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Bunge

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TEXT-BOOK
OF
ORGANIC CHEMISTRY
FOR
MEDICAL STUDENTS

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R. H. ADERS PLIMMER, D.Sc.

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TEXT-BOOK
OF
ORGANIC CHEMISTRY
FOR
MEDICAL STUDENTS

BY
DR. G. v. BUNGE
PROFESSOR OF PHYSIOLOGICAL CHEMISTRY IN THE
UNIVERSITY OF BASEL

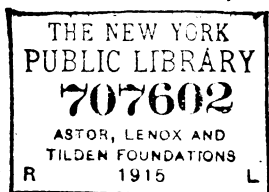
TRANSLATED WITH ADDITIONS
BY
R. H. ADERS PLIMMER, D.Sc. (LOND.)

ASSISTANT-PROFESSOR OF PHYSIOLOGICAL CHEMISTRY
AND FELLOW OF UNIVERSITY COLLEGE, LONDON

NEW IMPRESSION

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PREFACE

THE domain of organic chemistry has been widened to such an enormous extent by the unceasing labours of the last decades, that even those who devote their life to the study of this science can no longer be masters of the whole subject. The medical student, however, is compelled to acquire some knowledge of all the branches of organic chemistry, for there is scarcely a chapter of the subject which has not already found application in Physiology, Pathology, Pharmacology, Hygiene, etc.

It is quite impossible for the student of Medicine to find out for himself what is for him important and essential amongst the immense mass of chemical facts at his disposal. The necessity has therefore arisen for treating the rudiments of organic chemistry in a manner especially adapted to the requirements of medical students, and it is with this object that I have written the present lectures. I have tried to select, and to call special attention to, those things which are most important, and at the same time to point out in which branch of Medicine these selected facts of organic chemistry have found application.

During my thirty years' experience of teaching I have seen that the majority of medical students are not in the position to assimilate even the most important results in organic chemistry from our present text-books, and I have therefore endeavoured to put the

matter into such form that the beginner will not be wearied or lose his interest. If, however, his interest be once awakened by such a very incomplete text-book, these deficiencies can be gradually filled in by repeated references to the more detailed epitomes. My lectures are not intended in any way to supplant those valuable and complete text-books on organic chemistry which we at present possess.

G. v. BUNGE.

BASEL: *February* 1906.

WHO WAS
DUBOIS
VIA BELL

TRANSLATOR'S PREFACE

SUFFICIENT apology for the appearance of another text-book on organic chemistry has been given by Professor Bunge in his Preface, and the same reasons should also suffice for this introduction of his book to English medical students. The subject has been presented by the author in such a new and interesting manner, that it seemed to me that his book would appeal to English as much as it has done to German students; if their interest in the subject be once aroused, the problems in biological chemistry which offer themselves will be no longer altogether devoid of meaning, since the facts brought forward are here set forth in their direct relationship to Physiology, Pathology, and Medicine. Physiological chemistry is really a branch of organic chemistry, and if the latter term were not exclusively used, as it is nowadays, for the chemistry of the carbon compounds, the term organic chemistry would still comprise, as it did before 1828 when Woehler synthesised urea, those chemical compounds which are found in animals and plants, their mode of formation, and their interactions—i.e. the subjects with which physiological chemistry now deals. Many, perhaps all, of the processes, as they occur in the animal and vegetable tissues, may follow lines identical with those produced by the chemist in the laboratory, and it is only by means of a knowledge of the chemistry of the carbon compounds that their relationship to one another in nature can be determined. The one is chemists' chemistry with organic substances, the other Nature's chemistry with the same substances. This knowledge of the chemistry of carbon compounds is essential to any further discoveries in the methods and processes of Nature's chemistry.

As the requirements of English medical students are somewhat

more extended than those of German students, several additions have been found necessary. These are indicated by the use of square brackets, in order that Prof. Bunge's work should be clearly visible. A few minor alterations have also been made with the view of better conforming to a more logical chemical arrangement—e.g. the chemistry of acetone has been removed from Lecture 4 to Lecture 5; Lecture 6 has been subdivided into two parts, and the glucosides removed from Lecture 15 to Lecture 9, with the consequent alteration of the subsequent lecture numbers. Chemists usually describe the glucosides with the carbohydrates, and this is especially necessary in connection with the modern work on the carbohydrates. The phenylhydrazine derivatives of the sugars have also been removed from the aromatic series to the chapter on the carbohydrates. Further, adrenaline has been placed at the end of Lecture 13 instead of Lecture 16, since it is, in reality, an aromatic compound and does not belong to the group of the alkaloids, in conjunction with which it was described. Again, in the chemistry of the proteins minor alterations have been made in order to conform to the new nomenclature as recommended by the Physiological and Chemical Societies; it was also desirable to briefly mention the work of E. Fischer on the synthesis of the proteins. These alterations do not essentially impair the value of Professor Bunge's book, since his exposition remains unchanged.

It was in the hope that organic chemistry might be brought nearer to physiological chemistry, and that their present wide separation might soon disappear, that I undertook this translation. Whether this hope will be realised remains in the hands of the readers of this excellent book by Professor Bunge.

R. H. ADERS PLIMMER.

UNIVERSITY COLLEGE, LONDON:

August 1907.

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ORGANIC CHEMISTRY

FOR

MEDICAL STUDENTS

LECTURE I

THE RISE OF ORGANIC CHEMISTRY DURING THE LAST DECADES

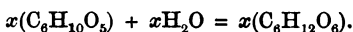
THE compounds of the element carbon constitute the subject of organic chemistry. Organic chemistry was called the chemistry of the carbon compounds, because, until recent times—up to about forty years ago—it was thought that the carbon compounds, with few exceptions, could only be formed in organic beings, whether plant or animal; they were a testimony of vital processes and could never arise outside the organism. The Swedish chemist Berzelius (1779–1848), one of the most distinguished investigators of all times and countries, in 1837 said: ‘In living nature the elements appear to obey laws quite different from those they obey in dead nature; the products of their mutual interactions are quite different in organic from those in inorganic nature, and the discovery of the causes of these differences between the behaviour of the elements in dead nature and in the living body will be the key to the theory of organic chemistry. It is hidden in such a way that we, at any rate at the present time, are entirely without hope of being able to discover it.’¹ And in 1842 Gerhardt (1816–1856), a chemist who made many important advances in organic chemistry, said: ‘The chemist works in a manner quite opposed to that of living nature: he burns, destroys, works by analysis; vital force alone works by synthesis: it reconstructs the edifice destroyed by chemical forces.’² This conception prevailed for nearly

¹ J. J. Berzelius, *Textbook of Chemistry*. Translated into German by F. Woehler. Vol. iv. p. 3. Dresden and Leipzig, 1837.

² Charles Gerhardt, *Compt. rend.* 1842, vol. xv. p. 498.

two decades, since all the attempts made to artificially synthesise compounds of carbon failed. A few compounds, however, could be artificially, but not synthetically, prepared; that is, simpler organic compounds could be prepared from the more complicated ones produced by plants and animals. A larger molecule with a greater number of carbon atoms could be divided into smaller molecules containing fewer atoms of carbon: but it was found impossible to work in the opposite direction. Starting from the elements, or, as in plant life, from simple compounds, such as carbonic acid, water and ammonia, it was not possible to attain to the more complicated ones. An example will make this clear.

Starch is a complicated substance which is very widely distributed in the tissues of plants, and it forms, as is well known, the chief constituent of cereals and potatoes. The size of its molecule is unknown to us; it is some multiple of the complex of atoms $C_6H_{10}O_5$. When boiled with dilute acids the starch molecule is broken up into a number of grape-sugar molecules, with absorption of water:



The sugar then, by oxidation with nitric acid, can be converted into oxalic acid—



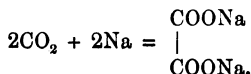
—which, on heating with concentrated sulphuric acid, breaks down into carbonic acid, water and carbon monoxide.

These changes were well known in Gerhardt's time, but the reverse processes could not then be carried out; sugar and oxalic acid could not be prepared from carbonic acid and water, which is what the plant does, but the discoveries in the last four decades of the past century have, however, made this possible. We are at present able to build up, atom by atom, synthetically from their elements, not only oxalic acid and sugar, but also a very large number—which is increasing every year—of other still more complicated compounds, and the possibility of preparing all those remaining, even the most complicated, can no longer be doubted: it is only a question of time.

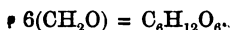
A few examples will show what ways and means, what forces and reagents are employed, by which the attainment of such syntheses has been accomplished.

