's "Paradise Lost." Narrated for the most part in the actual words of the Poet. Arranged by GEORGE CARTER, M.A., Headmaster of New College School, Oxford. Crown 8vo, 1s. 6d.

The main feature of this book is that the story of "Paradise Lost" is narrated for the most part in the actual words of the poet, but where this was found to be impracticable, short original passages are introduced to preserve the continuity of the story. Most of the classical and other allusions, which contribute little or nothing to the development of the story, are omitted. Concise footnotes are added to explain difficult or obsolete words.

The book is prefaced with a "Short Sketch of the Life and Works of Milton," and a Synopsis of "Paradise Lost" is also added.

Poetry

An Easy Poetry Book. Selected and Arranged by W. WILLIAMSON, B.A. Third Edition. Crown 8vo, 1s. [*Beginner's Books.*]

A little book for pupils of twelve or thereabouts. It is believed that all the selections are good as poetry, healthy and invigorating in thought, and suited to the capacity of beginners.

Ballads of the Brave: Poems of Chivalry, Enterprise, Courage, and Constancy. From the Earliest Times to the Present Day. By F. LANGBRIDGE, M.A., D.Litt., Canon of St. Munchin's, St. Mary's Cathedral, Limerick. Fifth Edition, Revised and Reclassified, with additional Notes. Crown 8vo, 3s. 6d.

In this new edition Canon Langbridge has replaced all outworn matter by new poems, carrying the story and the interest down to the present hour. In addition to the best chivalric verse of Scott, Byron, Campbell, Keats, Tennyson, Browning, Macaulay, Aytoun, Kingsley, William Morris, Sir F. Hastings Doyle, the edition includes many copyright poems in praise of gallant thought or gallant deeds by the Poet Laureate, Watts-Dunton, George Barlow, Conan Doyle, Owen Seaman, Kipling, Newbolt, Noyes. It is a book for all who love and are proud of England, for all who love chivalry, adventure, and gallant pastime; pre-eminently, it is a book for high-spirited boys. It begins with the "Siege of Troy" and ends with a "Song of Federation," a call to the Boy Scouts, and England's claim to wield for ever "The Sceptre of the Sea." Careful notes, historical, critical, philological, are given separately from the text.

Readers

The Rose Reader. By EDWARD ROSE. With numerous Illustrations, some of which are Coloured. In Four Parts. Parts I. and II., 6d. each; Part III., 8d.; Part IV., 10d. Introduction for the Teacher separately, 6d.

A reader on a new and original plan. The distinctive feature of this book is the entire avoidance of irregularly-spelt words until the pupil has mastered reading.

Tommy Smith's Animals. By EDMUND SELOUS. With 8 Illustrations by G. W. ORD. Twelfth Edition. Fcap. 8vo, 1s. 6d.

This new and charming continuous reader, besides inculcating kindness to animals, conveys much natural history information. The animals dealt with are—frog, toad, rook, rat, hare, grass-snake, adder, peewit, mole, woodpigeon, squirrel, barn-owl.

An edition in a superior binding, suitable for prizes, is also issued at 2s. 6d.

Tommy Smith's Other Animals. By EDMUND SELOUS. With 12 Illustrations by AUGUSTA GUEST. Sixth Edition. Fcap. 8vo, 1s. 6d.

Uniform with the above. The animals dealt with are—rabbit, nightjar, weasel, blackbird, thrush, hedgehog, dabchick, moorhen, woodpecker, fox, cuckoo, watervole.

An edition in a superior binding, suitable for prizes, is also issued at 2s. 6d.

Health Readings for Elementary Schools. By C. J. THOMAS, M.B., B.Sc., D.P.H., University Scholar in Medicine, Member of the Examining Board of the Royal Sanitary Institute. Second Edition. Crown 8vo, 1s. 6d.

This volume has been written in accordance with the recommendations of the Board of Education. It treats the subject in a simple way as a part of Nature Study, and deals with questions of health from the point of view of the natural interests of the child in his surroundings.

A Health and Temperance Reader. By H. MAJOR, B.A., B.Sc., Inspector to the Leicester Education Committee. Crown 8vo, 1s.

In diction and style suitable for children in Standards V., VI., and VII. in Elementary Schools.

The Baring-Gould Selection Reader. By S. BARING-GOULD, M.A. Arranged by G. H. ROSE. With 15 Illustrations and a Map. Crown 8vo, 1s. 6d.

The Baring-Gould Continuous Reader. By S. BARING-GOULD, M.A. Arranged by G. H. ROSE. With 5 Illustrations and a Map. Crown 8vo, 1s. 6d.

Two readers for Upper Standards, from the novels and topographical works of Mr. Baring-Gould.

A London Reader for Young Citizens. [See under "Civics."]

For further Readers see Messrs. Methuen's Stories, in the following Series, "Stories from the Histories," "Stories from Old Romance," "Stories from the Great Writers." They cover a wide ground, avoid hackneyed material, and aim at a high standard of style and treatment, so that they may be used by Secondary Schools and the Upper Standards of Elementary Schools. The Volumes are 1s. 6d. each (with one exception) and include the following:—

Stories from Ancient History. By E. BOWYER.

Stories from Modern History. By E. M. WILMOT-BUXTON.

Stories from Roman History. By E. M. WILMOT-BUXTON.

- Easy Stories from English History.** By E. M. WILMOT-BUXTON, IS.
Stories from French History. By TAYLOR DYSON.
Tales from Irish History. By ALICE BIRKHEAD.
Stories from Scottish History. By E. M. WILMOT-BUXTON.
Stories from American History. By ALICE BIRKHEAD.
Stories from Old French Romance. By E. M. WILMOT-BUXTON.
Stories from Old Italian Romance. By SUSAN CUNNINGTON.
Stories from Old English Romance. By JOYCE POLLARD.
Stories from Dickens. By JOYCE COBB.
Stories from Bunyan. By EDITH L. ELIAS.
Stories from Chaucer. By ADA HALES.
Stories from the Old Testament. By E. M. WILMOT-BUXTON.
Stories from the New Testament. By E. M. WILMOT-BUXTON.

FRENCH

Grammars, etc.

Intuitive French. A Year's Course for Beginners. By M. VERDON, Modern Language Master at Rotherham Grammar School. Cr. 8vo, 2s.

This book is intended for children between the ages of twelve and fourteen in Secondary Schools. It aims at teaching elementary French according to the "New" or "Direct" Method, and follows the lines of moderate Reformers. It is divided into thirty-six lessons, providing ample material for a whole year's work. Each lesson, with the exception of a few made of songs and rhymes, consists of a reading piece, which is the résumé of several conversation lessons, drill exercises for oral practice, questions and written exercises. The latter form an Introduction to free composition in French. The grammar evolved from each piece is systematically given in another part of the book. Its vocabulary of about eleven hundred words is simple, practical and useful.

A Junior French Grammar. By L. A. SORNET and M. J. ACATOS, Modern Language Masters at King Edward's School, Birmingham. Fourth Edition. Crown 8vo, 2s. [*Junior School Books.*]

This book comprises a complete course of French Grammar, with Exercises and Examination Papers suitable for candidates preparing for the Oxford and Cambridge Local and College of Preceptors' Examinations. It also includes numerous Vocabularies and materials for Conversation Lessons.

Nouvelle Grammaire Française, à l'usage des écoles Anglaises. By J. G. ANDERSON, B.A., Examiner to London University. Cr. 8vo, 2s.

A textbook for Middle and Higher Forms, written in French, with the exception of a long introduction on Phonetics. Emphasis is laid on points where English and French differ. The conjugation of the verb is simplified, and there are many other special features.

Exercices de Grammaire Française. By J. G. ANDERSON, B.A. Crown 8vo, 1s. 6d.

This book of exercises is primarily intended as a companion volume to the "Nouvelle Grammaire Française," but there is no reason why it should not be used in conjunction with any grammar. These books cover all the ground for the London Matriculation.

- A Junior French Prose.** By R. R. N. BARON, M.A., Modern Language Master at Cheltenham Grammar School. Sixth Edition. Crown 8vo, 2s. [*Junior School Books.*]

This book has been written for pupils beginning continuous French Prose. It contains : (1) Examples and Rules in Syntax. These are not professedly exhaustive, but deal rather with points in which the two languages are seen to differ; and, as they deal with such points occurring in over a hundred passages and exercises, it is hoped they may be found sufficiently complete for the general purposes at which the book aims. (2) Exercises in *every-day language*, illustrative of the rules. (3) Graduated continuous passages.

- French Prose Composition.** By R. R. N. BARON, M.A. Fifth Edition. Crown 8vo, 2s. 6d. **Key** (Second Edition). 3s. net.

A collection of passages from standard English authors for composition in Upper Forms and by Army Candidates; Notes and Vocabulary are provided.

- French and English Parallels.** By F. R. M. FURSDON. Fcap. 8vo, 3s. 6d. net.

The first part of this volume consists of a selection of French and English idiomatical phrases and idioms, and the second of over a thousand examples of French and English metaphors. The third section is an interwoven sequence of ideas, expressed by means of some of the most beautiful maxims and proverbs of both languages.

- Junior French Examination Papers,** in Miscellaneous Grammar and Idioms. By F. JACOB, M.A., Assistant Master at Felsted School. Third Edition. Fcap. 8vo, 1s. [*Junior Examination Series.*]

A collection of 72 papers of ten questions each suitable for class teaching and revision work for the Local and similar Examinations.

- A Manual of French Commercial Correspondence.** By S. E. BALLY. With Vocabulary. Fourth Edition. Crown 8vo, 2s. [*Commercial Series.*]

This book provides the student with materials for French correspondence. Almost every paragraph has been taken from actual letters.

By A. M. M. Stedman, M.A.

- Steps to French.** Eleventh Edition. 18mo, 8d.

One of the easiest French books in existence. Contains both grammar and exercises.

- First French Lessons.** Eleventh Edition. Crown 8vo, 1s.

A short course for beginners written to make a boy's knowledge of Latin help his French.

- Easy French Passages for Unseen Translation.** Seventh Edition. Fcap. 8vo, 1s. 6d.

Many of the passages have been actually set at the Local, Public School, and Naval and Military Examinations. Some of the most charming French lyrics are included.

- Easy French Exercises on Elementary Syntax.** With Vocabulary. Fourth Edition, Revised. Crown 8vo, 2s. 6d. **Key**, 3s. net.

These exercises are for pupils who have mastered their accidence and require a more advanced book to accompany their syntax.

French Vocabularies for Repetition: Arranged according to Subjects. Fifteenth Edition. Fcap. 8vo, 1s.

A collection of upwards of 2000 words arranged in sets of 12 each, according to the subject.

French Examination Papers in Miscellaneous Grammar and Idioms. Sixteenth Edition. Crown 8vo, 2s. 6d. **Key** (Sixth Edition), issued to Tutors and Private Students only, 6s. net.

These Papers have been compiled for those who have passed beyond the Elementary Stages of Grammar. They cover the whole of the ground usually taught.

Texts

Easy French Rhymes. By HENRI BLOUET. Illustrated. Second Edition. Fcap. 8vo, 1s. [*Beginner's Books.*]

This little book, containing the time-honoured English nursery rhymes translated into French rhyme, will supply children with a fairly extensive and easily acquired vocabulary of French words. The English and French versions are given on opposite pages.

Simplified French Texts

Edited by T. R. N. CROFTS, M.A.,
Headmaster of Roan School, Greenwich.

This Series, consisting of 16 volumes, provides pupils who have been studying French about two or three years with simple translation books which they can understand, and at the same time complete stories, instead of a succession of little anecdotes. It thus makes possible the more rapid reading of a greater variety of authors. Vocabularies have been added, in which the chief idioms are explained. Each volume is Fcap. 8vo, 1s.

L'Équipage de la Belle-Nivernaise. By ALPHONSE DAUDET. Adapted from "La Belle-Nivernaise," by T. R. N. CROFTS, M.A. Third Edition.

L'Histoire de Pierre et Camille. By ALFRED DE MUSSET. Adapted from "Pierre et Camille," by J. B. PATTERSON, M.A., Modern Language Master at Merchant Taylors' School, London.

Mémoires de Cadichon. By MADAME DE SÉGUR. Adapted from "Mémoires d'un Âne," by J. F. RHOADES, Modern Language Master at Fettes College, Edinburgh. Second Edition.

L'Histoire d'une Tulipe. By ALEXANDRE DUMAS. Adapted from "La Tulipe Noire," by T. R. N. CROFTS, M.A. Third Edition.

La Bouillie au Miel. By ALEXANDRE DUMAS. Adapted from "La Bouillie de la Comtesse Berthe," by P. B. INGHAM, B.A., Modern Language Master at Merchant Taylors' School, London.

Edmond Dantès. By ALEXANDRE DUMAS. Adapted from "Monte Cristo," by M. CEPPI, Head Modern Language Master at King's College School, Wimbledon.

D'Ajaccio à Sainte-Hélène. By ALEXANDRE DUMAS. Adapted from "Napoléon," by F. W. M. DRAPER, B.A., Modern Language Master, City of London School.

M. de Beaufort à Vincennes. By ALEXANDRE DUMAS. Adapted from "Vingt Ans Après" by P. B. INGHAM, B.A.

- Le Docteur Mathéus.** By ERCKMANN-CHATRIAN. Adapted from "L'illustre Docteur Mathéus," by W. P. FULLER, M.A., Headmaster of the Holborn Estate Grammar School, London.
- Le Conscrit de 1813.** By ERCKMANN-CHATRIAN. Adapted from "L'Histoire d'un Conscrit," by H. RIEU, M.A., Modern Language Master at Merchant Taylors' School, London.
- La Bataille de Waterloo.** By ERCKMANN-CHATRIAN. A Sequel to the above. Adapted from "Waterloo," by G. H. EVANS, M.A., Modern Language Master at Oundle School.
- Jean Valjean.** By VICTOR HUGO. Adapted from "Les Misérables," by F. W. M. DRAPER, B.A., Modern Language Master at City of London School. Second Edition.
- Abdallah.** By EDOUARD LABOULAYE. Adapted from "Abdallah, ou le trèfle à quatre feuilles," by J. A. WILSON.
- Deux Contes.** By P. MÉRIMÉE. Adapted from "Mateo Falcone" and "Tamango," by J. F. RHOADES.
- La Chanson de Roland.** Adapted by H. RIEU, M.A. Second Edition.
- Remy, Le Chevrier.** By EMILE SOUVESTRE. Adapted from "Le Chevrier de Lorraine," by E. E. CHOTTIN, B.-es-L., Modern Language Master at St. Laurence College, Ramsgate.

Advanced French Texts

Edited by T. R. N. CROFTS, M.A.,
Headmaster of Roan School, Greenwich.