The synthesis of oxalic acid was effected by Edmund Drechsel

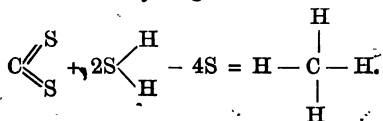
(1843-1897) in the year 1868, when assistant to Kolbe at Leipzig; he passed a current of carbonic acid over molten sodium, and by this simple process obtained sodium oxalate: ¹



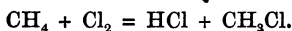
The synthesis of sugar was accomplished in 1861 by the Russian chemist A. Butlerow (1828-1886), who did not, however, start from the elements, but from formaldehyde, that is the aldehyde of formic acid, which in alkaline solution polymerises to certain kinds of sugar: ²



The French chemist Berthelot (1827-1907) was the first to show how this original material, formaldehyde, could be synthesised. He ³ first prepared from its elements the simplest hydrocarbon, marsh gas or methane. Carbon and sulphur combine together at a high temperature to form carbon disulphide, a compound of a constitution analogous to that of carbonic acid, in which the two divalent oxygen atoms are replaced by two divalent sulphur atoms. Carbon disulphide is a liquid which boils at 46° C. If a mixture of the vapours of carbon disulphide and hydrogen sulphide be passed over copper heated to dull redness, the copper takes up the whole of the sulphur, and the two elements carbon and hydrogen, which are set free, combine with one another forming the simplest hydrocarbon, marsh gas, in which the tetravalent carbon atom has its four valencies saturated by four univalent hydrogen atoms:



Marsh gas is a colourless gas. If it be mixed with chlorine and the mixture exposed to diffused daylight, one atom of chlorine combines with one of the hydrogen atoms of the marsh gas forming hydrochloric acid, whilst a second atom of chlorine takes up the position of the hydrogen atom which has been separated: ⁴



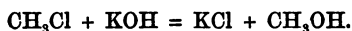
¹ E. Drechsel, *Woehler and Liebig's Ann. d. Chem.* 1868, vol. cxlvi. p. 140.

² A. Butlerow, *Compt. rend.* 1861, vol. liii. p. 145, or *Liebig's Ann. d. Chem.* 1861, vol. cxx. p. 295. See also O. Loew, *Journ. f. prakt. Chem.*, 1896, vol. xxxiii. p. 321, and vol. xxxiv. p. 51; and Emil Fischer, *Ber. d. d. chem. Gesellsch.* 1888, vol. xxi. p. 989.

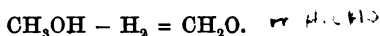
³ M. Berthelot, *Ann. de Chim. et de Phys.* 1858 (iii.), vol. liii. p. 121.

⁴ M. Berthelot, *ibid.* vol. lii. p. 97.

The methyl chloride, or marsh gas in which one of the hydrogen atoms has been replaced by chlorine, which is thus formed, is a gas liquefying at -24°C . When this gas is heated for a long time with caustic potash at 100°C ., potassium chloride is formed, and a hydroxyl group enters the molecule and takes up the position of the chlorine atom in the marsh gas, methyl alcohol being obtained : ¹



Methyl alcohol is a liquid, which boils at 66°C . If its vapour be mixed with air and passed over a heated platinum spiral, the oxygen of the air removes two hydrogen atoms from the alcohol molecule and its aldehyde results : ²



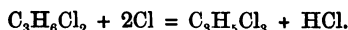
This aldehyde, formaldehyde, is a pungent smelling gas, which is absorbed by water. On shaking its aqueous solution with milk of lime the above-mentioned polymerisation of the aldehyde takes place, and the solution is found to contain several kinds of sugar, which can be isolated and purified by precipitation with phenylhydrazine. (Cf. Lecture 8.)

A second method of building up a molecule of sugar, atom by atom from its elements, consists in first preparing glycerine, which is a simpler but equally important physiological compound, and is a constituent of all the fats of our food and of our tissues.

By passing marsh gas, the synthesis of which has been just described, through a red-hot tube, we obtain, amongst other hydrocarbons, propylene, C_3H_6 , hydrogen being split off : ³



Propylene again is a colourless gas; and if it be passed through a solution of iodine chloride a liquid of the composition $\text{C}_3\text{H}_6\text{ICl}$ is formed : ⁴ on passing a current of chlorine through this liquid in the presence of water the iodine is replaced by chlorine, and the compound propylene dichloride, $\text{C}_3\text{H}_6\text{Cl}_2$, is obtained. When this liquid is sealed up in a tube with iodine chloride and heated to 140°C ., the iodine chloride behaves like nascent chlorine, and a hydrogen atom of the propylene dichloride is substituted by chlorine : ⁵



This propylene, in which three hydrogen atoms have been

¹ Berthelot, *Ann. de Chim. et de Phys.* 1858 (iii.), vol. lii. p. 97.

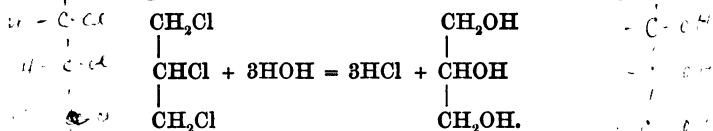
² Aug. Wihl. Hofmann (1818-1892), *Liebig's Ann. d. Chem.* 1868, vol. cxlv. p. 357.

³ Berthelot, *Ann. de Chim. et de Phys.* 1869 (iv.), vol. xvi. p. 148.

⁴ C. Friedel and R. D. Silva, *Compt. rend.* 1873, vol. lxxvi. p. 1596.

⁵ Friedel and Silva, *l.c.*

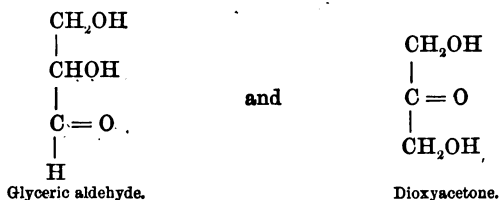
substituted by chlorine, the so-called trichlorhydrin, is separated from other products which are formed at the same time by fractional distillation, and is then heated with water in a sealed tube to 180° C. when three hydroxyl groups take up the positions of the three chlorine atoms, and the aqueous solution is now found to contain glycerine :¹



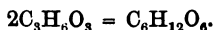
We have thus built up glycerine, one of the most important constituents of all living organisms and of every living cell, from its elements.

These compounds are described in greater detail later, when the reasons for writing their formulæ in this manner will be understood. In this place only an approximate idea of the physical forces and chemical means which are employed in their artificial synthesis can be given.

Glycerine is a syrupy liquid, and when it is warmed with dilute nitric acid on the water bath oxidation takes place, two hydrogen atoms being removed from it, and two isomeric compounds, glyceric aldehyde and dioxycetone, are formed :²



In alkaline solution these compounds polymerise to sugars :



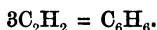
The nitrogen-containing compound hippuric acid, which is more complicated than those substances already considered, containing as it does nine atoms of carbon in its molecule, serves admirably as a further example of the synthesis of an organic compound occurring in our bodies. This acid is formed in our tissues by the combination of benzoic acid with amino-acetic acid. Each of these components can be put together atom by atom from

¹ Friedel and Silva, *l.c.*, p. 1597.

² Emil Fischer and Julius Tafel, *Ber. d. d. chem. Gesellsch.* 1887, vol. xx, p. 1088.

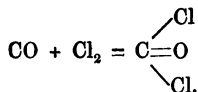
their elements, and further, the union of both can be effected artificially.

It is better to consider first the synthesis of benzoic acid. When an electric arc is formed between two carbon poles in a vessel filled with hydrogen, the carbon and hydrogen atoms combine together to form acetylene, a hydrocarbon of the composition C_2H_2 .¹ Acetylene is a colourless gas; when it is heated in a glass vessel to the temperature at which glass begins to melt, condensation takes place and another hydrocarbon is formed, which has the same percentage composition, but which in the gaseous state has a density three times as great, and therefore has a molecular weight three times as great, namely benzene :²



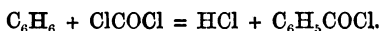
Benzene is a liquid which boils at $80^\circ C$.

Carbon and oxygen combine together at a high temperature, forming, when insufficient oxygen is present, carbon monoxide. This is a colourless gas of the composition CO ; it is an unsaturated compound, two of the four valencies of the carbon atom being still uncombined. If this gas be mixed with an equal volume of chlorine, and the mixture exposed to sunlight, a contraction to half the original volume³ takes place very quickly. In this newly-formed gas the two free valencies of the carbon monoxide are saturated by a molecule of chlorine, i.e. by two univalent chlorine atoms :



It is called carbon oxychloride or phosgene, and is a gas with a suffocating smell, which can be condensed to a liquid at $+8^\circ C$.

Phosgene is absorbed by benzene, the liquid hydrocarbon whose synthesis has been just described; and if aluminium chloride be added to such a solution the following reaction will take place at the ordinary temperature :⁴



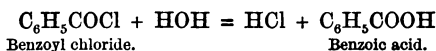
¹ Berthelot, *Ann. de Chim. et de Phys.* 1863 (iii.), vol. lxxvii, p. 67. A description and diagram of the apparatus employed is given in *Ann. de Chim. et de Phys.* 1868 (iv.), vol. xliii, p. 143.