This series aims at supplying translation books for fairly rapid class-reading among pupils who have already been through some of the volumes in the Simplified Texts, or who have acquired a good working knowledge of elementary French. The first volumes are:—

Bernard de Mergy. By P. MÉRIMÉE. Adapted by P. B. INGHAM, B.A., Assistant Master at Merchant Taylors' School. Crown 8vo, 2s.

This is a condensation of Prosper Mérimée's one historical novel, "Chronique du Règne de Charles IX," considered the best of its type in the French language. Passages have been omitted, but no changes have been made in the text.

Ursus et sa Troupe. Adapted from "L'Homme qui Rit," of Victor Hugo, by EM. B. LE FRANÇOIS, French Tutor at Redcliff House, Clifton, and Wolsey Hall, Oxford. Crown 8vo, 2s.

A complete and exciting story, divided into twenty chapters. Each chapter becomes a theme for conversation, by means of questions based upon it. There is a vocabulary of difficult words and idiomatic expressions.

GENERAL INFORMATION

General Knowledge Examination Papers. By A. M. M. STEDMAN, M.A. Seventh Edition. Crown 8vo, 2s. 6d. **Key** (Fifth Edition), issued to Tutors and Private Students only, 7s. net.

[*School Examination Series.*

Compiled to furnish practice for those who are preparing for Scholarships at the Public Schools and at the Universities. This edition has been carefully revised and brought up to date by Mr. C. G. BOTTING, B.A., and a number of new questions have been added.

Junior General Information Papers. By W. S. BEARD. Second Edition. Fcap. 8vo, 1s. **Key**, 3s. 6d. net. [*Junior Examination Series.*

An easier book on the same lines as Stedman's "General Knowledge Examination Papers." It will be found suitable for the Junior Examinations and Candidates for County Scholarships.

GEOGRAPHY

A Systematic Geography of the World

By G. W. WEBB, B.A.,
Master at Owen's School, Islington.

This series provides for a study of the Geography of the World on logical lines as recommended by the Board of Education. It is intended for those who have passed beyond the elementary stages of the subject and wish to acquire a more detailed and advanced knowledge. Emphasis is placed on the distinctive character of the natural regions by a consideration of geological structure and its bearing on physical features, and again constant reference is made to the causal connection between the facts of physical and political geography. The books will be found suitable for use in the Middle and Upper Forms of Secondary Schools and for all who wish to prepare for the Oxford and Cambridge Local, the London Matriculation, and similar examinations.

A Systematic Geography of the British Isles. With 13 Diagrams and Maps. Second Edition. Crown 8vo, 1s.

A Systematic Geography of Europe. With 5 Diagrams and Maps. Crown 8vo, 1s.

A Systematic Geography of Asia. With 8 Diagrams and Maps. Crown 8vo, 1s.

A Systematic Geography of America. With 10 Maps and Diagrams. Crown 8vo, 1s.

A Systematic Geography of Africa, Australia, and Polynesia. With Maps and Diagrams. Crown 8vo, 1s.

By Road and River. A Descriptive Geography of the British Isles. By E. M. WILMOT-BUXTON, F.R.Hist.S. With 12 Illustrations and 12 Maps. Crown 8vo, 2s.

Suitable for children in the Lower Forms of all grades of schools. It aims at making them familiar with the scenery and most striking features, political, historical, and literary, of their land by the natural and interesting process of making imaginary journeys through the different districts of these islands. Physical geography has been closely connected with political aspects, and throughout an appeal has been made to the common sense as well as to the imagination of the child. Interesting questions are set at the end of each chapter, and the text is fully illustrated by photographs and outline maps.

The Dominion of Man. Geography in its Human Aspect. By E. PROTHEROE. With 36 Illustrations. Third Edition, Revised. Crown 8vo, 2s.

A bright and readable geographical textbook for teachers and upper classes, dealing mainly with the way in which life is affected by its surroundings and conditions. Many interesting particulars are given of manufactures and industries. It contains thirty-six full-page Illustrations beautifully printed in double tone ink.

- A Commercial Geography of the British Empire.** By L. W. LYDE, M.A., Professor of Economic Geography at University College, London. Tenth Edition. Crown 8vo, 2s. [*Commercial Series.*]

The first section gives the general principles of the science and their application to the larger areas of the British Empire. The second section takes each of the Colonies and considers its surroundings, fisheries, harbours, surface, agriculture, and minerals separately.

- A Commercial Geography of Foreign Nations.** By F. C. BOON, B.A., Assistant Master at Dulwich College. Crown 8vo, 2s. [*Commercial Series.*]

A companion volume to Prof. L. W. Lyde's "Commercial Geography of the British Empire."

- A Historical Geography of the British Empire.** By HEREFORD B. GEORGE, M.A., Fellow of New College, Oxford. Fifth Edition. With Map. Crown 8vo, 3s. 6d.

The purpose of this work is twofold—to describe in outline the British Empire, with its component parts so grouped as to show forth the diversity of their relations to the mother country—and to point out the nature of the relations between the geography and the history of the British Islands, from the beginning, and from the time of their becoming British in the case of the other possessions.

- Historical and Modern Atlas of the British Empire.** Specially prepared for Students. By C. GRANT ROBERTSON, M.A.(OXON.), and J. G. BARTHOLOMEW, F.R.S.E., F.R.G.S. Demy Quarto, 4s. 6d. net.

The Atlas contains 64 Maps, with numerous insets, Historical Tables and Notes, an Introduction, a Historical Gazetteer, a Bibliography, and an Index. The combination of modern maps on physical geography, trade, industry, etc., with the special and extensive historical maps of the Empire as a whole and of each part of it (e.g. India, Canada, etc.), give the Atlas a character and completeness not hitherto offered by any other Atlas.

- Junior Geography Examination Papers.** By W. G. BAKER, M.A. Fcap. 8vo, 1s. [*Junior Examination Series.*]

72 Papers each containing 10 questions, covering all branches of the subject required by pupils of 12 to 16 years. By an ingenious arrangement the papers can be used either as general papers or to test some particular part of the subject.

- History and Geography Examination Papers.** By C. H. SPENCE, M.A., Assistant Master at Clifton College. Third Edition, Revised. Crown 8vo, 2s. 6d. [*School Examination Series.*]

The present edition was practically rewritten and a large number of new questions added.

GERMAN

Grammars, etc.

- A Junior German Grammar.** By H. C. A. SECKLER, Senior German Master, Owen's School, E.C. Crown 8vo, 2s. 6d. [*Junior School Books.*]

This book is for the Middle Forms of schools, and meets the requirements of the Oxford and Cambridge Junior Local and the College of Preceptors' Examinations. It consists of grammar and exercises, and a particular feature is the co-ordination of accidence and syntax. It aims throughout at training pupils to use their knowledge for composition. The latter part of the book gives various examination papers, with some useful model solutions.

German Passages for Unseen Translation. By E. M'QUEEN GRAY. Crown 8vo, 2s. 6d.

A selection of passages from standard authors for the use of Middle and Upper Forms. No notes or vocabularies are included.

German Vocabularies for Repetition. By SOPHIE WRIGHT. Fcap. 8vo, 1s. 6d.

A collection of useful German words arranged under subjects.

A German Commercial Reader. By S. E. BALLY. With Vocabulary. Crown 8vo, 2s. [Commercial Series.]

The object of this manual is not only to offer the student material for translation, but to bring to his notice some practical hints on commerce, industry, and commercial history and geography. Roman type and the new spelling have been adopted in this book.

A Manual of German Commercial Correspondence. By S. E. BALLY. With Vocabulary. Second Edition, Revised. Crown 8vo, 2s. 6d. [Commercial Series.]

The specimen letters which illustrate the chapters are preceded by analyses and followed by numerous exercises, each containing in a few German words the gist of the letter to be composed. Roman type and the new spelling have been adopted in this book.

German Examination Papers in Miscellaneous Grammar and Idioms. By R. J. MORICH, late of Clifton College. Eighth Edition. Cr. 8vo, 2s. 6d. Key, Third Ed., 6s. net. [School Examination Series.]

A series of Advanced Papers compiled—(1) to avoid the tediousness and length of constant grammar repetition, and (2) to make the student acquainted with some, at least, of the endless number of German idiomatic phrases.

Junior German Examination Papers in Miscellaneous Grammar and Idioms. By A. VOEGELIN, M.A., Modern Language Master at St. Paul's School. Fcap. 8vo, 1s. [Junior Examination Series.]

An easier book, on the same lines as German Examination Papers.

Texts

Simplified German Texts

Edited by T. R. N. CROFTS, M.A.,
Headmaster of Roan School, Greenwich.

The aim of this Series is to provide pupils who have been studying German about two or three years with simple translation books which they can understand, and which at the same time provide complete stories, instead of a succession of little anecdotes. Vocabularies have been added, in which the chief idioms are explained. Each volume is fcap. 8vo, 1s.

Der Müller am Rhein. By C. BRENTANO. Adapted from "Das Märchen von dem Rhein und dem Müller Radlauf," by Miss A. F. RYAN, Modern Language Mistress at the High School, Derby.

Die Geschichte von Peter Schlemihl. By A. VON CHAMISSE. Adapted from "Peter Schlemihl's Wundersame Geschichte," by R. C. PERRY, M.A., Modern Language Master at Merchant Taylors' School, London.

Undine und Huldbrand. By DE LA MOTTE FOUQUÉ. Adapted from "Undine," by T. R. N. CROFTS, M.A.

Die Nothelfer. By W. H. RIEHL. Adapted from "Die Vierzehn Nothelfer," by P. B. INGHAM, B.A., Modern Language Master at Merchant Taylors' School, London.

Simplified German Unseens. By T. R. N. CROFTS, M.A.

GREEK

Grammars, Exercises, etc.

Easy Greek Exercises. By C. G. BOTTING, M.A., Assistant Master at St. Paul's School. Second Edition. Crown 8vo, 2s.

These exercises have been compiled to accompany Stedman's "Shorter Greek Primer," from which the rules have, by permission, been for the most part taken.

Passages for Unseen Translation. By A. M. COOK, M.A., Assistant Master at St. Paul's School, and E. C. MARCHANT, M.A., Tutor of Lincoln College, Oxford. Selected from Latin and Greek Literature. Sixth Edition. Crown 8vo, 3s. 6d.

Two hundred Latin and two hundred Greek passages, arranged in order of increasing difficulty. The book has been carefully compiled to meet the wants of V. and VI. Form boys at the Public Schools, and is also well adapted for the use of honourmen at the Universities. Prose and verse alternate throughout.

Notes on Greek and Latin Syntax. By G. BUCKLAND GREEN, M.A., Assistant Master at Edinburgh Academy. Third Edition, Revised. Crown 8vo, 3s. 6d.

The book discusses and explains the chief difficulties of Greek and Latin Syntax, so as to afford a preparation for the higher classical examinations. The treatment throughout is comparative. There are chapters on the cases, tenses, moods, and their uses, on Homeric peculiarities, the article, etc.; and, besides the examples quoted in illustration of the text, numerous passages are added, by working through which the student may obtain practice in dealing with points of syntax.

By A. M. M. Stedman, M.A.

Steps to Greek. Fifth Edition. 18mo, 1s.

Easy Lessons on Elementary Accidence, with exercises and vocabularies.

A Shorter Greek Primer. Revised by C. G. BOTTING, M.A. Fifth Edition. Crown 8vo, 1s. 6d.

This book contains the elements of Greek Accidence and Syntax.

Easy Greek Passages for Unseen Translation. Revised by C. G. BOTTING, M.A. Fifth Edition. Fcap. 8vo, 1s. 6d.

The pieces are graduated in length and difficulty, and the early pieces present no serious obstacles.

Greek Vocabularies for Repetition. Revised by C. G. BOTTING, M.A. Fifth Edition. Fcap. 8vo, 1s. 6d.

A collection of over 2000 useful words arranged in sets of twelve each according to subjects.

Greek Examination Papers in Miscellaneous Grammar and Idioms. Eleventh Edition. Crown 8vo, 2s. 6d. **Key** (Fourth Edition), issued to Tutors and Private Students only, 6s. net.

[*School Examination Series.*]

A collection of Advanced Papers.

Junior Greek Examination Papers. By T. C. WEATHERHEAD, M.A., Headmaster of King's College Choir School, Cambridge. Fcap. 8vo, 1s.

[*Junior Examination Series.*]

A volume of 72 Junior Papers.

Examination Papers on Thucydides. By T. NICKLIN, M.A., Assistant Master at Rossall School. Crown 8vo, 2s.

In this volume the eight books have been divided into short sections, and a paper has been set on each section, as well as recapitulatory papers on each book.

Texts

Aristotle.—THE ETHICS OF ARISTOTLE. Edited, with an Introduction and Notes, by JOHN BURNET, M.A., Professor of Greek at St. Andrews. Cheaper issue. Demy 8vo, 10s. 6d. net.

An elaborate edition, based on the assumption that the Nicomachean Ethics is the authentic work of Aristotle, and that it has hardly suffered from interpolation or dislocation. It is also assumed that the Eudemian Ethics is our most authoritative commentary, and the parallel passages from it are printed under the text to which they refer. The commentary shows that most of the difficulties which have been raised disappear when the work is interpreted in the light of Aristotle's own rules of Dialectic.

Demosthenes.—AGAINST CONON AND CALLICLES. Edited by F. DARWIN SWIFT, M.A. Second Edition, Revised. Fcap. 8vo, 2s.

The new text edited for Middle and Upper Forms, with vocabulary and notes.

Greek Testament Selections. With Introduction, Notes, and Vocabulary, by A. M. M. STEDMAN, M.A. Fourth Edition. Fcap. 8vo, 2s. 6d.

This small volume contains a selection of passages, each sufficient for a lesson, from the Gospels, forming a life of Christ. In schools where only a limited time can be given to the study of the Greek Testament an opportunity is thus supplied for reading some of the most characteristic and interesting passages.

Translations

Æschylus.—AGAMEMNON, CHOEPHOROE, EUMENIDES. Translated by LEWIS CAMPBELL, LL.D. Crown 8vo, 5s.

[*Classical Translations.*]

Lucian.—SIX DIALOGUES (Nigrinus, Icaro-Menippus, The Dream, The Ship, The Parasite, The Lover of Falsehood). Translated by S. T. IRWIN, M.A., Assistant Master at Clifton. Crown 8vo, 3s. 6d.

[*Classical Translations.*]

Sophocles.—AJAX AND ELECTRA. Translated by E. D. A. MORSEHEAD, M.A. Crown 8vo, 2s. 6d.

[*Classical Translations.*]

HISTORY

Classical

Stories from Ancient History. By E. BOWYER, B.A., B.Sc., Assistant Master, Owen's School, Islington. With 2 Maps. Crown 8vo, 1s. 6d.

[*New Historical Series.*]

This volume—the first of a new historical series on the lines of the recent circular of the Board of Education on the teaching of History—is intended as an introduction to the story of ancient history for pupils up to the age of twelve.