² Berthelot, *ibid.* 1866 (iv.), vol. ix, p. 446, and 1867 (iv.), vol. xii, p. 54.

³ John Davy, *Gilbert's Ann. d. Phys.* 1812, vol. xl, p. 225, and 1813, vol. xliii, p. 296.

⁴ C. Friedel, J. M. Crafts and Ador, *Ann. de Chim. et de Phys.* 1884 (vi.), vol. i, p. 517.

The rôle which the aluminium chloride plays in this reaction has not yet been satisfactorily explained.¹ The newly-formed product, benzoyl chloride, reacts with water at the ordinary temperature in such a way that the chlorine atom is replaced by the univalent radical hydroxyl, thus :

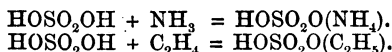


Benzoic acid which is thus formed is one of the constituents of hippuric acid, and at the ordinary temperature consists of colourless crystals which are soluble in water.

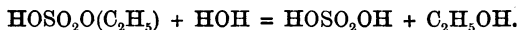
The synthesis of the other constituent, amino-acetic acid, is carried out in the following manner: Nascent hydrogen is allowed to act upon acetylene (p. 6) at the ordinary temperature, and another hydrocarbon, ethylene, is then formed : ²



This is also a colourless gas, which can be absorbed by concentrated sulphuric acid; it adds itself to sulphuric acid in a similar way to ammonia :



Just as ammonia is no longer contained in ammonium sulphate as such, but as a new radical, ammonium, so also, in this newly-formed compound, ethylene is not contained as such, but as the new radical ethyl, C_2H_5 . The new compound bears the name ethyl-sulphuric acid. If a large quantity of water be added to this compound, and the solution be warmed, free sulphuric acid is again formed, water being taken up, and the ethyl radical combines with the hydroxyl group, forming ethyl alcohol, which distils over : ³



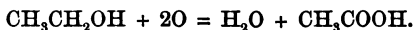
Ethyl alcohol, or ordinary alcohol, can be converted into acetic acid by the ordinary oxidising agents—chromic acid, manganese dioxide and sulphuric acid, nitric acid, ozone, etc. Atmospheric oxygen at a slightly raised temperature and in the presence of

¹ Upon attempts at explanation see Friedel and Crafts, *Ann. de Chim. et de Phys.* 1888 (vi.) vol. xiv. pp. 433, 434, 457, and G. Gustavson, *Compt. rend.* 1903, vol. cxxxvi. p. 1065.

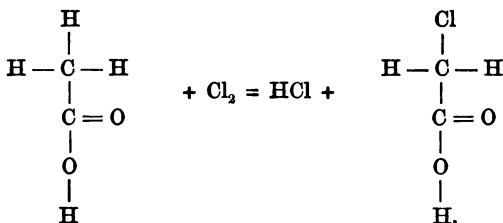
² Berthelot, *Ann. de Chim. et de Phys.* 1863 (iii.), vol. lxvii. p. 57.

³ Michael Faraday, *Poggendorff's Ann. d. Phys. u. Chem.* 1827, vol. ix. p. 21. H. Hennel, *Poggendorff's Ann. d. Phys. u. Chem.* 1828, vol. xiv. p. 281. Berthelot, *Ann. de Chim. et de Phys.* 1855 (iii.), vol. xliii. p. 385.

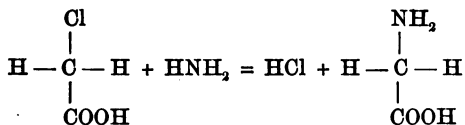
platinum black is also able to bring about this oxidation ; the platinum black acts by 'catalysis,' a process which is as yet not completely understood :



Acetic acid is a liquid which boils at 118°C . If a current of chlorine be passed through warmed acetic acid, one of its hydrogen atoms is substituted by chlorine, and monochloroacetic acid is obtained :

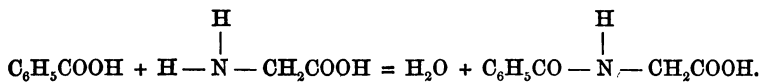


Monochloroacetic acid forms colourless crystals, which melt at 63°C . and boil at 186°C . When ammonia or ammonium carbonate is allowed to act upon this compound at a high temperature, the following reaction takes place :¹



and amino-acetic acid, or glycocoll, which consists of colourless crystals, is formed.

If dry glycocoll be sealed up in a glass tube with dry benzoic acid, and if this tube be heated for twelve hours at 160°C ., a combination of these two compounds will occur with the separation of water, and hippuric acid is obtained :²



This complicated body has thus been built up atom by atom from its elements.

As a final example of an artificial preparation, the synthesis of the intensely poisonous alkaloid muscarine may be selected.

¹ M. Nencki (1847-1901), *Ber. d. d. chem. Gesellsch.* 1883, vol. xvi. p. 2827.

² V. Dessaignes, *Jour. Pharm.* 1857 (iii.), vol. xxxii. p. 44.

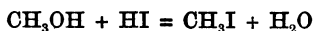
Muscarine is a compound, which, although it does not occur in our body, stands in very close relationship to a constituent of every cell ; it also demands the attention of the medical student from a toxicological point of view.

By alkaloids are understood certain organic bases occurring in plants : they are distinguished by their intensely poisonous action and are used, and also misused, as drugs, e.g. quinine, atropine, morphine, nicotine, cocaine. (Cf. Lecture 16.)

Muscarine was discovered by Schmiedeberg, who with his pupils¹ was searching for the active constituent of the poisonous toad-stool. They succeeded in isolating two organic bases, which they named Amanitine and Muscarine, after the botanical name of the fungus, *Amanita muscaria*. Amanitine was found to be not very poisonous, but muscarine, on the other hand, was found to be a very powerful poison. Further chemical investigation showed that amanitine was identical with the already known base choline, which had been synthesised by Ad. Wurtz² (1817-1884). Choline is found in combination with glycerophosphoric acid and fatty acids in lecithin (cf. Lecture 7), a complex compound occurring in all vegetable and animal tissues. Muscarine was found to differ from amanitine or choline only in elementary composition, by containing one more atom of oxygen. It was therefore hoped that muscarine might be obtained by the oxidation of synthetically prepared choline, and thus the first alkaloid be built up from its elements.

If a concentrated aqueous solution of choline be heated to its boiling point, it is decomposed into trimethylamine and glycol. Both of these constituents can be synthetically prepared, and their combination again together can be effected in the laboratory.

Methyl alcohol, the synthesis of which has been already described (p. 4), is the starting point in the synthesis of trimethylamine. It reacts with hydriodic acid forming methyl iodide, with the loss of a molecule of water, thus :³



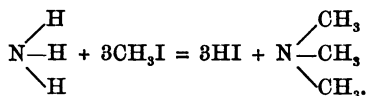
and methyl iodide reacts with aqueous ammonia in the cold, but more quickly when heated in a sealed tube, in such a way that the three

¹ Schmiedeberg and Koppe, *Muscarine, the Poisonous Alkaloid of the Toad-stool* (Leipzig, 1869) ; E. Harnack, *Arch. f. exper. Pathol. u. Pharmacol.* 1875, vol. iv. p. 168 ; Schmiedeberg and Harnack, *ibid.* 1876, vol. vi. p. 101.

² Ad. Wurtz, *Compt. rend.* 1867, vol. lxxv. p. 1015, and 1868, vol. lxxvi. p. 772.

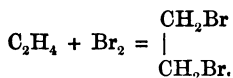
³ J. Dumas and E. Peligot, *Ann. d. Pharmacie*, 1835, vol. li. p. 20.

hydrogen atoms of the ammonia combine with the iodine forming hydriodic acid, and are replaced by three methyl radicals : ¹

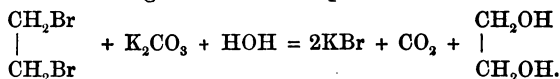


The resulting substituted ammonia, in which the three hydrogen atoms are replaced by methyl radicals, is called trimethylamine, and is a colourless gas, which at 3° C. becomes liquid ; it is very easily soluble in water.

Ethylene, the synthesis of which has been already given (p. 7), is the substance used as the starting point in the synthesis of glycol. At the ordinary temperature this gas is absorbed and combines with bromine, as was observed by Balard ² (1802-1876), the discoverer of bromine. The gas is passed into bromine until this is decolourised :

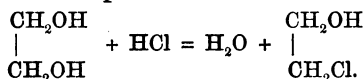


The resulting colourless liquid, ethylene bromide, boils at 131·5° C. ; it is not miscible with water, but sinks in it. When ethylene bromide is boiled with an aqueous solution of potassium carbonate the following reaction takes place : ³



Two hydroxyl groups take the place of the two bromine atoms, and the dihydric alcohol, glycol, the other constituent of choline, results. This is an oily liquid, which boils at 197° C. ; it is miscible with water in all proportions, and has a sweet taste, hence its name.

Glycol cannot be directly combined with trimethylamine ; one of its hydroxyl groups must be first replaced by chlorine. This is effected very simply by heating glycol in a distilling apparatus to 148° C. and passing a slow current of hydrochloric acid gas through it for sixteen hours. Glycolchlorhydrin, which is thereby formed, distils over with the steam produced at the same time : ⁴



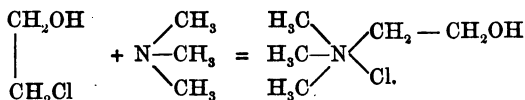
¹ Aug. Wilh. Hofmann, *Phil. Transactions of the Royal Society* (London, 1850), part i. p. 93 ; and *Liebig's Ann. d. Chem.* 1850, vol. lxxiii. p. 91.

² Balard, *Ann. de Chim. et de Phys.* 1826, vol. xxxii. p. 376.

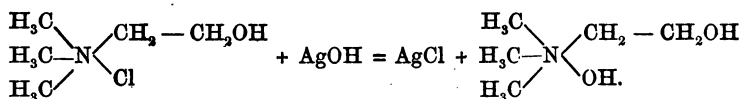
³ A. Zeller and G. Hüfner, *Journ. f. prakt. Chem.* 1875, n. F. vol. xi. p. 229 ; Emil Erlenmeyer, *Liebig's Ann. d. Chem.* 1878, vol. xcii. p. 250.

⁴ A. Ladenburg, *Ber. d. d. chem. Gesellsch.* 1883, vol. xvi. p. 1407. (Completion of the method of Wurtz.)

Glycolchlorhydrin is a liquid boiling at 130° C. and miscible with water. If it be heated with an aqueous solution of trimethylamine in a sealed tube for twenty-four hours in a steam bath, and the tube be then allowed to cool, the hydrochloride of choline crystallises out :¹



In this compound the nitrogen can be regarded as pentavalent, just as it is in ammonium chloride. By decomposing it with freshly precipitated silver oxide the free base, choline or amanitine, is obtained in the form of deliquescent crystals :



By the action of fuming nitric acid on this base Schmiedeberg² obtained an alkaloid containing one atom of oxygen more than choline. This artificial product, which is muscarine, showed a poisonous action similar to that of the product prepared from toad-stools ; in particular, it had the same action upon the heart. The two alkaloids, however, are not identical, but isomeric³ ; and as yet the constitution of the alkaloid occurring in the toad-stool has not been definitely determined.⁴

The synthesis of artificial muscarine is more worthy of notice because we learn from it that we can prepare more alkaloids than those which actually occur in nature. If we could only fathom the relation between the chemical constitution and the physiological action of a substance, we should then be in a position to deduce, *a priori*, how an alkaloid must be constituted in order to produce any desired action, and the doctor could order from the chemist any such alkaloid as he required for his therapeutical purposes.

If the synthesis of the practically important alkaloids—morphine, quinine, etc.—be accomplished, and if it should be found possible to

¹ Wurtz, *Compt. rend.* 1867, vol. lxxv. pp. 1016 and 1017.

² Schmiedeberg and Harnack, *Arch. f. exper. Pathol. u. Pharmacol.* 1876, vol. vi. p. 101.

³ R. Boehm, *ibid.* 1885, vol. xix. p. 87.

⁴ For the latest investigations upon the constitution of natural muscarine, see Emil Fischer, *Ber. d. d. chem. Gesellsch.* 1893, vol. xxvi. p. 468, and 1894, vol. xxvii. p. 166.

prepare them with a less expenditure of time and energy than is required in their present production by agriculture, it would be of the greatest importance from an economical point of view. Large stretches of land, which are now sown with poppies or which serve for the production of quinine, would become free, and could be utilised for the production of foodstuffs. Even if we never attain to the synthetical preparation of our foodstuffs, we shall be able indirectly to increase their amount in this way. Nowadays in almost all civilised countries one-tenth of the harvested cereals is used for the production of alcohol. But we can obtain alcohol by synthesis; one method has been already described, and we know of several others. The question is, to know how to prepare the synthetical product more cheaply by artificial than by agricultural methods. We may believe that it will always be cheaper, as it is at present, to obtain an organic substance from the earth rather than from the chemical factories; but there are several instances proving the contrary. It has actually happened in a not unimportant department of husbandry and industry, that the production of an organic substance by agricultural methods has been supplanted by its production by chemical methods, as in the cases of madder and indigo.

Up to the year 1868 the beautiful and permanent madder dye, alizarin, could only be obtained from the madder root, in which it is contained in the form of a glucoside, ruberythric acid (cf. Lecture 9); by the action of acids and ferments this is broken down into sugar and alizarin. The production of this dye-stuff is as old as the history of mankind: in the oldest Egyptian tombs we find mummies which have been enveloped in cloths dyed with madder. Its cultivation spread from the East into Europe, and large tracts of land, chiefly in Holland and in France, were planted with madder-root, and in the single department of Vaucluse the value of its annual production was £1,000,000 sterling. But in 1868, in Baeyer's laboratory, the artificial synthesis of alizarin was discovered by Carl Graebe and Carl Theodor Liebermann¹ (cf. Lecture 15), and a few years later, in 1875, twelve factories in Germany artificially produced £750,000 worth of synthetical alizarin. Since that time this industry has greatly increased, and the agricultural production has now almost entirely ceased. Large stretches of land have thus been made again available for the cultivation of foodstuffs, and this young science of

¹ C. Graebe and C. Liebermann, *Liebig's Ann. d. Chem.* 1870, supplementary vol. vii. p. 257, and 1871, vol. clx. p. 120.

synthetical chemistry has thus actually—if only indirectly—enabled us to increase the quantity of our foodstuffs.

A very similar economic revolution is at the present time being accomplished in the production of indigo. The indigo dye (cf. Lecture 14) is now being prepared commercially by chemical means, and its agricultural production is being proportionally lessened. The export of indigo from Indian ports has diminished almost to one-half of its former amount. There is only one direction at present in which we must not indulge in too sanguine hopes; it is still doubtful whether in the immediate future, in spite of all the investigations upon artificial syntheses, we shall gain an insight into the conditions underlying those synthetical processes which occur in living tissues.

We have seen what agents have been used in the accomplishment of artificial syntheses: high temperatures, powerful galvanic currents, red-hot copper, molten sodium, concentrated sulphuric acid, free chlorine—all factors which not only never play any part in the processes of life, but which would immediately destroy the life of every cell.

But we already know of one synthetical process which takes place at the ordinary temperature, and under conditions which may be similar to those which actually occur in our tissues. This is the union of benzene with phosgene, at the ordinary temperature, in the presence of aluminium chloride (p. 6). The way in which the aluminium chloride acts is unknown, but nevertheless expressions are not wanting for this kind of activity: for we talk of contact action, catalytic action, ferment action. We must assume that substances exist in our tissues which exercise such a ferment action. There is no doubt that our tissues contain ferments which can break up compounds, and it is very probable that syntheses also are carried out by ferments; but as to the nature of the ferments in our tissues nothing definite is known. We have never yet isolated one, but they are supposed to belong to the group of the proteins (p. 240). In spite of this we must not relinquish the hope of being able to find out the conditions of the synthetic processes carried out in the bodies of plants and animals; we may fairly imagine that the conditions and the forces of artificial syntheses, and of the syntheses by living processes, must have something in common with one another, and we must continue to hope that this common factor may soon be discovered.

These preliminary remarks have shown what gigantic strides this young science of synthetical chemistry has made during the last decades—its founder, Berthelot, has only recently passed away—and

if we look back upon the state of chemistry half a century ago we shall see that then physiological chemistry scarcely existed, that organic chemistry lay in its cradle, and that synthetical chemistry was unknown. We must remember that to-day chemistry is one of the principal foundations of Medicine, and that in the future it must be of ever-increasing importance: therefore it is both worth while and necessary to become thoroughly conversant with this science, in order that its progress may be followed with full understanding.

LECTURE II

THE HYDROCARBONS

IN the first lecture it was shown how the barriers, which appeared to separate organic chemistry from inorganic, that is the chemistry of the compounds of carbon from the rest of chemistry, had disappeared under the persistent enquiries of the last decades. We can now build up atom by atom from their elements compounds of carbon which are produced by plant and animal life, with the help of the same chemical reagents and the same physical forces which we make use of in inorganic chemistry. The chemistry of the carbon compounds is only a chapter of general chemistry, just as is the chemistry of the compounds of nitrogen, the compounds of platinum, etc.