In accordance with the suggestions made in the above-mentioned circular, it deals with the "chief events and characters from the history of the most important nations in their traditional form." It aims also at "giving some idea of the nature of the great nations and stages in civilisation, centred round certain individuals or events in the chronological succession" in such a way that young children shall be able at least to "place" the most notable characters of ancient history

The Ancient World. Outlines of Ancient History for the Middle Forms of Schools. By E. M. WILMOT-BUXTON, F.R.Hist.S. With 12 Maps and 20 Illustrations. Crown 8vo, 3s. 6d.

This book tells the stories of the great civilizations of the Ancient World, as made known by recent excavation and discovery, from the dawn of Egyptian history to the days of the Roman Empire.

The Greek View of Life. By G. LOWES DICKINSON, M.A., Fellow of King's College, Cambridge. Eighth and Revised Edition. Crown 8vo, 2s. 6d. net.

A revised edition, reset in new type, of this admirable book, which is a general introduction to Greek literature and thought. Among the subjects dealt with are the Greek View of Religion, the State and its relation to the Citizen, Law, Artisans and Slaves, Sparta, Athens, Manual Labour and Trade, Athletics, Pleasure, Greek View of Women, Friendship, Art, Sculpture, Painting, Music, etc.

A First History of Greece. By EDITH E. FIRTH, History Mistress of Croydon High School. With 7 Maps. Second Edition. Crown 8vo, 1s. 6d. [*Beginner's Books.*]

This book has been written in the hope of supplying a History of Greece suitable for young children. It is written in biographical form, and those lives have been selected which best explain the rise and decline of the Greeks.

A Junior Greek History. By W. HORTON SPRAGGE, M.A., Assistant Master at City of London School. With 4 Maps and 4 Plates. Crown 8vo, 2s. 6d. [*Junior School Books.*]

It describes the main features in the history of Greece down to the time of its absorption in the Roman Empire, suitably presented for junior pupils in schools. The greater part of it is taken from ancient authorities, Greek and Latin, but the views of modern writers have also been consulted.

A Short History of Greece to the Death of Alexander the Great. By W. S. HETT, B.A., Assistant Master at Brighton College. With many Maps. Crown 8vo, 3s. 6d.

This book is intended primarily for the use of students reading for the Oxford and Cambridge Higher Certificate, and secondarily as an introduction to a wider study of the subject. An attempt has been made to render some of the recently acquired archæological evidence accessible to those who have no expert knowledge. The recent papers set for the Higher Certificate have demanded far more than a mere collection of facts, and accordingly the present work has been written with a view to giving a general survey of the Greek race and of the broad principles underlying its history.

Stories from Roman History. By E. M. WILMOT-BUXTON, F.R.Hist.S. Third Edition. Crown 8vo, 1s. 6d. [*Beginner's Books.*]

The object of this book is to provide an introduction to the study of Roman history by a series of stories in chronological order dealing with the main events and characters of the history of Rome.

An Introduction to the History of Rome. By H. N. ASMAN, M.A., B.D., Second Master of Owen's School, Islington. With 2 Maps and 14 Illustrations. Crown 8vo, 2s. 6d.

This book gives to pupils learning Latin some knowledge of the history of the great people whose language they are studying. It has been insisted by educational authorities that some knowledge of the history of Rome is essential not only for a proper appreciation of Roman literature, but that it is also a necessary part of a complete education. This book occupies a place between the primer and the larger works on the subject. It gives a brier survey of the history of Rome to the death of Augustus. It will also be found useful for the general reader who desires some knowledge of the subject.

- A Short History of Rome to the Death of Augustus.** By J. WELLS, M.A., Fellow and Tutor of Wadham College, Oxford. With 3 Maps and 4 Plates. Thirteenth Edition. Crown 8vo, 3s. 6d.

"The schoolmasters who have felt the want of a fifth-form handbook of Roman history may congratulate themselves on persuading Mr. Wells to respond to it. His book is excellently planned and executed. Broken up into short paragraphs, with headings to arrest the attention, his manual does equal justice to the personal and the constitutional aspects of the story."—*Journal of Education.*

- A Constitutional and Political History of Rome.** From the Earliest Times to the Reign of Domitian. By T. M. TAYLOR, M.A., Fellow of Gonville and Caius College, Cambridge. Third Edition. Crown 8vo, 7s. 6d.

It contains an account of the origin and growth of the Roman institutions, and a discussion of the various political movements in Rome from the earliest times to the reign of Domitian.

Modern Great Britain

- Easy Stories from English History.** By E. M. WILMOT-BUXTON, F.R.Hist.S. Seventh Edition. Crown 8vo, 1s. [*Beginner's Books.*]

A historical reader arranged on the century method; that is, it aims at enabling the learner, before any detailed study is attempted, to run his eye over the centuries, and point out the main feature of each succeeding epoch. A special point in the method here adopted is the personal representation rather than the abstract idea. Each event has been grouped round the life or character of some "maker" of his country. The book contains thirty-five stories, well and simply told.

- A Junior History of Great Britain.** By E. M. WILMOT-BUXTON, F.R.Hist.S. Second Edition. Crown 8vo, 2s.

This book gives a systematic and interesting account of the history of Great Britain to pupils of ages ten to fourteen, who have hitherto studied the subject in the form of "Stories." To prevent it from being a mere outline, and in accordance with the Board of Education's Circular, many unimportant facts have been omitted, and the aim has been to give (1) a clear apprehension of the chief events in chronological sequence; (2) a fairly detailed study of those aspects which should specially appeal to young pupils. Not only have the more dramatic episodes of history been purposely selected for treatment, but these have been illustrated, wherever possible, by dramatic literature and by tableaux. The connection of history with literature has been maintained throughout.

- A History of Great Britain.** From the Coming of the Angles to the Year 1870. By E. M. WILMOT-BUXTON, F.R.Hist.S. With 20 Maps. Fourth Edition. Crown 8vo, 3s. 6d.

This book attempts to break through the conventional lines on which History Class-books are laid down. With very few exceptions these books make the reign the chapter-limit, and take each event in chronological order. In this book the old system has been entirely discarded, and each chapter will be found to deal with one great movement, which is traced in cause, events, and result. Another feature is the close connection which has been maintained throughout with European History. Since it is clearly impossible to grasp a great part of our internal history or any of our external relations without understanding the contemporary position of affairs on the Continent, almost every chapter will be found to commence with a brief explanation of the latter, pointing out the particular crisis with which England was especially concerned.

Methuen's Historical Readers

Illustrated. Crown 8vo.

This series has been published in response to a demand for a well-written and thoroughly up-to-date set of History Readers. The primary aim of these books is "to furnish the scholars with a connected knowledge in outline of the main course of English history, and of a few leading events in the history of other nations which have influenced our own country." The underlying idea of each volume is set out in the title, but throughout the series an attempt has been made to combine with the historical record, in a manner calculated to appeal to young minds, some idea of the qualities that make for good citizenship.

The Pageant of British History. By E. M. WILMOT-BUXTON, F.R.Hist.S. With 2 Plates in Colour and 8 other Illustrations. 1s. 6d.

This book attempts to show, as in a pageant, the course of English history by a series of word pictures, and thus by a vivid appeal to the imagination of the children to arouse their interest in the drama of the past.

The Romance of British History; or, Britain's Rise from Savagery to Civilization. By JOSIAH TURNER. With a Frontispiece in Colour and 8 other Illustrations. 1s. 6d.

This volume contains a more systematic treatment of the subject on concentric lines, with special emphasis on the great movements that have left a permanent mark on the history of the country, and tracing the influence of geographical conditions on historical development.

The Growth of Modern Britain. An Outline History of the British People from 1830 to 1910. By B. H. SUTTON. With a Frontispiece in Colour, and 8 other Illustrations. 2s.

This volume, after summarising the leading events up to 1830, deals in greater detail with the modern period from 1830 to 1910. It is written on entirely new lines, and a considerable amount of space is devoted to industrial progress and social conditions. The development of local government is sketched in simple language, and the moral of history is applied to the practical problems that confront the democracy of to-day. The book aims also at giving, in a small space, some knowledge of modern political conditions such as will enable the child on leaving school to take his place as a citizen, and play his part in the government of the Empire.

Methuen's School History of England

In Three Volumes

A Short History of Early England. To 1485. By H. J. CAPE, M.A., B.A., B.Sc., F.R.Hist.S., Headmaster of the Mathematical School, Rochester. With 6 Maps. Crown 8vo, 2s. 6d.

The author has endeavoured to carry out the suggestions contained in two recent and most valuable Memoranda of the Board of Education. By limiting the space devoted to the less instructive reigns, it has been possible to treat at greater length the events of outstanding importance, while the great movements of history are discussed in their European bearing and not merely from the influence which they exercised upon our own country.

It is, however, hoped that the book will satisfy the requirements of those who need a practical textbook for examination purposes.

A Short History of Tudor and Stuart England. 1485-1714. By L. OLDERSHAW, M.A. With Maps. Crown 8vo, 2s. 6d.

This volume aims at showing the position of England in Europe, and at sketching her internal development during the period when the foundations of the modern State and the Empire were being laid.

The Reformation and the counter Reformation, and England's attitude in regard to these movements, the Irish policy of the Tudors, and of

Methuen's School History of England—continued

Cromwell, the great struggle of the Executive and the Legislature, and the increasing attention paid to commercial problems and in foreign relations are among the larger questions dealt with in broad and simple outlines. As in the other volumes of the series, each chapter deals with a particular phase of the subject; illustrative extracts drawn from typical "sources" are added to many of the chapters, and its usefulness has been further increased by the inclusion of summaries and a biographical index.

- A Short History of Modern England. 1714-1910.** By ERNEST BOWYER, B.A., B.Sc. With 7 Maps and Genealogical Tables. Crown 8vo, 2s. 6d.

This volume has been written, on modern lines, expressly for Upper Forms of Schools. In order to enable the young pupil to grasp the history of his country during the last two centuries as an intelligible whole, the economic side of England's history and the part she has played in international politics have been dealt with in greater detail than is usual in textbooks written for schools. Each chapter deals with a particular phase of the subject; illustrative extracts drawn from typical "Sources" are added to many of the chapters, and the usefulness of the volume is further increased by the inclusion of biographies and summaries.

School County Histories

Illustrated. Crown 8vo, 1s. 6d. each

This series is designed to enforce the idea, so all-important in young people's education, that history begins at home. The volumes are meant to bring history into connexion with scenes which their readers know, to illustrate manners by local examples, and to teach that every place has its interest and its story. Maps and illustrations are freely added, and each county volume is written by an author who has made a special study of the county he treats.

- A School History of Middlesex, including London.** By VICTOR G. PLARR, M.A., and F. W. WALTON, M.A. With 45 Illustrations and a Plan of London.
- A School History of Surrey.** By H. E. MALDEN, M.A. With 4 Maps and 50 Illustrations.
- A School History of Somerset.** By WALTER RAYMOND. With 70 Illustrations. Second Edition.
- A School History of Warwickshire.** By Sir B. C. A. WINDLE, D.Sc., F.R.S., President of Queen's College, Cork. With 47 Illustrations.
- A School History of Lancashire.** By W. E. RHODES, M.A. With 3 Maps and 43 Illustrations.
-
- A Handy Digest of British History.** By C. E. SNOWDEN. Demy 8vo, 4s. 6d.

A guide and companion that aims at presenting a clear and easily graspable analysis of the course of events to students who are reading, and at refreshing, at a minimum cost of time and trouble, the memories of those who have read. It supplies a commentary on the more important and leading questions of each period, while it contents itself with the barest mention of episodes, the details of which can be found in most textbooks,

English Life Three Hundred Years Ago. Being the first two chapters of "England under the Stuarts." By G. M. TREVELYAN, M.A., late Fellow of Trinity College, Cambridge. Edited by J. TURRAL, B.A., Headmaster of the Blackpool Secondary School. Crown 8vo, 1s.

A graphic account of the state of England and English Society from 1603 to 1640.

A Constitutional History of England. By A. M. CHAMBERS, Honours School of Modern History, Oxford; History Mistress, Bedford High School. Second Edition, Revised. Crown 8vo, 6s.

This book is meant primarily for use in the Upper Forms in schools and for Students beginning more advanced work. It deals mainly with Saxon and Feudal Organization, and with the evolution of the Central Government out of earlier institutions. The development of each branch of the Constitution—Executive, Legislature, and Judicature—is traced separately, but, as far as possible, the history of each subject is dealt with chronologically. The difference between the English and other constitutions is examined, and its chief characteristics are pointed out, while the relationship of the several branches of the Constitution to each other, now and in the past, is shown, and an attempt is made to suggest the practical effects of the present balance of power in the State on the Constitution.

Original Illustrations of English Constitutional History. Comprising a Selected Number of the Chief Charters and Statutes. By D. J. MEDLEY, M.A., Professor of History in the University of Glasgow. Crown 8vo, 7s. 6d. net.

This volume covers the whole period from the Anglo-Saxon laws to the Act of Union with Ireland. University teachers have long desired such a collection in a single volume. In those already published the pieces are translated. But since the object of this selection is that it should serve as an introduction to more extended study, the documents written in French or Latin are presented in the original language, and they are annotated throughout with extracts from other original material bearing on all important points, in order that each passage may be as far as possible its own interpreter.

The Industrial History of England. By H. DE B. GIBBINS, Litt.D., M.A. With Maps and Plans. Nineteenth Edition, Revised. Crown 8vo, 3s.

An introduction to the subject, giving in concise and simple form the main outlines of England's economic history. As far as possible the economic questions are connected with the social, political, and military movements.

British Commerce and Colonies from Elizabeth to Victoria. By H. de B. GIBBINS, Litt.D., M.A. Fifth Edition. Crown 8vo, 2s.
[Commercial Series.]

A review of the history of British Commerce, written in simple and concise form, without elaborate detail.

Battles of English History. By H. B. GEORGE, M.A., Fellow of New College, Oxford. With numerous Plans. Fifth Edition, Revised. Crown 8vo, 3s. 6d.

This book is intended to give a clear general idea of all the most important Battles of English History, and, without being technical, to bring out their meaning. It is suitable for an Upper Form textbook or school prize.

MESSRS. METHUEN'S

Revision Notes on English History. By F. WALLACE-HADRILL, Assistant Master at Kingston-on-Thames Grammar School. Cr. 8vo, 1s.

This book is not intended to supersede, but rather to supplement the use of the ordinary class-book, and has been written chiefly for the use of candidates preparing for the Local Examinations. It contains a chronological analysis of the leading events of English history, together with general notes on each reign.

Examination Papers in English History. By J. TAIT WARDLAW, B.A. Crown 8vo, 2s. 6d. [*School Examination Series.*]

These papers are designed for candidates for a pass degree in History in the Universities, and for students taking Historical Scholarships, Army Candidates, and the ordinary work in Public Schools.