[Physiological chemistry, or Biochemistry, is that chapter of organic chemistry which deals with the compounds of carbon found in animals and plants, principally with the carbohydrates, fats and proteins. Its main object is to find out the chemical composition of the substances contained in the tissues of the organism, their relation to one another, and the stages they go through in passing from a more complicated state to a less, and *vice versa*. It also deals with the methods by which the animal and plant build up these complex compounds from simpler ones, and how they again break them down. The only essential difference between physiological and organic chemistry is in the manner by which these changes are produced. The physical and chemical means described in the last lecture are not employed by living tissues, but they make use of much subtler reagents, namely, the soluble ferments or enzymes, which are occasionally used by chemists as special reagents, particularly for determining the constitution of certain classes of compounds, e.g. the glucosides and proteins.

Physiological Chemistry is sometimes called Chemical Physiology, but this latter designation should be applied rather to the study of the changes taking place in defined substances in the organism; whereas the term physiological chemistry should be applied to the

study of their exact chemical constitution, which must be known before any attempt can be properly made to find out what happens to these substances in the organism.

Physiological Chemistry is therefore the investigation of physiological substances from a purely chemical point of view, whereas Chemical Physiology is the application of chemical knowledge to the elucidation and explanation of the various processes taking place within the organism.]

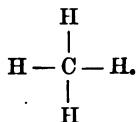
Therefore, it is only on practical grounds that we are justified in treating the chemistry of the carbon compounds as a special branch of chemistry, [and physiological chemistry as a special branch of organic chemistry.] It is justifiable on the principle of division of labour, because the number of carbon compounds known to us is already far greater than the number of all the other chemical compounds taken together.¹ This fact is accounted for by the one peculiarity of carbon, by the property which distinguishes this element from all others, which is, that it is a tetravalent element capable of combining with itself in any number of multiples. The other elements can only combine with one another in a few different proportions by weight: e.g. hydrogen can only combine with chlorine, bromine, or iodine, in one proportion; hydrogen and oxygen, hydrogen and sulphur can combine together in two different proportions; whilst phosphorus and oxygen can combine together in three. It is a rare occurrence in inorganic chemistry for two elements to combine together in more than three proportions, but nitrogen and oxygen can combine together in five different proportions, and manganese and oxygen in six. Carbon alone is an exception to this rule. Carbon can, as it appears, combine with hydrogen in an unlimited number of different proportions. Several hundred different hydrocarbons have been carefully studied and described—they are gaseous, liquid, or solid, with the most varied physical and chemical properties; new ones are continually being discovered, and it seems as if their number could be increased to an unlimited extent. [This peculiarity of the carbon atom, of being able to combine with hydrogen in an unlimited number of different proportions, depends upon the property which it possesses of being able to combine with itself, whereas this seldom occurs in the other elements, e.g. ozone.]

In each of the hydrocarbons the hydrogen atoms can be replaced either partially or completely by other elements, or by whole groups of atoms or radicals; hence the endless number of compounds which

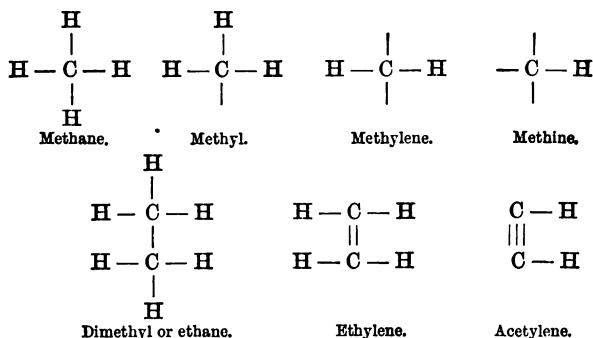
[The number of carbon compounds now known exceeds seventy-five thousand.]

form the material of organic chemistry. It is therefore necessary, first of all, to properly and clearly arrange this infinite series of compounds, for by commencing with the hydrocarbons, which can be arranged and grouped in a natural manner, and then starting from one member of each group, we can derive all the other compounds by the substitution of the hydrogen atoms.

The simplest hydrocarbon is marsh gas or methane (synthesis, p. 3). It contains one carbon atom, the four valencies of which are fully satisfied by four univalent hydrogen atoms:



The question now arises, can there be unsaturated compounds of carbon atoms with hydrogen atoms, i.e. do the compounds CH_3 , CH_2 , CH exist? In the free state these hypothetical compounds are not known; they constitute, however, important radicals, i.e. groups of atoms which can be separated from more complicated compounds and enter into new combinations. They have the names methyl (CH_3), methylene (CH_2), and methine (CH). If these radicals become free and do not enter into new combinations, they link themselves to one another, as is seen from the following formulæ:



It is now necessary to ask ourselves why we know that the colourless gas called ethane contains two atoms of carbon in its molecule, but methane only one. Elementary analysis gives us no answer to this question; it can only determine the percentage composition from which the ratio of the elements to one another can be calculated; it tells us that ethane contains one atom of carbon to

three atoms of hydrogen, but it cannot differentiate between CH_3 , or C_2H_6 , or C_3H_8 , etc.

The fact that ethane contains two atoms of carbon in its molecule follows from its density and from the law of Avogadro (1776–1856). According to his hypothesis, equal volumes of gases contain the same number of molecules: the weights of equal volumes of gases must be to one another as the weights of their molecules. If the molecule of ethane had the composition CH_3 , then the gas must be lighter than methane, but as a matter of fact ethane is almost twice as heavy as methane. Their densities are to one another as $\frac{2 \cdot 12 + 6}{12 + 4} = \frac{30}{16}$.

In a similar way it can be proved that the compound methylene (CH_2) cannot exist in the free state, but as soon as methylene radicals are set free two of them combine together and form ethylene. We must here assume that a double linking takes place, because we should not otherwise be able to understand why, by the action of nascent hydrogen, a compound C_2H_4 is not formed; such a compound, however, does not exist in the free state. Whenever hydrogen enters a molecule two atoms always enter at the same time, because two valencies—one to each carbon atom—are set free. In general, no hydrocarbon occurs with an uneven number of hydrogen atoms, and further, the carbon atom is tetravalent.¹

If the radical methine becomes free, a triple linking takes place and acetylene is obtained. We must hypothetically assume the triple linking in order to explain the following facts: If nascent hydrogen be allowed to act upon acetylene (p. 6) two atoms of hydrogen enter the molecule at the same time, and we obtain ethylene;² and if we allow hydrogen to act upon ethylene in the presence of platinum black or nickel powder, two hydrogen atoms again enter the molecule and ethane is formed.

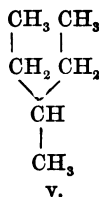
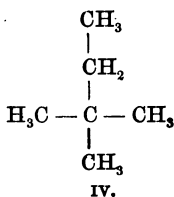
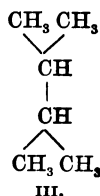
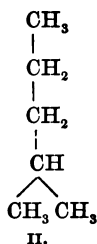
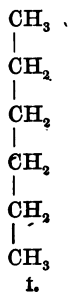
We see from the above one of the sources from which the great number of different hydrocarbons arises; the extent of the linking of the carbon atoms amongst themselves can vary, and thereupon depends the varying saturation with hydrogen atoms (see above formulæ). A second reason for the great number of hydrocarbons is that the number of carbon atoms in their molecule can vary within wide limits, and can be very considerable, for hydrocarbons containing sixty atoms of carbon in their molecule have been

¹ [In carbon monoxide the carbon atom must be assumed to be divalent, unless the oxygen atom is regarded as tetravalent. Other compounds are known, but their number is small, in which the carbon atom may be regarded as divalent.]

² Berthelot, *Ann. de Chim. et de Phys.* 1863 (iii), vol. lxvii. p. 57.

accurately investigated.¹ A third reason is that with the same number of carbon atoms in a molecule, and with the same degree of linking, different groupings of the carbon atoms themselves can occur: one carbon atom can be united either with one other carbon atom, or with two, three, or four carbon atoms. An example will explain this. Let us take the case of the hydrocarbons containing six carbon atoms in their molecule, because from these hydrocarbons compounds can be derived which play a very important part in the metabolism of animals and plants. Leucine, that decomposition product of proteins which makes up a great part of the protein molecule, has six atoms of carbon in its molecule, as have also the sugars, of which all the carbohydrates of our food and of our tissues are composed. Further, benzene has six carbon atoms in its molecule; this is the mother substance of the whole 'aromatic group' of compounds, several members of which play an important rôle in our metabolism.

If all the six carbon atoms be simply combined with one another and all the valencies be saturated with hydrogen, then five different arrangements are conceivable; all the hydrocarbons corresponding to these have been actually prepared. The five possibilities can be seen in the following formulæ:

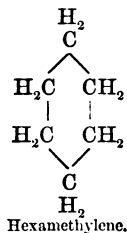


These five hydrocarbons have not only the same percentage composition, but also the same vapour density, and hence the same

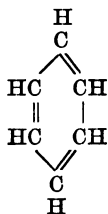
¹ Carl Hell and C. Hägele, *Ber. d. d. chem. Gesellsch.* 1889, vol. xxii. p. 502.

molecular weight; they have, however, different physical properties—e.g. different boiling points. Such compounds which have the same elementary composition, but different structural formulæ, are called *isomers*. Many cases of isomerism will be studied later in greater detail, and then the reasons will be given for assigning a particular structure to a particular isomeric compound; here, only the reasons for the large number of different hydrocarbons can be stated.

The five isomeric saturated hydrocarbons, each containing six atoms of carbon in their molecule, have the same empirical formula, C_6H_{14} , and bear the common name, Hexane. If elementary analysis and the determination of the vapour density should both give the same empirical formula C_6H_{12} for a hydrocarbon, we must either assume that two of the carbon atoms are doubly linked together, or that there is a closed ring of carbon atoms, in which there is no end member having three hydrogen atoms attached to it, as in the following formula :



The important hydrocarbon benzene with the empirical formula C_6H_6 is assumed by most chemists to have a closed ring made up of six carbon atoms with three double linkings :



The reasons why we assign this structure to it will be given later, when we come to the large group of 'aromatic' compounds, of which benzene is the mother substance.

These outlines will suffice, for the present, to indicate that peculiarity of carbon, of being able to combine with hydrogen in such a great number of different proportions. The great number of hydrocarbons can arise in three ways: (1) The number of carbon atoms

in the molecule can be different; (2) the degree of linking may be different; (3) the grouping of the atoms may be different.

We will first examine the most important groups and series of the hydrocarbons, and will then consider the derivatives of the individual members of these series. Commencing with the marsh gas series, three members of which (marsh gas or methane, ethane, and the isomeric hexanes) have been already mentioned, we can derive all the hydrocarbons of this series from marsh gas, by the substitution of one of its hydrogen atoms by the radical methyl, then again a hydrogen atom in this methyl by another methyl group, and so on. We shall shortly see that the hydrocarbons of this series can be actually prepared in this way. Every subsequent member will consequently contain a hydrogen atom less, but a methyl group more, than the preceding one, e.g.:



or, every subsequent member will contain one carbon atom and two hydrogen atoms more than the preceding one. The general formula for the whole series is therefore C_nH_{2n+2} .

Such a series is termed an homologous series. The marsh gas series is distinguished from all the other series of hydrocarbons by having the greatest hydrogen content, since all its members are saturated with hydrogen. On account of this, it is known as the series of saturated hydrocarbons, because the capacity of the carbon chain for taking up hydrogen has here reached its limit. The most important of the accurately investigated members of this series are:

CH_4	.	.	Methane.	$C_{11}H_{24}$.	Undecane.
C_2H_6	.	.	Ethane.	$C_{12}H_{26}$.	Dodecane.
C_3H_8	.	.	Propane.	$C_{14}H_{30}$.	Tetradecane.
C_4H_{10}	.	.	Butane.	$C_{16}H_{34}$.	Hexadecane.
C_5H_{12}	.	.	Pentane.	$C_{20}H_{42}$.	Eicosane.
C_6H_{14}	.	.	Hexane.	$C_{21}H_{44}$.	Heneicosane.
C_7H_{16}	.	.	Heptane.	$C_{23}H_{48}$.	Tricosane.
C_8H_{18}	.	.	Octane.	$C_{31}H_{64}$.	Hentriacontane.
C_9H_{20}	.	.	Nonane.	$C_{35}H_{72}$.	Pentatriacontane.
$C_{10}H_{22}$.	.	Decane.	$C_{60}H_{122}$.	Hexacontane.

The boiling and melting points of these compounds rise as the number of the carbon atoms in the molecule increases; the first four members at the ordinary temperature are gases, the next members up to those with sixteen carbon atoms are liquids, and the rest are solids.¹

¹ [This series exemplifies the first and the third ways, mentioned above, as reasons for the numerous hydrocarbons, and the following tables of the most important unsaturated hydrocarbons exemplify the second, as well as the other two ways

The majority of the members of this series are contained in petroleum, together with hydrocarbons belonging to the other series, the gaseous ones being absorbed, and the solid ones dissolved. On account of its containing the easily volatile hydrocarbons raw petroleum cannot be directly employed as an illuminating and heating material; for the easily volatile hydrocarbons form, when mixed with air, an explosive mixture, and raw petroleum therefore is an extremely inflammable substance. In order to obtain the illuminating and heating material from it, raw petroleum is submitted to fractional distillation. The hydrocarbons which distil over at a temperature below 150°C . are not allowed to be used for illuminating and heating purposes. They are known commercially as petroleum ether, benzine, ligroin, petrol, etc., and they are used as solvents for fats, oils, resins, for scouring and polishing in the technical arts, as fuel for internal combustion engines, and also in analytical chemistry.

The hydrocarbons which distil between 150 and 300°C . form commercial petroleum which is ordinarily used for lighting and heating purposes; unfortunately, it is usually not completely free from the more volatile hydrocarbons, and therefore is dangerous. When a fire is occasioned by the upsetting of a lighted petroleum lamp, the easily volatile constituents of the petroleum mix with the air and take fire from the flame. But if, on the contrary, the petroleum be entirely free from the easily volatile constituents, the flame is extinguished by immersion in it. Such petroleum carefully purified by fractional distillation forms the commercial substance kerosene, or refined petroleum.

Vaseline is obtained from those residues of raw petroleum which are not volatile at 300°C .; it is a mixture of hydrocarbons, and is a mass of the consistency of butter; it is employed in the preparation of ointments, and for greasing metallic surfaces, etc.

A mixture of the highest members of the series of hydrocarbons, which at the ordinary temperature is solid, is known commercially as paraffin wax; it is used in the manufacture of candles and for

It should be noticed that the terminology -ane, -ene, -ine shows the difference in saturation between the members of each series, and that the prefixed Greek numeral shows the number of carbon atoms. No account is taken of isomerism in this nomenclature.

Ethylene Series.

General formula . . .	C_nH_{2n}
Ethylene or Ethene . .	C_2H_4
Propylene or Propene . .	C_3H_6
Butylene or Butene . . .	C_4H_8
Amylene or Pentene . .	C_5H_{10}

Acetylene Series.

General formula . . .	C_nH_{2n-2}
Acetylene or Ethine . .	C_2H_2
Propyne . . .	C_3H_4
Butyne . . .	C_4H_6
Pentyne . . .	C_5H_8

embedding purposes in microscopical technique. The paraffin waxes which come into the market are not identical, but consist of mixtures of different hydrocarbons, according to the material from which they are obtained and the manner of their preparation. Their melting points vary between 45 and 80° C.

The word paraffin is corrupted from *parum affinis*, little affinity, on account of the inertness of these hydrocarbons towards other substances at the ordinary temperature. Thus, paraffin wax is not attacked by acids and alkalis; and it is used in the laboratory for the stoppers of caustic potash bottles. Upon this inertness towards other substances depend the great advantages which vaseline possesses over the fats as a basis for ointments. When fats decompose, free acids are formed (cf. Lecture 7), which attack metals, and if employed as ointments, cause irritation of the skin and of the surfaces of wounds. The hydrocarbons, on the other hand, are perfectly neutral compounds; they do not dissolve in water, and have no affinity for any of the constituents of our tissues, and hence cannot in any way act as either irritants or caustics.

Petroleum occurs in the most various geological formations in all parts of the world in enormous quantities. The most abundant petroleum fields are in North America, especially in Pennsylvania and in Canada, and at the foot of the Caucasus mountains, especially at Baku on the Caspian Sea. How great is the stored-up quantity of oil in all these places we can roughly estimate from the quantities which are obtained every year from the borings: for instance, in 1902, from the springs at Baku 11,000,000 tons, or 11,000,000,000 kilogrammes, of petroleum were obtained.¹

It is a question of the greatest interest to chemistry, as well as to geology, to know how these enormous quantities of hydrocarbons have been formed, but the origin of the hydrocarbons in nature has not as yet been satisfactorily explained. All those hydrocarbons, whose method of formation under natural conditions has up to the present been investigated, arise from the decomposition of carbon compounds which have been formed by plant life; but it is not known in what way the hydrogen atoms combine with the carbon atoms in plant life. Carbon enters the plant organism as carbonic acid; the plant cell removes oxygen from the carbonic acid and the water, gradually forming compounds poorer in oxygen and richer in hydrogen, until finally pure hydrocarbons, such as the terpenes, result (cf. Lecture 15). It has been known that this decomposition

¹ V. Brackel and J. Leis, *The Thirty Years Petroleum Strife* (Guttentag: Berlin, 1903), p. 41.

could only take place in sunlight in the green chlorophyll-containing parts of the plants, but recently we have succeeded in artificially producing this change with the help of sunlight and chlorophyll outside the living cell.¹