Junior History Examination Papers. By W. O. P. DAVIES. Crown 8vo, 1s. [*Junior Examination Series.*]

For pupils preparing for the Oxford and Cambridge Locals, College of Preceptors, and other Junior Examinations. They have been modelled on papers actually set by the various examining bodies, and the answers required will prove useful exercises in Composition. They are all most carefully graduated, and can be used either to test one particular period, or as Examination Papers of the subject generally.

The Rights and Duties of the English Citizen. [*See under "Civics."*]

Student's History of Scotland. By DAVID W. RANNIE, M.A. With 4 Maps. Crown 8vo, 3s. 6d.

A history written throughout in simple language, and putting as clearly as possible the results of the most careful recent criticism from original sources.

Europe and the Empire

Six Ages of European History

FROM A.D. 476 TO 1878

Edited by A. H. JOHNSON, M.A., Fellow of All Souls' College, Oxford.

With Maps. Crown 8vo, 2s. 6d. each

The Dawn of Mediæval Europe, 476-918. By J. H. B. MASTERMAN, M.A., Professor of History in the University of Birmingham. With 12 Maps. Second Edition.

It is hardly possible to understand European history without some knowledge of the settlement of Europe after the Teutonic immigrations and the fall of the Empire in the West. This volume traces the successive rise of the Gothic and Frankish Kingdoms, leading to the establishment of the Holy Roman Empire under Charles the Great, and its break up under his descendants. The influence of the Eastern Empire, and the rise and conquests of the Mohammedan faith, are considered chiefly in their bearing on the development of Western Europe. Attention is directed especially to the central figures of the period: Theodoric, S. Benedict, Justinian, Clovis, Charles the Great.

The Central Period of the Middle Age, 918-1273. By B. A. LEES, Resident History Tutor, Somerville College, Oxford. With 10 Maps. Second Edition.

Opening with the election of Henry the Fowler, and closing with the rise of the House of Hapsburg to power, it covers the period of the struggle for supremacy between Empire and Papacy and of the gradual building up of the nations of modern Europe on the ruins of Imperial Rome. It traces the development of feudalism and monasticism, of chivalry and the Crusades, of scholasticism and the Universities, and connects these great movements with the great men who inspired and led them,

The End of the Middle Age, 1273-1453. By E. C. LODGE, Vice-Principal and History Tutor, Lady Margaret Hall. Second Edition.

The period which it covers is one of great importance. It marks the decay of the political system of the Middle Ages, and the disappearance of the old unity in Western Europe; whilst it can be traced the growth of new ideals to take the place of the old, and above all the rise of nations. It is essentially a time of transition, a period of effort and experiment rather than of finished work. Its great interest lies in the fact that all the details of the history are part of this gradual change from the Middle Ages to Modern days.

Europe in Renaissance and Reformation, 1453-1660. By M. A. HOLLINGS, M.A. Third Edition.

This book deals with the formation of the modern European state-system, the Renaissance and Reformation (both Protestant and Catholic), the consolidation and ascendancy of France in Europe, and the Wars of Religion, ending with the Thirty Years War.

The Age of the Enlightened Despot, 1660-1789. By A. H. JOHNSON, M.A., Fellow of All Souls'. With 11 Maps. Third Edition.

The period covered by this volume opens with the triumph of the monarchy of Louis XIV. and closes with the failure of the rule of Louis XVI. The aim of the volume is to bring clearly before the young reader the theory of monarchical rule represented by these kings, and to show when and why they succeeded or failed.

The Remaking of Modern Europe: From the Outbreak of the French Revolution to the Treaty of Berlin, 1789-1878. By J. A. R. MARRIOTT, M.A. With 10 Maps. Fifth Edition.

It contains a sketch of European history, presenting a vivid picture of the revolutionary period, of the rise and fall of Napoleon, and of the larger movements of European politics since Waterloo.

Stories from Modern History. By E. M. WILMOT-BUXTON, F.R.Hist.S. Crown 8vo, 1s. 6d. [*New Historical Series.*]

An introduction to the story of modern history for pupils up to the age of twelve. In accordance with the suggestions made in the late circular of the Board of Education, it deals with "the chief events and characters from the history of the most important nations in their traditional form." It aims also at "giving some idea of the nature of the great nations and stages in civilisation, centred round certain individuals or events in their chronological succession" in such a way that young children shall be able at least to "place" the most notable characters of history.

Makers of Europe. Outlines of European History for the Middle Forms of Schools. By E. M. WILMOT-BUXTON, F.R.Hist.S. With 12 Maps. Thirteenth Edition. Crown 8vo, 3s. 6d.

A Textbook of European History for Middle Forms and Pupil Teachers.

Tales from Irish History. By A. BIRKHEAD, B.A. With a Map. Crown 8vo, 1s. 6d. [*Stories from the Histories.*]

Stories from French History. By TAYLOR DYSON, M.A. With a Map. Crown 8vo, 1s. 6d. [*Stories from the Histories.*]

Stories from Scottish History. By E. M. WILMOT-BUXTON, F.R.Hist.S. With a Map. Crown 8vo, 1s. 6d. [*Stories from the Histories.*]

Stories from American History. By ALICE BIRKHEAD. With a Map. Crown 8vo, 1s. 6d. [*Stories from the Histories.*]

The Story of the British Empire for Children. By F. M. ANDERSON. With many Illustrations. Revised Edition. Crown 8vo, 2s.

This book gives the story of the Empire in simple language for children. Part I. gives a rapid survey of the Colonies and Dependencies to show the unity of the whole under the Crown. Part II. describes in greater detail India, Canada, New Zealand, Australia, and Tasmania.

History and Geography Examination Papers. By C. H. SPENCE, M.A., Assistant Master at Clifton College. Third Edition. Crown 8vo, 2s. 6d. [*School Examination Series.*]

The French Revolution. By J. E. SYMES, M.A., Principal of University College, Nottingham. With a Map. Second Edition. Crown 8vo, 2s. 6d.

A short general account of the French Revolution, bringing out the significance of the chief facts and their relation to problems of our own time.

LATIN

Grammars, Exercises, etc.

A School Latin Grammar. By H. G. FORD, M.A., Assistant Master at Bristol Grammar School. Second Edition. Crown 8vo, 2s. 6d.

[*Junior School Books.*]

Both in the Accidence and Syntax what is essential for beginners is carefully separated, by a system of typing or paging, from what they may neglect. The book may thus be used by boys of all forms.

An Elementary Latin Exercise Book. By H. G. FORD, M.A., and L. V. CAUDWELL, M.A., Assistant Masters at Bristol Grammar School. Crown 8vo, 2s. 6d.

This book covers a two years' course divided into six parts, each part containing twelve explanations and twelve vocabularies of uniform length (10 words), with twenty English-Latin sentences and fifteen Latin-English to each explanation. Throughout only words and constructions found in *Cæsar B. G.* are used.

It is a companion book to Mr. Ford's "A School Latin Grammar."

Elementary Latin. Being a First Year's Course. By F. J. TERRY, B.A., Assistant Master at Preston House School, East Grinstead. Crown 8vo, Pupils' Book, 2s. ; Masters' Book, 3s. 6d. net.

A year's school course arranged for class teaching, with text written to allow the gradual introduction of all inflected forms. Nouns and verbs are built up according to their stem formation throughout, so that the learner gradually acquires the Accidence systematically. As a matter of practical experience, boys 10 or 11 years of age are able to construe *Cæsar* at the end of the course with but little help. The book contains Vocabularies, Grammar, and Exercises, and no other textbook is required by the pupils. The *Masters' Book* is a commentary on the *Pupils' book*, and explains the system of teaching. It directs attention consistently throughout to the *meaning* of words, and thus explains the Grammar.

A Junior Latin Prose. By H. N. ASMAN, M.A., B.D. Crown 8vo, 2s. 6d. [*Junior School Books.*]

The "Junior Latin Prose" is written primarily, though not exclusively, with a view to the Junior Locals. It contains explanation of, and exercises on, the chief rules of Syntax, with special attention to points which cause difficulty to boys, and concludes with exercises in Continuous Prose.

Exercises in Latin Accidence. By S. E. WINBOLT, M.A. Crown 8vo, 1s. 6d.

This book is adapted for Lower Forms, and is intended to accompany the Shorter Latin Primer.

Latin Passages for Unseen Translation. By A. M. COOK, M.A., Assistant Master at St. Paul's School, and E. C. MARCHANT, M.A., Tutor of Lincoln College, Oxford. Sixth Edition. Crown 8vo, 1s. 6d.

Two hundred Latin passages, arranged in order of increasing difficulty. Has been carefully compiled to meet the wants of V. and VI. Form boys at the Public Schools, and is also well adapted for the use of honoursmen at the Universities. Prose and verse alternate throughout.

Notes on Greek and Latin Syntax. By G. BUCKLAND GREEN, M.A., Assistant Master at Edinburgh Academy. Third Edition. Crown 8vo, 3s. 6d.

For description, see under "Greek."

Latin Hexameter Verse. An Aid to Composition. By S. E. WINBOLT, M.A. Crown 8vo, 3s. 6d. Key, 5s. nct.

This book contains the fruit of several years' class teaching. It is offered as a help to Fifth and Sixth Forms at Public Schools, and Undergraduates at Universities.

The principle adopted is to aid in the composition of hexameter verse, by showing to some extent the development of this literary form, by inferring from the evolution what is the best workmanship, and by hinting how technique depends largely on thought.

By A. M. M. Stedman, M.A.

Initia Latina. Easy Lessons on Elementary Accidence. Revised by C. G. BOTTING, M.A. Fourteenth Edition. Fcap. 8vo, 1s.

A very easy Latin course for quite young pupils, containing Grammar, Exercises, and Vocabularies.

First Latin Lessons. Revised by C. G. BOTTING, M.A. Thirteenth Edition. Crown 8vo, 2s.

This book is much fuller than "Initia Latina," and while it is not less simple, it will carry a boy a good deal further in the study of elementary Latin. The Exercises are more numerous, some easy translation adapted from Cæsar has been added, and a few easy Examination Papers will afford a useful test of a boy's knowledge of his grammar. The book is intended to form a companion book to the "Shorter Latin Primer."

A First Latin Reader. With Notes adapted to the Shorter Latin Primer, and Vocabulary. Revised by C. G. BOTTING, M.A. Seventh Edition. 18mo, 1s. 6d.

A collection of easy passages without difficulties of construction or thought. The book commences with simple sentences and passes on to connected passages, including the history of Rome and the invasion of Britain, simplified from Eutropius and Cæsar.

Easy Latin Passages for Unseen Translation. Fourteenth Edition. Fcap. 8vo, 1s. 6d.

A collection of short passages for beginners. The pieces are graduated in length and difficulty.

Exempla Latina. First Exercises in Latin Accidence. With Vocabulary. Fifth Edition. Crown 8vo, 1s.

This book is intended to be used midway between a book of elementary lessons and more difficult Exercises on Syntax. It contains simple and copious exercises on Accidence and Elementary Syntax,

Easy Latin Exercises on the Syntax of the Shorter and Revised Latin Primers. Revised by C. G. BOTTING, M.A. With Vocabulary. Fourteenth Edition. Crown 8vo, 1s. 6d. **Key**, 3s. net.

This book has been compiled to accompany Dr. Kennedy's "Shorter Latin Primer" and "Revised Latin Primer." Special attention has been paid to the rules of *oratio obliqua*, and the exercises are numerous.

The Latin Compound Sentence. Rules and Exercises. Second Edition. Crown 8vo, 1s. 6d.; with Vocabulary, 2s.

This book has been compiled to meet the requirements of boys who have worked through a book of easy exercises on Syntax, and who need methodical teaching on the Compound Sentence. In the main the arrangement of the Revised Latin Primer has been followed.

Notanda Quædam. Miscellaneous Latin Exercises on Common Rules and Idioms. Sixth Edition. Fcap. 8vo, 1s. 6d.; with Vocabulary, 2s. **Key**, 2s. net.

This volume is designed to supply miscellaneous practice in those rules and idioms with which boys are supposed to be familiar. Each exercise consists of ten miscellaneous sentences, and the exercises are carefully graduated. The book may be used side by side with the manuals in regular use.

Latin Vocabulary for Repetition. Arranged according to Subjects. Revised by C. G. BOTTING, M.A. Eighteenth Edition. Fcap. 8vo, 1s. 6d.

In this book an attempt has been made to remedy that scantiness of vocabulary which characterises most boys. The words are arranged according to subjects in vocabularies of twelve words each, and if the matter of this little book of eighty-nine pages is committed to memory, the pupil will have a good stock of words on every subject.

A Vocabulary of Latin Idioms and Phrases. Sixth Edition. 18mo, 1s.

Seven hundred useful Latin phrases arranged alphabetically, Latin-English.

Latin Examination Papers in Miscellaneous Grammar and Idioms. Sixteenth Edition. Cr. 8vo, 2s. 6d. **Key** (Seventh Edition), issued to Tutors and Private Students only, 6s. net.

The papers have been compiled to provide boys who have passed beyond the elementary stages of grammar and scholarship with practice in miscellaneous grammar and idioms.

Considerable space has been given to the doctrines of the moods (a real test of accurate scholarship), and to those short idioms and idiomatic sentences which illustrate the differences between the English and Latin languages.

Junior Latin Examination Papers. By C. G. BOTTING, M.A., Assistant Master at St. Paul's School. Eighth Edition. Fcap. 8vo, 1s. **Key**, 3s. 6d. net. [*Junior Examination Series.*]

An easier book on the same lines as Stedman's "Latin Examination Papers." It is intended for use in the Lower Forms of Public Schools, and by candidates preparing for the Oxford and Cambridge Junior Local Examinations. The volume contains 720 carefully graduated original questions, divided into papers of ten questions each.

Examination Papers on Vergil. By W. G. COAST, B.A., Assistant Master at Feltes College. Crown 8vo, 2s.

Three papers are given to each *Georgic*, five to each *Æneid*, and one to each *Eclogue*, and in addition there are a number of general papers.

Examination Papers on Horace. By T. C. WEATHERHEAD, M.A. Crown 8vo, 2s.

In this volume the whole of Horace has been divided into short sections, and a paper has been set on each section, as well as (usually) two recapitulatory papers on each part, e.g. the first book of the *Odes*.

Texts

Simplified Latin Texts

Edited by H. N. ASMAN, M.A., B.D., Second Master of
Owen's School, Islington.

This series is being prepared to meet the real need in schools of a more varied selection of authors for young pupils. The texts have been abridged with a view to economy of time, and also with a view to simplification. This has been done by omission, and not by alteration. Notes have been added sparingly, vocabularies have been given, and naturally long vowels marked throughout. A few questions on the subject-matter have been appended to furnish materials and suggestions for oral work and written composition. The texts are Fcap. 8vo, 1s. each. The first volumes are:—

The Catiline of Sallust. By A. J. BARNETT, M.A., Assistant Master, Emanuel School, Wandsworth, S.W.