It can therefore be easily imagined that the hydrocarbons in these oil-wells may have arisen from plant and animal substances. It is tempting to think of a slow 'dry distillation,' i.e. a decomposition in the absence of oxygen, and to bring the formation of petroleum into line with the formation of coal beds, because in the artificial dry distillation of vegetable substances, namely, wood, peat, etc.,

¹ [It was suggested in 1870 by Baeyer^a that the first stage in the synthesis by the green plant was the formation of formaldehyde from carbonic acid, and though numerous experiments were made it was only quite recently, in 1906, that this supposition was actually confirmed. It had been found by Bach^b that formaldehyde and hydrogen peroxide resulted when a current of carbonic acid was passed through a solution of uranium acetate, or palladium hydrogen, in sunlight. Euler,^c and Usher and Priestley^d repeated these experiments and found that formic acid was an intermediate product. Usher and Priestley further showed that the chlorophyll of the green plant also effected the conversion of carbonic acid into formaldehyde and hydrogen peroxide. Both these products are injurious to the vital mechanism employed by the plant, but in nature they are removed as fast as they are formed: the hydrogen peroxide by an enzyme—catalase—which converts it into water and oxygen, and the formaldehyde by the living protoplasm by condensation into sugar. Usher and Priestley showed this in the following way: They first found that the enzyme occurred very near the chloroplasts at the seat of the photosynthetic process, so that the hydrogen peroxide is removed as fast as it is formed. Green sprigs of *Elodea* were placed in boiling water, which destroys both protoplasm and enzyme, and then in water saturated with carbonic acid, and exposed to sunlight. The chlorophyll was bleached by the hydrogen peroxide and the process ceased, but formaldehyde was detected. Other sprigs of *Elodea* were exposed to chloroform, which destroys the protoplasm but not the enzyme, and treated as before; formaldehyde was again formed, and this destroyed the enzyme. The process has also been artificially carried out. Chlorophyll was prepared from grass or wheat leaves; a glass plate coated with gelatine was painted over with a solution of chlorophyll in petroleum ether or benzene, so as to form a very thin layer, placed in carbonic acid and exposed to sunlight in such a way that the light passed through the several layers as follows: carbonic acid, chlorophyll, gelatine; after some time the gelatine was found to contain formaldehyde. In another experiment a solution of a catalysing enzyme was prepared from sheep's liver and mixed with the gelatine, and in this case both formaldehyde and oxygen could be detected. Thus a process occurring in nature has been imitated in the laboratory, and the first stage in the change of carbonic acid to other compounds in the green plant has been determined. It is interesting to note that formic acid is produced by the action of sodium amalgam, and by the electrolytic reduction of carbonic acid or solutions of carbonates. The further reduction to formaldehyde only occurs with magnesium, as has been very recently shown by Fenton,^e who simply immersed a rod of magnesium in a solution of formic acid or water saturated with carbonic acid, and obtained formaldehyde.]

^a A. Baeyer, *Ber. d. d. chem. Gesellsch.* 1870, vol. iii. p. 63.

^b Bach, *Compt. rend.* 1893, vol. cxvi. p. 1145; 1898, vol. cxxvi. p. 479.

^c Euler, *Ber. d. d. chem. Gesellsch.* 1904, vol. xxxvii. p. 3415.

^d F. L. Usher and J. H. Priestley, *Proc. Roy. Soc.* 1906, vol. lxxvii. B, p. 369 1906, vol. lxxviii. B, p. 318.

^e H. J. H. Fenton, *Jour. Chem. Soc.* 1907, vol. xci. p. 687.

similar products are obtained. We may imagine that illuminating gas which arises from artificial distillation may correspond to the gaseous hydrocarbons which stream from the surface of the earth in the neighbourhood of the oil springs, as in Baku, where the everlasting fire burns; the tar which collects in the receivers during the artificial distillation corresponds to the petroleum, and the carbon remaining in the retort corresponds to the coal. In all branches of chemistry we can find analogies to those phenomena in which the same processes take place quickly at high temperatures and slowly at low temperatures, with the formation of the same end-products. But against such conceptions there is the fact that in the neighbourhood of most of the oil wells coal cannot be found, and on this account modern geologists are almost unanimous in believing that petroleum arises by the slow decomposition of animal remains. The investigation of coal has shown that it has been formed out of vegetable tissues rich in cellulose. Animal tissues on decomposition in the absence of air do not leave behind residues of this kind. This supposition is strengthened by the investigations of Karl Engler,¹ who subjected fish oil and other fats to distillation at a temperature of 320 to 400° C. under a pressure of four to ten atmospheres, and obtained a distillate which, for the most part, consisted of a mixture of hydrocarbons similar to those in American petroleum.

The following objections have, however, been urged against these suppositions.

Petroleum is lighter than water, which permeates all the sedimentary layers of the earth's crust, and it can therefore only rise from the deeper layers, and cannot penetrate into these, which are rich in organic remains, from the superficial layers. As a matter of fact, petroleum is found in all layers: in the Caucasus it occurs in the most superficial, i.e. in the tertiary strata; and in North America in the Devonian and Silurian, i.e. the oldest and deepest strata. The quantity of animal remains in the Silurian layers is small in comparison with the enormous bulk of the oil fields. As petroleum cannot have penetrated from the upper layers into the Silurian formation, it must be assumed that it has arisen from the deeper layers; that is, from layers which contain no organic remains whatsoever. If petroleum had been formed in the Silurian layers, it would have been expected that the carbonised remains of organisms of all kinds would be present as a residue; but these cannot be

¹ K. Engler, *Ber. d. d. chem. Gesellsch.* 1888, vol. xxi. p. 1816; 1889, vol. xxii. p. 592; 1893, vol. xxvi. p. 1436. Cf. Fr. Heusler, *Nachr. von d. k. Gesellsch. d. W. zu Göttingen, math. phys. Klasse*, 1896, p. 74.

found in corresponding quantities. If petroleum has arisen from the slow distillation of animal remains, various kinds of nitrogen compounds would also be expected as residues, but these are not found in any appreciable quantities.

These and other similar views led certain chemists—Berthelot, Mendelejeff, Moissan—to make experiments, in order to explain the formation of petroleum by chemical processes in *inorganic* nature.

If we wish to understand such attempts at explanation, it will be necessary first of all to study a little more closely the chemical behaviour of carbon to hydrogen, and to all the other elements.

Carbon at the ordinary temperature shows scarcely any affinity for other elements; this property of carbon can be explained hypothetically by assuming that the four valencies of the carbon atoms are mutually saturated by each other in the carbon molecule, and only when the linkings of the carbon atoms are loosened by high temperatures or by strong electric currents, can combination with other elements take place. Only one single element can combine with carbon at the ordinary temperature, namely fluorine. Henri Moissan¹ (1852–1907) on passing a current of fluorine over finely divided charcoal—lampblack or charcoal from light wood—found that the charcoal immediately began to glow, and that in the presence of an excess of fluorine, carbon tetrafluoride was formed, which is a colourless gas, liquefiable at 10° C. under five atmospheres pressure.

Carbon and hydrogen cannot be made to combine directly at the highest temperature obtainable by heating, but in the electric arc Berthelot succeeded in effecting their union, as already described (p. 6). Acetylene (C_2H_2) was formed, and at the same time small quantities of methane (CH_4), and ethane (C_2H_6). In the same manner the union of carbon with chlorine to form hexachlorethane (C_2Cl_6), and hexachlorbenzene (C_6Cl_6) has been accomplished.²

At high temperatures carbon easily combines with oxygen, forming carbon monoxide when the supply of oxygen is insufficient, and carbonic acid or carbon dioxide when the supply of oxygen is in excess. Under similar conditions carbon combines with sulphur forming carbon disulphide, CS_2 , a compound analogous in composition to carbon dioxide. Sulphur vapours are passed over glowing charcoal and gaseous carbon disulphide is formed, which condenses to a liquid in a cooled receiver. How the hydrocarbon marsh gas

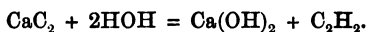
¹ Henri Moissan, *Compt. rend.* 1890, vol. cx. p. 276.

² Werner von Bolton, *Z. f. Elektrochemie*, 1902, vol. viii. p. 165; 1903, vol. ix. p. 209. Cf. Richard Lorenz, *ibid.* 1902, vol. viii. p. 203.

is prepared from carbon disulphide was first shown by Berthelot (p. 3).

With many elements—nitrogen, phosphorus, arsenic, antimony, bismuth—carbon has not yet been made to unite directly under any conditions.