Selections from Catullus. By H. N. ASMAN, M.A., B.D.

Stories from Martial. By H. N. ASMAN, M.A., B.D.

Cæsar.—EASY SELECTIONS FROM CÆSAR. The Helvetian War. With Notes and Vocabulary. By A. M. M. STEDMAN, M.A. Revised by C. G. BOTTING, M.A. Fifth Edition. 18mo, 1s.

Livy.—EASY SELECTIONS FROM LIVY. The Kings of Rome. With Notes and Vocabulary. By A. M. M. STEDMAN, M.A. Illustrated. Second Edition. 18mo, 1s. 6d.

Plautus.—THE CAPTIVI. Edited, with an Introduction, Textual Notes, and a Commentary, by W. M. LINDSAY, Fellow of Jesus College, Oxford. Demy 8vo, 10s. 6d. net.

The editor has recollated all the important MSS. The book contains a long Introduction and an important Appendix on the accentual elements in early Latin verse. The textual Notes are complete and the Commentary is full.

Tacitus.—TACITI AGRICOLA. With Introduction, Notes, Maps, etc. By R. F. DAVIS, M.A. Crown 8vo, 2s.

— TACITI GERMANIA. By R. F. DAVIS, M.A. Crown 8vo, 2s. The text, edited with an Introduction, Notes, and Critical Appendix for Middle Forms.

Translations

Cicero.—DE ORATORE I. Translated by E. N. P. MOOR, M.A., late Assistant Master at Clifton. Second Edition. Crown 8vo, 3s. 6d.

— SELECT ORATIONS (Pro Milone, Pro Murena, Philippic II., In Catilinam). Translated by H. E. D. BLAKISTON, M.A., Fellow and Tutor of Trinity College, Oxford. Crown 8vo, 5s.

— DE NATURA DEORUM. Translated by F. BROOKS, M.A., late Scholar of Balliol College, Oxford. Crown 8vo, 3s. 6d.

— DE OFFICIIS. Translated by G. B. GARDINER, M.A. Crown 8vo, 2s. 6d.

- Horace.**—THE ODES AND EPODES. Translated by A. D. GODLEY, M.A., Fellow of Magdalen College, Oxford. Crown 8vo, 2s.
- Juvenal.**—THIRTEEN SATIRES OF JUVENAL. Translated by S. G. OWEN, M.A. Crown 8vo, 2s. 6d.
- Tacitus.**—AGRICOLA AND GERMANIA. Translated by R. B. TOWNSEND, late Scholar of Trinity College, Cambridge. Crown 8vo, 2s. 6d.

MATHEMATICS

Algebra

- Easy Exercises in Algebra for Beginners.** Containing 3500 Original Problems. By W. S. BEARD. Third Edition. Crown 8vo. With Answers, 1s. 9d. ; Without Answers, 1s. 6d.
A preparatory course in Algebra for the Local Examinations. This book contains many distinctive features.
- Test Cards in Euclid and Algebra.** By D. S. CALDERWOOD, Headmaster of the Provincial Training College, Edinburgh. In three packets of 40, with Answers, 1s. each; or in three books, price 2d., 2d., and 3d.
- Junior Algebra Examination Papers.** By S. W. FINN, M.A., Headmaster of Sandbach School. With or Without Answers. Fcap. 8vo, 1s. [*Junior Examination Series.*
Seventy-two Papers of ten questions each. The problems, which are original, will be found suitable for candidates for the Local Examinations.

Arithmetic

- Easy Exercises in Arithmetic.** Containing 5000 Examples. By W. S. BEARD. Seventh Edition. Fcap. 8vo. With Answers, 1s. 3d. ; Without Answers, 1s. [*Beginner's Books.*
A course of Arithmetic for Lower Forms in Secondary Schools and pupils preparing for Public Schools, Naval Cadetships, the Oxford and Cambridge Preliminary Local Examinations. The examples are very numerous, carefully graduated, and do not involve the use of big numbers.
- Junior Arithmetic Examination Papers.** By W. S. BEARD. With or Without Answers. Sixth Edition. Fcap. 8vo, 1s. [*Junior Examination Series.*
Contains 900 Questions arranged in Papers of ten each. Suitable for candidates for the Local Examinations, County Scholarships, etc.
- The Metric System.** By LEON DELBOS. With numerous Examples. Crown 8vo, 2s.
A clear and practical account of the subject, stating its advantages and disadvantages, the general principles of the system, linear measures, square and land measure, cubic measure and measures of capacity.
- A South African Arithmetic.** By H. HILL, B.A. Cr. 8vo, 3s. 6d.
Contains a number of examples on the South African Weights and Measures.

- Technical Arithmetic and Geometry.** By C. T. MILLIS, M.I.M.E., Principal of the Borough Polytechnic Institute. For use in Technical Institutes, Modern Schools, and Workshops. Second Edition, Revised. Crown 8vo, 3s. 6d. [*Textbooks of Science.*
A course in Arithmetic, Geometry, and Mensuration intended more especially for students in the engineering and building trades.
- Exercises and Examination Papers in Arithmetic, Logarithms, and Mensuration.** By C. PENDLEBURY, M.A., Senior Mathematical Master at St. Paul's School. Sixth Edition. Crown 8vo, 2s. 6d. **Key**, 5s. net. [*School Examination Series.*
- A New Junior Arithmetic.** By H. BOMPAS SMITH, M.A., Headmaster of King Edward VII. School, Lytham. Second Edition. Crown 8vo. With Answers, 2s. 6d.; Without Answers, 2s.
In this book Arithmetic is taught as the habitual application of common sense to questions involving number, not as the acquisition of mechanical facilities in certain rules. It is the cheapest Arithmetic on reform lines issued.
- A Short Commercial Arithmetic.** By F. G. TAYLOR, M.A. Fifth Edition. Crown 8vo, 1s. 6d. [*Commercial Series.*
A treatise for those with a fair knowledge of Arithmetic and Algebra. Special attention is given to quick methods of approximation. Contains an excellent chapter on the slide rule.

Book-keeping

- Double-Entry Book-keeping.** A Complete Treatise on its Theory and Practice. By JAMES CUSACK, LL.D., Principal of the Business Training College, Finsbury Square. Crown 8vo, 3s. 6d.
Covers the requirements for all the Elementary, Junior, and Intermediate Examinations held by the London Chamber of Commerce, the Royal Society of Arts, the National Union of Teachers, the Oxford and Cambridge Senior Locals, the College of Preceptors, and other similar Examinations.
- The Principles of Book-keeping by Double Entry.** By J. E. B. M'ALLEN, M.A., Headmaster of Lowestoft Secondary Day School. Crown 8vo, 2s. [*Commercial Series.*
A clear and intelligible account of the principles for those who have no previous knowledge of the subject.
- Examination Papers in Book-keeping.** By J. T. MEDHURST. Tenth Edition. Crown 8vo, 3s. **Key**, 2s. 6d. net. [*School Examination Series.*

Geometry

- Practical Geometry for Schools.** By SIDNEY A. SWITZER, Art Master and Honours Medallist in Geometry, Examiner to the Examination Board of the N.U.T. Fully Illustrated. Crown 8vo, 2s.
This up-to-date textbook is the result of twenty years' practical experience. It is designed to assist students generally, and is suited to the requirements of candidates taking the Board of Education, Oxford and Cambridge Local, and College of Preceptors Examinations. The problems are well graduated; suggestive dimensions are inserted in their enunciation; and they are all illustrated. Each page is self-contained, so that there is no turning over in the study of any one problem. Each page has a corresponding set of exercises. These exercises are mostly original.

Geometry on Modern Lines. By E. S. BOULTON, M.A., Lecturer on Mathematics, Merchant Venturers' Technical College, Bristol. Crown 8vo, 2s.

A textbook on the new method. Only necessary propositions have been retained, and the proofs are based on the simplest process of reasoning.

A Preliminary Geometry. By NOEL S. LYDON, Assistant Master at Owen's School, Islington. With 159 Diagrams. Crown 8vo, 1s.

The "Preliminary Geometry" is intended for the use of beginners. The treatment of the subject is mainly experimental and practical, and the ground covered is sufficient to enable the pupil to pass easily to the study of a formal course of theorems. Problems involving accurate measurement and arithmetical applications of geometrical principles are freely used; the book is copiously illustrated and a large number of useful exercises is provided.

A Junior Geometry. By NOEL S. LYDON. With 276 Diagrams. Eighth Edition. Crown 8vo, 2s. [*Junior School Books.*]

The method of treatment is the outcome of the author's long practical experience as teacher of the subject at Owen's School, Islington. The grouping of kindred propositions, the demonstrations attached to the practical problems, the copious series of questions and exercises, and the methodical division of the subject into lessons of practical length, are features calculated to commend themselves to both master and pupil.

Trigonometry

A New Trigonometry for Beginners. By R. F. D'ARCY, M.A., Lecturer on Mathematics at Gonville and Caius College, Cambridge. With numerous Diagrams. Crown 8vo, 2s. 6d.

Among the special features of this book are:—The introduction of experiments in practical geometry to lead up to many of the topics considered; the use throughout the book of four-figure tables; the regulation of the special consideration of the trigonometrical ratios of angles of 30, 45, 60, 120, 135, and 150 degrees to a few worked-out examples.

Trigonometry Examination Papers. By the Rev. G. H. WARD, M.A. Fourth Edition. Crown 8vo, 2s. 6d. **Key**, 5s. net.

[*School Examination Series.*]

SCIENCE

Nature Study

Methuen's Nature Books

These books have been specially written by eminent naturalists to serve the purpose of Nature Study class-books. The respective authors have had a long experience in teaching and organizing this important branch of school-work, and have attempted to produce volumes which will combine the functions of a school Reader, and at the same time deal in a systematic way with the elements of Nature Study as carried out in the most up-to-date schools. The importance of scientific method has been specially emphasized, and the whole subject is treated in a manner calculated to arouse the interest and curiosity of children, so that the educational value of Nature Study may be fully and adequately realized.

Some Secrets of Nature. Short Studies in Field and Wood. With an Introduction by W. J. P. BURTON, late Lecturer in Nature Study, Derby Training College, and Organizer of Rural Education, North Riding of Yorkshire Education Committee. Illustrated with Coloured Plates and Photographs from Nature. Crown 8vo, 1s. 6d.

This book is designed primarily as a class-book for children of eleven years of age and upwards. Its aim is to supplement and give unity to

the ordinary Nature lesson, to inculcate a love of the study of plants and animals as they live and grow, and to teach children to see and to think. It will be of great assistance to teachers in framing an introductory course of lessons in Nature Study, and will serve to indicate some of the directions in which definite lines of thought may be pursued.

The Romance of Nature. *Studies of the Earth and its Life.* With a Preface by the Rev. ALFRED THORNLEY, M.A., Superintendent of Nature Study to the Nottingham and Leicestershire Education Committees; Lecturer on Nature Study to the Midland Agricultural and Dairy College, Kingston, Derby. Illustrated with Coloured Plates and Photographs from Nature. Crown 8vo, 2s.

This book will serve as a more advanced class-book. It will also be useful to teachers as an indication of the lines to be followed in planning a systematic course of lessons in this subject. While in no sense attempting to exhaust any one branch, the book gives a brief account of earth-lore, dealing successively with the history and structure of the earth, and the common forms of plant and animal life that inhabit it. The aim throughout is to provide material to stimulate observation and independent thought.

Biology

Outlines of Biology. By P. CHALMERS MITCHELL, LL.D., F.R.S., F.Z.S., F.L.S., Secretary to the Zoological Society. Third Edition, Revised and Supplemented by GEO. P. MUDGE, A.R.C.Sc.(Lond.), F.Z.S., Lecturer on Biology, London Hospital Medical College, University of London, and at London School of Medicine for Women, University of London. With 11 Plates and numerous Diagrams. Crown 8vo, 6s. net.

The book is primarily written to meet the needs of students preparing for the examinations of the Conjoint Board of the Royal Colleges of Physicians and Surgeons of England. But it covers to a great extent the syllabuses of other examining bodies and students reading for the L.L.A., for Durham University, for the Conjoint Colleges of Scotland, and for the first Medical examination of London University will find a great deal of the required ground covered by its contents. The book has been brought up to date, and the additional types recently introduced into the syllabus of the Conjoint Colleges are now included. New Chapters on Histology, on the structure of stem, root, and leaf, and many fresh illustrations in half-tone have been added.

Elementary Zoology. By C. A. EALAND, M.A., F.L.S., late Principal of the County Laboratories, Chelmsford. With numerous Diagrams and Illustrations. Crown 8vo, 2s. 6d.

Primarily designed to meet the needs of students reading for the Cambridge Junior and Senior Local Examinations, the London Matriculation Examination and Stage I. Zoology Examination of the Board of Education, this book also serves as a general introduction to Zoology.

With structural adaptation as the keynote, members of all the more important classes of the animal kingdom are reviewed, and certain types are selected for detailed consideration, in the laboratory and in the field. Suggestions for practical work and for obtaining and preserving specimens are given in each chapter.

Agricultural Zoology. By Dr. J. RITZEMA BOS. Translated by J. R. AINSWORTH DAVIS, M.A. With 155 Illustrations. Third Edition. Crown 8vo, 3s. 6d.

A condensed review of the entire animal kingdom, treating in some detail the animals harmful or helpful to agriculture. It is a manual suitable not only for students, but also for the practical farmer and general reader.

Preliminary Physiology. By WILLIAM NARRAMORE, F.L.S., M.R.San.Inst., Lecturer in Physiology, Hygiene, Biology, and Botany, Municipal Technical School, Liverpool. Crown 8vo, 3s. 6d.

[*Textbooks of Science.*

This book aims at giving systematic instruction in relation to the essential functions of the human body. The many original drawings, sketches, and photomicrographs have been prepared directly from specimens. The book meets the requirements of the Board of Education, the Oxford and Cambridge Locals (Senior), the College of Preceptors, Candidates for Matriculation, and the several examinations in Physiology held for students in Hygiene, Physical Culture, Cookery, for nurses in Probation, and students preparing for examinations in Law, Insurance, and Accountancy, where Physiology is now demanded.

Dairy Bacteriology. A Short Manual for Students in Dairy Schools, Cheese-makers, and Farmers. By Dr. ED. VON FREUDENREICH. Translated by J. R. AINSWORTH DAVIS, M.A. Second Edition, Revised. Crown 8vo, 2s. 6d.

A brief treatise on bacteriology as applied to dairying. For students who mean to become cheese-makers or dairymen, it is only necessary to get a general idea of bacteriology and to become familiarized with the results so far attained by bacteriological research as regards dairying, and the practical application of the same. The author has therefore introduced only so much of the general part of bacteriology as is absolutely necessary for the comprehension of the bacteria of milk, and has made the whole as brief and elementary as possible.

Insect Life. By F. V. THEOBALD, M.A. Illustrated. Second Edition, Revised. Crown 8vo, 2s. 6d.

A short account of the more important characteristics of insects, dealing with their economic value at the same time.

Botany

An Elementary Textbook of Agricultural Botany. By M. C. POTTER, M.A., F.L.S., Professor of Botany, Armstrong College, Newcastle-on-Tyne. Illustrated. Third Edition. Crown 8vo, 4s. 6d.

A textbook of Botany intended more especially for agricultural students. Considerable space is devoted to vegetable physiology.

Elementary Lessons on Plant Life. By D. G. SCOTT, M.Sc., Assistant Lecturer and Demonstrator in Botany in the University of Liverpool. With many Diagrams and Illustrations. Crown 8vo, 2s. 6d.

Designed for use in the Lower Forms of Secondary Schools, and for private study in the Upper Standards of Elementary Schools, the book will be found useful for the Oxford and Cambridge Junior Locals, the National Froebel Union Certificate, and other Examinations. Suggestions for practical work head each chapter, and special attention has been paid to the difficulties experienced in nature-study in town schools.

Plant Life. Studies in Garden and School. By HORACE F. JONES, Science Master, Uxbridge County School. With 320 Illustrations. Crown 8vo, 3s. 6d.

[*Textbooks of Science.*

A handbook for teachers of botany. A large number of experiments are included, and full nature-study notes on all plants usually studied in the class-rooms are given. It is recommended by the Board of Education in "Suggestions on Rural Education," page 42.

"This volume furnishes just the right kind of course, both in garden work and in class-room experiments, which is likely to stimulate a permanent interest in the mind of the pupil and lead him to continue his investigations after he has left school. We have great pleasure in recommending the book."—*Schoolmaster*.

Chemistry

General

A Concise History of Chemistry. By T. P. HILDITCH, D.Sc. (London), A.I.C., F.C.S. Crown 8vo, 2s. 6d. [*Textbooks of Science*.

Primarily intended as a help to chemical students, more particularly those studying for University or advanced technical examinations, this book will also, it is hoped, prove serviceable to general readers who may wish to have a concise outline of the development of chemistry. Commencing with a general survey of the chemistry of the Ancients and the Middle Ages, the author shows how the modern science evolved from these, and then proceeds to the history of the various branches—elements, minerals, organic, technical and physical chemistry, etc. A glossary of the most notable names in chemistry is added, and, as far as possible, the sequences of facts or theories have been summarized in tables which, while assisting the memory of the student preparing for examinations, may be omitted by the casual reader.

Elementary Chemical Theory. By J. M. WADMORE, M.A., Senior Science Master at Aldenham School. With Diagrams. Crown 8vo, 3s. 6d. [*Textbooks of Science*.

This book is intended principally for the middle and senior students of Chemistry at Public and Secondary Schools. It deals, among other things, with the chief aspects of the atomic and molecular theories, and will be found most valuable in supplementing a course of practical work.

"We know of no book on elementary chemical theory which we could more strongly recommend."—*Journal of Education*.

"If we were asked to recommend a guide to the elements of chemical theory suitable for students at an early period of their work, we could suggest nothing better than this book."—*Knowledge*.

Higher Mathematics for Chemical Students. By J. R. PARTINGTON, B.Sc., Graduate Scholar and Beyer Fellow of the University of Manchester. With Forty-four Diagrams. Crown 8vo, 5s.

In this book the principles of the Infinitesimal Calculus and Differential Equations are developed from the most elementary foundations, and with special reference to chemistry. Since the application of mathematics is now necessary, not only in physical chemistry, but also in organic and inorganic chemistry and metallurgy, the book is addressed to a wide circle of readers.

Inorganic

Elementary Experimental Chemistry. By A. E. DUNSTAN, D.Sc. (Lond.), Head of the Chemical Department, East Ham Technical College. With 109 Diagrams. Fourth Edition, Revised. Crown 8vo, 2s. [*Junior School Books*.

The arrangement for this book is modelled on that of "Elementary Experimental Science." The subject is treated experimentally, and covers the necessary ground for Oxford and Cambridge Junior Locals, College of Preceptors (Second Class), and Board of Education (First Stage) Examinations. The author believes that the method adopted is truly educational. The subject is developed in a logical sequence, and wherever possible, historically.

An Elementary Textbook of Inorganic Chemistry. By R. LLOYD WHITELEY, F.I.C., Principal of the Municipal Science School, West Bromwich. Second Edition. Crown 8vo, 2s. 6d.

This book has been written primarily for the use of those who are commencing the Study of Theoretical Inorganic Chemistry on the lines laid down for Stage I. of that subject in the Syllabus issued by the Board of Education. The subject-matter of that Syllabus has consequently been fully discussed.

A Junior Chemistry. By E. A. TYLER, B.A., F.C.S., Head of the Chemical Department, Swansea Technical College. With 78 Illustrations. Seventh Edition. Crown 8vo, 2s. 6d. [*Junior School Books.*]

The first twenty-three pages are devoted to the necessary physical laws and processes. The purification and properties of water are used to illustrate these processes. The student is thus led by a *continuous chain of reasoning* through the preparation of pure water to the chemistry of water, and hence to a knowledge of the fundamental principles of chemistry. The middle portion of the book treats of these principles, and then follows the study of certain typical elements and compounds. Problems and Examination Papers are appended.

A Textbook of Inorganic Chemistry. By G. SENTER, D.Sc., Ph.D., Lecturer at St. Mary's Hospital Medical School, Author of "Outlines of Physical Chemistry." With many Diagrams. Second Edition. Crown 8vo, 6s. 6d. [*Textbooks of Science.*]

The book is designed as a general introduction to the study of Inorganic Chemistry. It is written throughout from the modern standpoint, so that the student who has worked through it should be in a position to profit from the reading of original papers, and to proceed without difficulty to the study of advanced works on the different branches of the subject. The theoretical part of the subject is distributed throughout the book, and as far as possible the facts on which the theories and hypothesis are based are given before the statement of the theories themselves. The great importance to the student of learning to draw a clear distinction between facts and theories is kept in mind throughout. The book is suitable for the Intermediate and Pass B.Sc. University Examinations and other examinations of similar scope.

The Complete School Chemistry. By F. M. OLDHAM, B.A., Senior Chemistry Master at Dulwich College. With 125 Illustrations. Seventh Edition. Crown 8vo, 4s. 6d. [*Textbooks of Science.*]

A complete course in practical and theoretical chemistry up to the standard of the London Matriculation and Army Entrance Examination. It is so arranged that a boy with no knowledge of chemistry may begin the book and use it throughout his progress up the school. Short courses on volumetric analysis and on the common metals are included.

Practical Chemistry. Part I. By W. FRENCH, M.A., Examiner in Chemistry for the Union of Lancashire and Cheshire Institutes. Sixth Edition. Crown 8vo, 1s. 6d. [*Textbooks of Science.*]

A course on purely inductive lines dealing with evaporations and distillations, filtration solubility, air, water, chalk, soda, common salt, sugar, compound and simple matter, etc.

Practical Chemistry. Part II. By W. FRENCH, M.A., and T. H. BOARDMAN, M.A., Science Master at Christ's Hospital. Crown 8vo, 1s. 6d. [*Textbooks of Science.*]

A continuation of the above dealing with gases, laws of chemical combination, equivalents, atomic theory, molecular weights, symbols, sulphur, nitrogen, carbon, and their compounds, salts, acids, bases, valency.

- A Practical Chemistry Notebook for Matriculation and Army Candidates.** Easy Experiments on the Commoner Substances. By S. E. BROWN, M.A., B.Sc., Head Master, Shaw Street Collegiate School, Liverpool. Crown 4to, 1s. 6d. net.

The method is based on practical experience, and aims at maintaining interest by ensuring success and accuracy in experimenting. The chief objects in view are:—(1) a logical sequence in work and accurate experimenting by demonstration of practical use of apparatus; (2) to allow the teacher more time for individual attention, and to keep the class together at work on the same experiment. This is done by providing a series of practical problems to keep the more rapid workers employed, as well as for use in revision. Working for two hours (practical) per week, the course should be completed in about three terms. There are spaces provided for notes to be taken by the pupil.

- A Senior Experimental Chemistry.** By A. E. DUNSTAN, D.Sc. (Lond.). With Diagrams and Illustrations. Crown 8vo, 3s. 6d.

[*Textbooks of Science.*

This volume is intended as a supplement to the author's well-known textbooks, "Elementary Experimental Science" and "Elementary Experimental Chemistry." It will contain sufficient matter to provide for the remainder of a boy's school career, and will build up a sound development of modern chemical theory on the experimental foundation of his first two years' work.

The treatment will be based on the Periodic Classification, preceded by a discussion of the Atomic and Molecular Theories with the rudiments of Physical Chemistry, Thermochemistry, and Crystallography. The necessary Practical Chemistry will be incorporated and a section on Qualitative Analysis with the elements of Volumetric Analysis will complete the course. It is believed that this book will be of use to Second Year Students in Technical Institutes.

- A Textbook of Practical Chemistry for Technical Institutes.** By A. E. DUNSTAN, D.Sc.; and F. B. THOLE, B.Sc., Lecturer in Organic Chemistry, East Ham Technical College. Crown 8vo, 3s. 6d.

[*Textbooks of Science.*

This Course of Practical Chemistry meets the requirements of the Upper Forms of Secondary Schools, where a good elementary foundation has been laid in the rudiments of manipulation. The book will be found useful also for classes in Technical Institutes and will cover the following ground:—

Qualitative Analysis of simple substances and of mixtures, Volumetric Analysis, Simple Gravimetric Analysis, Preparation of Pure Compounds, More difficult Quantitative Analysis, Qualitative Organic Analysis, Ultimate Organic Analysis, General Organic Determinations, Determination of Physical Constants.

- An Introduction to Quantitative Analysis.** By S. J. M. AULD, D.Sc.(Lond.), Ph.D.(Würzburg), F.I.C., F.C.S., Head of the Chemical Department, South-Eastern Agricultural College, Wye. With many Diagrams. Crown 8vo, 5s.

[*Textbooks of Science.*

This book is a carefully selected study of the elements of quantitative analysis, providing a thorough introductory course, whereby the student is prepared for his more specialised analytical work, details and considerations of which are best obtained from the standard treatises and monographs.

Duplication is largely avoided by giving alternative methods for subsequent estimations of the same type. Special features are a theoretical chapter on indicators, and a description of exact laboratory methods for the determination of equivalents, etc.

The textbook contains all the inorganic quantitative work required for the Board of Education examinations and the Inter. and Final B.Sc. Courses.

It will be noted that a complete and consistent school course in Experimental Chemistry, extending over five years, can be covered from Messrs. Methuen's list, as follows :—

- First Year Elementary Experimental Science Chemistry Section, by A. E. Dunstan.
 Second Year Elementary Experimental Chemistry, by A. E. Dunstan.
 Third and Fourth Years . A Senior Experimental Chemistry, by A. E. Dunstan.
 Fifth Year A Practical Chemistry for Technical Institutes, by A. E. Dunstan and F. B. Thole ; and
 A First Year Course of Organic Chemistry, by A. E. Dunstan.

Organic

- A First Year Course of Organic Chemistry.** By A. E. DUNSTAN, D.Sc. With 2 Plates and many Diagrams. Crown 8vo, 2s. 6d.
 [*Textbooks of Science.*]

This book, which has not been prepared to meet the requirements of any particular examining body, is intended for the use of the higher forms of schools taking the Special Science Course, and as a first-year textbook in Technical Institutes. The author does not follow the conventional separation of Organic Chemistry into the two *ipso facto* inseparable domains of Aliphatic and Aromatic compounds, but endeavours to give a bird's-eye view of the more prominent features in the Science.

- A Second Year Course of Organic Chemistry.** By F. B. THOLE, B.Sc., Lecturer in Organic Chemistry, East Ham Technical College. With Plates and Diagrams. Crown 8vo, 2s. 6d.
 [*Textbooks of Science.*]

This book forms Vol. II. of a series designed to meet the requirements of students in technical institutes. It deals with that portion of the subject necessary for the second year student, and covers the syllabus for Stage II. of the examination held by the Board of Education. It is hoped, however, that it will be found useful for those students taking the first year of their B.Sc. Course.

The book contains an account of the properties of the carbo-cyclic compounds, their general synthesis, and their utilisation for industrial and scientific purposes. Questions of constitution and the chief reactions associated with this class of compound are fully discussed and carefully explained.

- A Third Year Course of Organic Chemistry.** By T. P. HILDITCH, D.Sc.(Lond.), F.I.C., Author of "A Concise History of Chemistry." With Plates and Diagrams. Crown 8vo, 6s. [*Textbooks of Science.*]

This book completes the course of organic chemistry whose earlier stages have been dealt with by Dr. Dunstan (Part I.) and Mr. Thole (Part II.). It is occupied for the most part with the systematic study of the different groups of heterocyclic compounds, especially those of practical or commercial value. The alkaloids, purines, and other cyclic urea derivatives, and numerous important dyestuffs fall within the scope of these chapters. The remainder of the book deals with the polypeptides, the terpenes, and some general problems such as the characteristics of residual affinity. The work is suited to the needs of honours students in this subject, either for the B.Sc. or the Board of Education examinations.

Qualitative Organic Analysis. By F. B. THOLE, B.Sc. With an Introduction by A. E. DUNSTAN, D.Sc. Crown 8vo, 1s. 6d.

[*Textbooks of Science.*

This book is reprinted, with additions, from the authors' "Practical Chemistry for Technical Institutes" in such a form as to be self-contained. It deals with Organic Qualitative Analysis, both of simple compounds and mixtures. A large range of organic derivatives is dealt with, and the author confidently believes that the scheme will carry a student through the Organic Section of his Honours Degree Course.

A complete list of melting and boiling points is given, the substances being classified into their groups. Throughout conciseness and compactness have been aimed at, so that the student will have the information needed always at hand in an accessible form.

Modern Research in Organic Chemistry. By F. G. POPE, B.Sc. (Lond.), F.C.S. With 261 Diagrams. Crown 8vo, 7s. 6d.

[*Textbooks of Science.*

This volume is an attempt to bring, in a concise form, the development of some of the more important branches of organic chemistry before the chemical student. The results of the most recent research work are embodied in the text, and a bibliography is given at the end of each chapter, so that the student may be able to make use of current literature.

Physical

A First Year Physical Chemistry. By T. P. HILDITCH, D.Sc. (Lond.), F.I.C. Crown 8vo, 2s.

[*Textbooks of Science.*

An attempt to render this branch of chemistry more easy to those commencing its study. The more elementary outlines of the subject are treated, as far as possible, from the standpoint of practical use in solving chemical problems; accordingly, the first part of the book is devoted to characteristic properties such as density or refractivity. Later chapters include introductions to the physico-chemical theories of gases and of solutions and the more important applications of these theories to pure chemistry. The book should prove useful to Inter. B.Sc. and Final (Pass) B.Sc. candidates, as well as those taking Board of Education examinations.

Outlines of Physical Chemistry. By GEORGE SENTER, D.Sc., Ph.D., Lecturer in Chemistry at St. Mary's Hospital Medical School. With many Diagrams. Fourth Edition, Revised and Enlarged. 5s.

[*Textbooks of Science.*

This book is designed to serve as a general introduction to Physical Chemistry, and is specially adapted to the needs of electrical engineers, to whom an acquaintance with the general principles of this subject is becoming of increasing importance. Particular attention is devoted to the theory of solutions and to the modern developments of electro-chemistry. Only an elementary knowledge of mathematics is assumed.

Physico-Chemical Calculations. By JOSEPH KNOX, D.Sc., Lecturer on Inorganic Chemistry, Aberdeen University. Crown 8vo, 2s. 6d.

[*Textbooks of Science.*

This book is intended for students of physical chemistry, as a supplement to the theoretical matter of lectures and textbooks. Here the theory is applied to the solution of practical problems. The book contains eleven chapters, dealing with the main subdivisions of physical chemistry. Each chapter consists of a short introduction dealing with the theory required for the solution of the problems, a series of typical problems with complete solutions, and a list of problems for solution with answers. Practically all the problems have been taken from the original literature of the subject, and by a careful study of the solved problems the student should learn much. The large collection of problems for solution should prove useful to teachers.

General Science

Elementary Experimental Science. **Physics** by W. T. CLOUGH, A.R.C.S., Head of the Physics and Electrical Engineering Department, East Ham Technical College; **Chemistry** by A. E. DUNSTAN, D.Sc. With 2 Plates and 154 Diagrams. Thirteenth Edition. Crown 8vo, 2s. 6d. [*Junior School Books.*]

This book is primarily intended for the use of candidates taking Experimental Science in the Junior Local Examinations. It will also be found of use to those competing for County Council Intermediate Scholarships, and as a general textbook in Science Schools. The great majority of the Diagrams have been specially drawn.

Practical Science for Engineering Students. By H. STANLEY, B.Sc., London and Bristol; F.I.C. Lecturer in the Merchant Venturers' Technical College, Bristol. Crown 8vo, 3s.

This book is intended for Technical School "Course" students in the earlier part of their training, and for use in Trade Schools. It contains a series of experiments in Heat, Mechanics, and in Magnetism and Electricity, together with some general experiments embodying important principles. Theoretical notes are appended where opportune, and there is a set of examples at the end of each section.

Elementary Science for Pupil Teachers. **Physics Section** by W. T. CLOUGH; **Chemistry Section** by A. E. DUNSTAN. With many Illustrations. Crown 8vo, 2s. [*Textbooks of Science.*]

A textbook to meet the new requirements of the Elementary Science section of the Preliminary Examination for the Certificate on the same lines as above.

General Elementary Science. By J. T. DUNN, D.Sc., and V. A. MUNDELLA, Principal of Sunderland Technical College. With 114 Illustrations. Second Edition, Revised. Crown 8vo, 3s. 6d.

An intermediate course in Physics and Chemistry for London Matriculation. It is the textbook adopted by the Admiralty for Elementary Science at Greenwich College.

The World of Science. By R. ELLIOTT STEEL, M.A., F.C.S., Science Master at Sherborne School. With 147 Illustrations. Second Edition. Crown 8vo, 2s. 6d.

An elementary account of Chemistry, Heat, Light, Sound, Magnetism, Electricity, Botany, Zoology, Physiology, Astronomy, and Geology written in an interesting manner for children.

Geology

The Scientific Study of Scenery. By J. E. MARR, F.R.S., Fellow of St. John's College, Cambridge. Fourth Edition. Illustrated. Crown 8vo, 6s.

An elementary treatise on geomorphology for geographers. As far as possible technical terms have been avoided to render it intelligible to the general reader who wishes to obtain some notion of the laws which have controlled the production of the earth's principal scenic features.

Agricultural Geology. By J. E. MARR, F.R.S. Illustrated. Crown 8vo, 6s.

A textbook of geology for agricultural students, more especially such as are preparing for the International Diploma in agriculture.

Physics

First Year Physics. By C. E. JACKSON. With 51 Illustrations. Second Edition. Crown 8vo, 1s. 6d. [*Textbooks of Science.*]

This book deals with such subjects as may reasonably be included in a first year course of Physics for Secondary Schools,—the processes of measurement and the elementary principles of Hydrostatics and Mechanics.

Examples in Physics. By C. E. JACKSON, M.A., Senior Physics Master at Bradford Grammar School. Third Edition. Crown 8vo, 2s. 6d. [*Textbooks of Science.*]

A collection of over one thousand original problems on Mensuration, Hydrostatics, Mechanics, Heat, Light, Magnetism, Frictional Electricity, Current Electricity and Sound, covering the average Physics course in Secondary Schools.

Elementary Practical Physics. By HENRY STROUD, D.Sc., M.A., Professor of Physics, Armstrong College, Newcastle-on-Tyne. With Diagrams. Third Edition. Crown 8vo, 4s. 6d.

An introduction to practical work in a Physical Laboratory and the standard works on the subject.

The Principles of Magnetism and Electricity. By P. L. GRAY, B.Sc. An Elementary Textbook. With 181 Diagrams. Crown 8vo, 3s. 6d.

Although not written to any special syllabus, the book will approximately cover the requirements of the Advanced Stage of the Board of Education Examination, and London B.Sc. Pass Examination. It is well illustrated with sketches such as a student may, with a little practice, draw for himself from the actual apparatus.

Examples in Elementary Mechanics, Practical, Graphical, and Theoretical. By W. J. DOBBS, M.A. With 52 Diagrams. Crown 8vo, 5s. [*Textbooks of Science.*]

This book is intended for use at Schools and Technical Institutes, for Army and Navy Candidates and Students of Engineering. It consists of some 1400 examples in Elementary Statics and Kinetics exhibiting the latest development in the methods of teaching these subjects. But it is something more than a mere collection of examples, being designed for use without an accompanying textbook. The preparation and use of simple inexpensive apparatus is described, and the numerous practical examples requiring the use of such apparatus have been found to give satisfactory results.

Weighing and Measuring. A Short Course of Practical Exercises in Elementary Mathematics and Physics, by W. J. DOBBS, M.A., Assistant Master at Oundle School. With 47 Diagrams. Crown 8vo, 2s.

Contents. I. Measurement of Length; II. Weighing; III. Measurement of Area; IV. Measurement of Volume; V. Density and Specific Gravity.

This volume covers that common ground between Elementary Mathematics and Physics which is necessary to give reality to the former, and which is indispensable before taking up any serious study of the latter. By common consent, a course of Weighing and Measuring is now an essential part of school training in Elementary Mathematics. Care has been taken to keep the scope of the book well within the reach of the great majority of senior school children of both sexes.

Practical Mechanics. By SIDNEY H. WELLS Wh.Sc., A.M. Inst.C.E., late Principal of the Battersea Polytechnic, London. An Elementary Manual for the use of Students in Science and Technical Schools and Classes. With 75 Illustrations and Diagrams. Sixth Edition. Crown 8vo, 3s. 6d. [*Textbooks of Science.*]

A laboratory handbook containing all the mechanics part of the elementary science syllabus of the Headmasters' Association and the London Matriculation.

A Handbook of Physics. By W. II. WHITE, M.A., B.Sc., A.R.C.Sc., Lecturer at the East London College and St. Mary's Hospital Medical School, Examiner in the University of London, etc. With over 300 Diagrams. Crown 8vo, 7s. 6d. [*Textbooks of Science.*]

The book traces the establishment of the Principles of Physics and draws from modern everyday life abundant instances of their application, instead

of giving detailed descriptions of time-honoured experiments. It amply covers the ground of the "Intermediate" examinations of London and other British Universities. Paragraphs are marked to facilitate its use by medical students, and some prominence is given to physiological matters.

Physics Examination Papers. By R. ELLIOTT STEEL, M.A., Science Master at Sherborne School. Crown 8vo, 2s. 6d.

[*School Examination Series.*

Papers on Sound, Light, Heat, Magnetism, and Electricity. Both book-work and problems are included.

TECHNOLOGY

(See also under "Domestic Science")

A Woodwork Class-Book. Beginner's Course. By H. HEY, Inspector of Day Manual and of Technological Classes, Surrey Education Committee, and G. H. ROSE, Headmaster, Coulsdon Council School, City and Guilds Woodwork Teacher. With full Diagrams and Photographs. 4to, 2s.

This class-book is the first of a series of three, in which the work is arranged on a threefold plan of Correlated Lessons in Drawing, Tools and Materials, and School Workshop Practice. The schemes have been approved by the Board of Education.

Manual Training Drawing (Woodwork). Its Principles and Application, with Solutions to Examination Questions, 1892-1905, Orthographic, Isometric, and Oblique Projection. By F. STURCH, Staff Instructor to the Surrey County Council. With 50 Plates and 140 Figures. Fcap., 5s. net.

A guide to the Examinations in Manual Training Woodwork of the City and Guilds of London Institute, the Board of Examinations for Educational Handwork, and the Examinations of the N. U. T., and for use in Secondary Schools and Training Colleges. It deals with the requirements in Geometrical and Mechanical Drawing of the Educational Department, University of London, London Chamber of Commerce, etc.

Carpentry and Joinery. By F. C. WEBBER, Chief Lecturer to the Building Trades Department of the Merchant Venturers' Technical College at Bristol. With 176 Illustrations. Sixth Edition. Crown 8vo, 3s. 6d.

[*Textbooks of Technology.*

An elementary textbook suitable for the Preliminary Grade of the City and Guilds of London Institute and as a book of reference for the apprentice.

Builders' Quantities. By H. C. GRUBB, Lecturer at Beckenham Technical Institute. With numerous Diagrams. Second Edition, Revised. Crown 8vo, 4s. 6d.

[*Textbooks of Technology.*

This treatise has been compiled to assist students who are preparing for the examination in Builders' Quantities, held by the City and Guilds of London Institute; while those studying for other examinations, such as Honours Building Construction, held by the Board of Education, etc., will find it covers that portion of the syllabus relating to Quantities.

Engineering Workshop Practice. By CHARLES C. ALLEN, Head of the Department of Engineering, Technical Institute, Auckland. With 152 Illustrations. Second Edition. Crown 8vo, 3s. 6d.

[*Textbooks of Technology.*

This deals with the manufacturing operations employed in modern workshops, and is intended chiefly for students who have opportunities of both examining and using the machines and tools required.

Répoûssé Metal Work. By A. C. HORTH. With Diagrams and 8 Plates. Crown 8vo, 2s. 6d. [*Textbooks of Technology.*]

This book provides students with a graded scheme of Sheet Metal Work for Schools, containing all the information necessary to those wishing to become expert.

Electric Light and Power. By E. E. BROOKS, B.Sc.(Lond.), Head of the Department of Physics and Electrical Engineering, Leicester Municipal Technical School, and W. H. N. JAMES, A.R.C.S., A.M.I.E.E., Lecturer in Electrical Engineering, Municipal School of Technology, Manchester. With 17 Plates and 230 Illustrations. Third Edition, Revised. Crown 8vo, 4s. 6d. [*Textbooks of Technology.*]

This work is an introduction to the study of Electrical Engineering, no previous knowledge being assumed, and very little mathematics being required. It is intended mainly for students employed in electrical industries.

An Introduction to the Study of Textile Design. By ALDRED F. BARKER, Head of the Textile Department, Bradford Technical College. With numerous Illustrations and Diagrams. Demy 8vo, 7s. 6d. [*Textbooks of Technology.*]

This work includes within its pages the information which the student of Textile Design should seek to thoroughly master during the first two years he attends the Textile School.

A Textbook dealing with Ornamental Design for Woven Fabrics. By C. STEPHENSON, of the Bradford Technical College, and F. SUDDARDS, of the Yorkshire College, Leeds. With 66 Full-page Plates and numerous Diagrams in the Text. Third Edition. Demy 8vo, 7s. 6d.

The subject-matter is arranged as far as possible in progressive order, and always with due regard to the practical application of ornament to the weaving process. Several chapters are devoted to the various methods of building up all-over repeating patterns.

Gas Testing and Air Measurement: A Manual for Deputies, Miners, etc. By CHARLES CHANDLEY, M.Inst.M.E. (of Nottingham). Fcap. 8vo, 1s. 6d.

This book gives in concise form the requirements of the Coal Mines Act, 1911, and of the Home Office in respect of what is commonly known as the "Fireman's" or "Deputy's" Certificate. The theory and practice of gas detection by the safety lamp are dealt with in detail. The methods of finding the velocities of air currents, and the areas of the various shapes of roadways, etc., ordinarily met with in mines are worked out with the aid of numerous figures. Little previous knowledge of the subjects is assumed throughout.

MESSRS. METHUEN'S SERIES

Particulars of the following Books will be found in the First Section of this Catalogue, under the Subjects. Further Series will be found under the Subjects, namely, Simplified French Texts, p. 12; Advanced French Texts, p. 13; New Geographical Series, p. 14; Simplified German Texts, p. 16; School County Histories, p. 21; Six Ages of European History, p. 24; Simplified Latin Texts, p. 29; Methuen's Nature Books, p. 32.

The Beginner's Books

EDITED BY W. WILLIAMSON, B.A., F.R.S.L.

A series of elementary class books for beginners of seven to twelve years, or thereabouts. They are adapted to the needs of preparatory schools, and are suitable for the use of candidates preparing for the Oxford and Cambridge Preliminary Local and the College of Preceptors Examinations. The series will be especially useful to lead up to Methuen's Junior School Books. The author of each book has had considerable experience in teaching the subject, while special attention has been paid to the arrangement of the type and matter, which is as clear and concise as possible. The books are beautifully printed and strongly bound.

The Beginner's Books—*continued*

- | | |
|---|---|
| <p>Easy French Rhymes. H. BLOUET. 1s.</p> <p>Easy Stories from English History. E. M. WILMOT-BUXTON. 1s.</p> <p>Stories from Roman History. E. M. WILMOT-BUXTON. 1s. 6d.</p> <p>Stories from the Old Testament. E. M. WILMOT-BUXTON. 1s. 6d.</p> <p>Stories from the New Testament. E. M. WILMOT-BUXTON. 1s. 6d.</p> | <p>A First Course in English. W. S. BEARD. 1s. 6d</p> <p>A First History of Greece. E. E. FIRTH. 1s. 6d.</p> <p>Easy Exercises in Arithmetic. W. S. BEARD. Without Answers, 1s.; With Answers, 1s. 3d.</p> <p>Easy Dictation and Spelling. W. WILLIAMSON. 1s.</p> <p>An Easy Poetry Book. W. WILLIAMSON. 1s.</p> |
|---|---|

Classical Translations

EDITED BY H. F. FOX, M.A., FELLOW AND TUTOR OF BRASENOSE COLLEGE, OXFORD.

Crown 8vo

A series of Translations from the Greek and Latin Classics, distinguished by literary excellence as well as by scholarly accuracy.

- | | |
|--|--|
| <p>Æschylus — AGAMEMNON, CHOPHOROS, EUMENIDES. Translated by L. CAMPBELL. 5s.</p> <p>Cicero — DE ORATORE I. Translated by E. N. P. MOOR. 3s. 6d.</p> <p>Cicero — SELECT ORATIONS. Translated by H. E. D. BLAKISTON. 5s.</p> <p>Cicero — DE NATURA DEORUM. Translated by F. BROOKS. 3s. 6d.</p> <p>Cicero — DE OFFICIIS. Translated by G. B. GARDINER. 2s. 6d.</p> | <p>Horace — THE ODES AND EPODES. Translated by A. D. GODLEY. 2s.</p> <p>Lucian — SIX DIALOGUES. Translated by S. T. IRWIN. 3s. 6d.</p> <p>Sophocles — AJAX AND ELECTRA. Translated by E. D. MORSHEAD. 2s. 6d.</p> <p>Tacitus — AGRICOLA and GERMANIA. Translated by R. B. TOWNSEND. 2s. 6d.</p> <p>Thirteen Satires of Juvenal. Translated by S. G. OWEN. 2s. 6d.</p> |
|--|--|

Commercial Series

EDITED BY H. DE B. GIBBINS, LITT.D., M.A.

Crown 8vo

A series intended to assist students and young men preparing for a commercial career, by supplying useful handbooks of a clear and practical character, dealing with those subjects which are absolutely essential in the business life.

- | | |
|--|--|
| <p>The Principles of Book-keeping by Double Entry. J. E. B. M'ALLEN. 2s.</p> <p>French Commercial Correspondence. S. E. BALLY. 2s.</p> <p>German Commercial Correspondence. S. E. BALLY. 2s. 6d.</p> <p>A German Commercial Reader. S. E. BALLY. 2s.</p> <p>A Commercial Geography of Foreign Nations. F. C. BOON. 2s.</p> <p>Commercial Law. W. D. EDWARDS. 2s.</p> <p>British Commerce and Colonies from Elizabeth to Victoria. H. DE B. GIBBINS. 2s.</p> | <p>The Economics of Commerce. H. DE B. GIBBINS. 1s. 6d.</p> <p>Commercial Examination Papers. H. DE B. GIBBINS. 1s. 6d.</p> <p>A Primer of Business. S. JACKSON. New and Revised Edition. 1s. 6d.</p> <p>An Entrance Guide to Professions and Business. H. JONES. 1s. 6d.</p> <p>A Commercial Geography of the British Empire. L. W. LUYDE. 2s.</p> <p>A Short Commercial Arithmetic. F. G. TAYLOR. 1s. 6d.</p> <p>Précis Writing and Office Correspondence. E. E. WHITFIELD. 2s.</p> |
|--|--|

Junior Examination Series

EDITED BY A. M. M. STEDMAN, M.A.

Fcap. 8vo, 1s.

This series is intended to lead up to the School Examination Series, and is for the use of teachers and pupils in Lower and Middle Forms, to supply material for the former and practice for the latter. The papers are carefully graduated, cover the whole of the subject usually taught, and are intended to form part of the ordinary class work. They may be used *visà voce* or as a written examination.

Junior Scripture Examination

Papers: Old Testament. Rev. S. A. P. KERMODE and Rev. W. WILLIAMSON.

Junior French Examination

Papers. F. JACOB.

Junior English Examination

Papers. W. WILLIAMSON.

Junior Arithmetic Examination

Papers. W. S. BEARD.

Junior Algebra Examination

Papers. S. W. FINN.

Junior Greek Examination

Papers. T. C. WEATHERHEAD.

Junior Latin Examination

Papers. C. G. BOTTING.

A Key to the above. 3s. 6d. net.

Junior General Information

Examination Papers. W. S.

BEARD.

A Key to the above. 3s. 6d. net.

Junior Geography Examination

Papers. W. G. BAKER.

Junior German Examination

Papers. A. VORGELIN.

Junior History Examination

Papers. W. O. P. DAVIES.

Junior School Books

EDITED BY O. D. INSKIP, LL.D., AND W. WILLIAMSON, B.A.

A series of school class books. They are adapted to the needs of the Lower and Middle Forms of the Public Schools, and are suitable for the use of candidates preparing for the Oxford and Cambridge Junior Local Examinations.

A Class-Book of Dictation

Passages. W. WILLIAMSON. 1s. 6d.

The First Book of Kings.

A. E. RUBIE. 2s.

The Gospel according to St. Matthew.

Edited by E. W. SOUTH. 1s. 6d.

The Gospel according to St. Mark.

Edited by A. E. RUBIE. 1s. 6d.

The Gospel according to St. Luke.

Edited by W. WILLIAMSON. 2s.

The Acts of the Apostles.

Edited by A. E. RUBIE. 2s.

A Junior English Grammar.

W. WILLIAMSON. 2s.

A Junior Greek History.

W. H. SPRAGGE. 2s. 6d.

A Junior Latin Prose.

H. N. ASMAN. 2s. 6d.

A Junior German Grammar.

H. C. A. SECKLER. 2s. 6d.

Elementary Experimental

Science. Physics by W. T.

CLOUGH; **Chemistry** by A. E.

DUNSTAN. 2s. 6d.

Elementary Experimental

Chemistry. A. E. DUNSTAN. 2s.

A Junior Chemistry.

E. A. TYLER. 2s. 6d.

A Junior French Grammar.

L. A. SORNET and M. J. ACATOS. 2s.

A Junior French Prose.

R. N. BARON. 2s.

A Junior Geometry.

N. S. LYDON. 2s.

A School Latin Grammar.

H. G. FORD. 2s. 6d.

English Literature for Schools.

E. E. FIRTH. 2s. 6d.

Methuen's Historical Readers

Illustrated. Crown 8vo.

This is a new series of History Readers on concentric lines.

The Pageant of British History. By E. M. WILMOT-BUXTON, F.R.Hist.S. 1s. 6d.

The Romance of British History; or, Britain's Rise from Savagery to Civilization. By JOSIAH TURNER. 1s. 6d.

The Growth of Modern Britain. An Outline History of the British People from 1820 to 1910. By B. H. SUTTON. 2s.

Methuen's New Historical Series

EDITED BY THE REV. H. N. ASMAN, M.A., B.D.

These are the first volumes of a new historical series for Schools under the General Editorship of the Rev. H. N. ASMAN, M.A., B.D., Second Master of Owen's School, Islington. The series is on the lines of the recent Circular of the Board of Education on the teaching of history.

A History of England for Schools. In Three Volumes. Crown 8vo, 2s. 6d. each. Vol. I., to 1485. By H. J. CAPPE, M.A. Vol. II., 1485-1714. By L. OLDERSHAW, M.A. Vol. III., 1714-1910. By E. BOWYER, B.A.

Stories from Ancient History. By E. BOWYER, B.A., B.Sc., Assistant Master Owen's School. Crown 8vo, 1s. 6d.

Stories from Modern History. By E. M. WILMOT-BUXTON, F.R.Hist.S. Crown 8vo, 1s. 6d.

School Examination Series

EDITED BY A. M. M. STEDMAN, M.A.

Crown 8vo, 2s. 6d.

These books are intended for the use of teachers and students—to supply material for the former, and practice for the latter. The papers are carefully graduated, cover the whole of the subject usually taught, and are intended to form part of the ordinary class work.

French Examination Papers. A. M. M. STEDMAN. Key. 6s. net.

Latin Examination Papers. A. M. M. STEDMAN. Key. 6s. net.

Greek Examination Papers. A. M. M. STEDMAN. Key. 6s. net.

German Examination Papers. R. J. MORICH. Key. 6s. net.

History and Geography Examination Papers. C. H. SPENCE.

Physics Examination Papers. R. E. STEEL.

General Knowledge Examina-

tion Papers. A. M. M. STEDMAN. Key. 7s. net.

Examination Papers in English History. J. TAIT WARDLAW.

Trigonometry Examination Papers. Rev. G. W. WARD, M.A. Key. 5s. net.

Exercises and Examination Papers in Arithmetic, Logarithms, and Mensuration. C. PENDLEBURY, M.A. Key. 5s. net.

Examination Papers in Book-keeping. J. T. MEDHURST. 3s. Key, 2s. 6d. net.

Stories from the Histories

EDITED BY E. M. WILMOT-BUXTON, F.R.Hist.Soc.

With a Map. Crown 8vo, 1s. 6d. each

This series will embrace the history of all the chief countries of the world. It is hoped that by supplying a series of interesting stories these volumes will promote a desire for a more detailed knowledge and remove the general complaint that English children grow up ignorant of the great events and characters in the history of other nations. The first volumes are:—

Tales from Irish History. A. BIRKHEAD, B.A.

Stories from Scottish History. E. M. WILMOT-BUXTON.

Stories from French History. TAYLOR DYSON, M.A.

Stories from American History. ALICE BIRKHEAD.

Stories from the Great Writers

EDITED BY E. M. WILMOT-BUXTON, F.R.Hist.Soc.

Crown 8vo, 1s. 6d. each

In this series incidents have been selected from the works of the best writers and abridged or retold to make them appeal to children. It is hoped that these stories will kindle a love for the works of the best writers and stimulate children to read, after schooldays, the originals and others by these authors. The first volumes are:—

Stories from Dickens. JOYCE COBB. | **Stories from Chaucer.** ADA HALES. | **Stories from Bunyan.** EDITH L. ELIAS.

Stories from Old Romance

EDITED BY E. M. WILMOT-BUXTON, F.R.Hist.Soc.

Crown 8vo, 1s. 6d. each

These volumes will serve as an introduction to world literature as well as form literary readers that will appeal to children between the ages of eight and twelve in all classes of schools. They will also be found suitable gift-books for all young lovers of stirring romance and tales of chivalry. The first volumes are:—

Stories from Old French Romance. E. M. WILMOT-BUXTON. | **Stories from Old English Romance.** JOYCE POLLARD. | **Stories from Old Italian Romance.** SUSAN CUNNINGTON.

Textbooks of Science

Fully Illustrated. Crown 8vo

A series of textbooks for Secondary Schools and Schools of Science

- | | |
|---|---|
| <p>A Preliminary Physiology. W. NARRAMORE. 3s. 6d.</p> <p>Plant Life. H. F. JONES. 3s. 6d.</p> <p>A Concise History of Chemistry. T. P. HILDITCH. 2s. 6d.</p> <p>Elementary Chemical Theory. J. M. WADMORE. 3s. 6d.</p> <p>A Textbook of Inorganic Chemistry. G. SENTER. 6s. 6d.</p> <p>The Complete School Chemistry. F. M. OLDHAM. 4s. 6d.</p> <p>Practical Chemistry. Part I. W. FRENCH. 1s. 6d.</p> <p>Practical Chemistry. Part II. W. FRENCH and T. H. BOARDMAN. 1s. 6d.</p> <p>A Senior Experimental Chemistry. A. E. DUNSTAN. 3s. 6d.</p> <p>A Textbook of Practical Chemistry for Technical Institutes. A. E. DUNSTAN and F. B. THOLE. 3s. 6d.</p> <p>An Introduction to Quantitative Analysis. S. J. M. AULD. 5s.</p> <p>A First Year Course of Organic Chemistry. A. E. DUNSTAN. 2s. 6d.</p> <p>A Second Year Course of Organic Chemistry. F. B. THOLE. 2s. 6d.</p> | <p>A Third Year Course of Organic Chemistry. T. P. HILDITCH. 6s.</p> <p>Qualitative Organic Analysis. F. B. THOLE. 1s. 6d.</p> <p>Modern Research in Organic Chemistry. F. G. POPE. 7s. 6d.</p> <p>A First Year Physical Chemistry. T. P. HILDITCH. 2s.</p> <p>Outlines of Physical Chemistry. G. SENTER. New Edition. 5s.</p> <p>Physico-Chemical Calculations. J. KNOX. 2s. 6d.</p> <p>Elementary Science for Pupil Teachers. W. T. CLOUGH and A. E. DUNSTAN. 2s.</p> <p>Examples in Physics. C. E. JACKSON. 2s. 6d.</p> <p>First Year Physics. C. E. JACKSON. 1s. 6d.</p> <p>Examples in Elementary Mechanics. W. J. DOBBS. 5s.</p> <p>Practical Mechanics. S. H. WELLS. 3s. 6d.</p> <p>A Handbook of Physics. W. H. WHITE. 7s. 6d.</p> <p>Technical Arithmetic and Geometry. C. T. MILLIS. 3s. 6d.</p> |
|---|---|

Textbooks of Technology

Fully Illustrated. Crown 8vo

How to Make a Dress. J. A. E. WOOD. 1s. 6d.	Builders' Quantities. I. C. GRUBB. 4s. 6d.
Carpentry and Joinery. F. C. WEBBER. 3s. 6d.	Réposé Metal Work. A. C. HORTH. 2s. 6d.
Millinery, Theoretical and Practical. C. HILL. 2s.	Electric Light and Power. E. E. BROOKS and W. H. N. JAMES. 4s. 6d.
Instruction in Cookery. A. P. THOMPSON. 2s. 6d.	Engineering Workshop Practice. C. C. ALLEN. 3s. 6d.
An Introduction to the Study of Textile Design. A. F. BARKER. Demy 8vo, 7s. 6d.	

A History of England

IN SEVEN VOLUMES

Edited by CHARLES OMAN, M.A.

With Maps. Demy 8vo, 10s. 6d. net, each Volume

- I. **England before the Norman Conquest.** By CHARLES OMAN, M.A., Fellow of All Souls', Chichele Professor of Modern History at Oxford. Third Edition, Revised.
- II. **England under the Normans and Angevins (1066-1272).** By H. W. C. DAVIS, Fellow and Tutor of Balliol College, sometime Fellow of All Souls', Author of "Charlemagne." Third Edition.
- III. **England in the Later Middle Ages (1272-1485).** By KENNETH H. VICKERS, M.A., Professor of Modern History in the University of Durham.
- IV. **England under the Tudors (1485-1603).** By ARTHUR D. INNES. Fourth Edition.
- V. **England under the Stuarts (1603-1714).** By G. M. TREVELYAN, late Fellow of Trinity College, Cambridge. Fifth Edition.
- VI. **England under the Hanoverians (1714-1815).** By C. GRANT ROBERTSON, Fellow of All Souls', Tutor in Modern History to Magdalen College, Examiner in the School of Modern History in the University of Oxford. Second Edition.
- VII. **England since Waterloo (1815-1900).** By J. A. R. MARRIOTT, Lecturer and Tutor in Modern History and Economics at Worcester College, Oxford.