It is important for the question we are now considering to call attention to the combinations of carbon with certain metals at a high temperature.¹ The combination of carbon with iron in cast iron has been long known. In 1836 Edmund Davy,² a cousin of Sir Humphry Davy (1778–1829), showed that when a mixture of tartar (acid potassium tartrate) and charcoal was strongly heated, a compound of carbon with potassium resulted, which was decomposed by water into potash and the hydrocarbon, acetylene (C_2H_2). As is well known, this process is nowadays used on a large scale for the preparation of acetylene for lighting purposes, but we do not use a potassium compound, but lime, which in the electric furnace combines with charcoal to form calcium carbide CaC_2 . With water this compound undergoes the following decomposition at the ordinary temperature :



Why, then, should not hydrocarbons be formed by similar processes in the interior of the earth? Why cannot the formation of the petroleum fields be explained by some such process? This idea was first put forward in 1866 by Berthelot,³ and in consequence of certain geological investigations it was extended by the Russian chemist, Dmitry Mendelejeff (1834–1907),⁴ the discoverer of the periodic system of the elements. He visited the petroleum springs at the foot of the Caucasus and in Pennsylvania, in order to personally investigate the conditions under which petroleum has been formed, and he arrived at the following hypothesis.

Starting from the fact that the most productive oil-wells are all situated at the feet of mountains and run parallel to the mountain chains, as in the spurs of the Caucasian Mountains and in the Alleghany Mountains in North America, Mendelejeff supposed that the pressure of these mountain masses caused rents in the earth's crust at their feet, and that through these rents water penetrated into

¹ Upon this see H. Moissan, *The Electric Furnace* (Steinheil: Paris, 1897), pp. 284–344.

² E. Davy, *Records of Gener. Science*, Nov. 1836; *Liebig's Ann. d. Pharmacie*, 1837, vol. xxiii. p. 144.

³ Berthelot, *Ann. de Chim. et de Phys.* 1866 (iv.), vol. ix. p. 481.

⁴ Dmitry Iwanowitsch Mendelejeff, *The Naphtha-production in America and in the Caucasus* (St. Petersburg, 1877); abstract by G. Wagner, in the *Ber. d. d. chem. Gesellsch.* 1877, vol. x. p. 229.

the interior of the earth where it came into contact with the carbon compounds of the metals, and that the various resulting hydrocarbons were formed in a way similar to acetylene when made by the method just described. The hydrocarbons then ascended in a gaseous condition through the rents, and condensed in the cooler layers to petroleum.

The assumption that the interior of the earth consists of metals, and of compounds of carbon with metals, is borne out by the specific gravity of the earth. The pendulum experiments of Cavendish, Maskelyne, Baily and Airy have shown that the specific gravity of the earth is between 5.5 and 6.5. Now, since the superficial layers of the earth consist of minerals whose specific gravity lies between 2 and 3, together with large quantities of water, it follows that the specific gravity of the interior of the earth must be greater than 5.5 to 6.5. These facts support the supposition of Mendelejeff, that iron whose specific gravity is 7.8 is the chief constituent of the interior of the earth, and we know that iron in a molten state can combine with carbon, as in cast iron. It can scarcely be doubted that the earth was once an igneous mass, just as the sun, from which it has separated according to the theory of Kant and Laplace, is at the present time. The supposition that the interior of the earth consists principally of iron is further strengthened by our knowledge of the composition of meteorites; it is supposed by astronomers that meteorites are fragments of shattered planets, which fragments consist either of siliceous minerals resembling those of the crust of our earth, or almost entirely of iron. In the iron of the meteorite carbon has been identified, and in some meteorites hydrocarbons have been found.

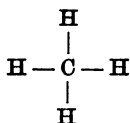
Similar views upon the formation of petroleum have recently been advocated by the great chemist Henri Moissan,¹ but his theories have as yet found little favour with the geologists, who, at present, continue to think that the only probable hypothesis is that petroleum has arisen from the slow decomposition of animal remains.

¹ H. Moissan, *The Electric Furnace* (Steinheil: Paris, 1897), pp. 337-344; *Re. Génér. d. Sci.* 1901, p. 946.

LECTURE III

METHANE AND ITS DERIVATIVES

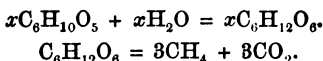
IN the last lecture we considered the marsh gas series, and saw how the members of this series of hydrocarbons are formed by the processes of dry distillation, and discussed the hypotheses which have been advanced in explanation of their formation on the large scale in nature. We will now consider the most important members of this series, and their derivatives, beginning with marsh gas or methane:



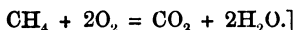
The method of preparing it synthetically by passing a mixture of carbon disulphide and sulphuretted hydrogen over heated metal has been described (p. 3). Methane is formed in the dry distillation of the most diverse organic substances, and hence it is contained in coal gas, of which it constitutes 30 to 40 per cent.; and its occurrence in the cavities of coal seams may perhaps be explained by this process of slow dry distillation (p. 24). By disturbance of the strata in working a mine, the gas may diffuse from the crevices and form with the oxygen of the atmosphere an explosive mixture, the so-called 'fire-damp,' through which so many miners' lives are yearly sacrificed. On account of its occurrence in coal pits methane also bears the name pit gas. We have already seen that methane occurs in association with petroleum, and issues with it from the earth in many places. Further, it is formed by the decomposition of organic substances under water, hence its common name marsh gas. Cellulose, which consists of the woody fibres of dead portions of plants, is decomposed by certain bacteria into marsh gas and carbonic acid, as was first demonstrated by Hoppe-Seyler,¹ who placed filter paper,

¹ F. Hoppe-Seyler, *Ber. d. d. chem. Gesellsch.* 1883, vol. xvi. p. 122, and *Z. f. physiol. Chem.* 1886, vol. x. p. 409.

which is almost pure cellulose, in a vessel with water, and adding to this some river mud, collected over mercury during several years the gases which were evolved. They consisted of almost equal volumes of marsh gas and carbonic acid, bye-products not being formed to any considerable extent. It is very probable that the cellulose is first split up into sugar molecules with absorption of water (cf. Lecture 8), and that the sugar then breaks down into equivalent quantities of carbonic acid and marsh gas :

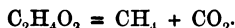


This process continually goes on at the bottom of ponds, etc. When, in winter, the water plants die and sink to the bottom, and the fallen leaves and withered twigs of trees growing at the edges do likewise, a material rich in cellulose is formed there, and this under the action of bacteria undergoes decomposition into these two gases. The carbonic acid has a high absorption coefficient, and dissolves quickly in the water ; but the marsh gas, which has an absorption coefficient twenty-five times smaller, collects in tiny bubbles in the mud, and if this be stirred up with a stick the little bubbles unite to form larger bubbles, which rise to the surface, where they can be collected in an inverted vessel filled with water. The collected gas can be lighted, and it will burn with a faintly luminous flame. [It forms a very explosive mixture when mixed with air or oxygen, and water and carbonic acid are formed :



Marsh gas is also formed in the intestines of man by a similar process of bacterial fermentation ; not only does it originate from the woody fibres of the food, but it also appears possible that it can be formed from purely animal food.¹

Just as the sugar molecules, which arise from the decomposition of cellulose, are split up into equal volumes of marsh gas and carbonic acid, so also acetic acid, of which sugar is a polymer, is split up into the same products :

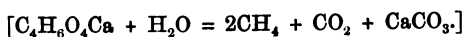


Hoppe-Seyler and Herter² showed that calcium acetate, when

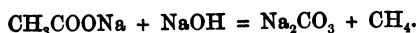
¹ E. Ruge, *Sitzungsber. d. k. Akad. d. W. zu Wien*, 1862, vol. xliv. p. 739. Tappeiner, *Z. f. physiol. Chem.* 1882, vol. vi. p. 432 ; *Z. f. Biologie*, 1883, vol. xix. p. 228 ; 1884, vol. xx. p. 52 ; *Collected Papers of the Path. Inst. Munich*, edited by O. Bollinger (F. Enke, Stuttgart : 1886), pp. 215, 236.

² F. Hoppe-Seyler, *Pflüger's Arch.* 1876, vol. xii. p. 12.

subjected to fermentation by the bacteria of river mud in the same way as cellulose, evolved marsh gas and carbonic acid ; but in this case half of the carbonic acid remained behind combined with the calcium :

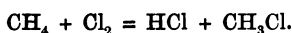


Acetic acid undergoes the same decomposition as is produced by the ferments of these bacteria when it is heated to a high temperature with excess of alkali :



This process will be discussed when we come to the constitution of acetic acid. The most convenient method of preparing marsh gas depends upon this reaction : a mixture of sodium acetate and soda lime is heated in a retort, and the evolved gas is collected over water. Soda lime, and not pure sodium hydrate, is used because soda lime, which consists of a mixture of one part of sodium hydrate and two parts of lime, neither melts nor swells up when it is heated, as does sodium hydrate ; consequently it allows of an easier passage for the evolved gas.

Methane, like all the hydrocarbons of this series, is either not attacked at all, or only with difficulty, by most chemical reagents. [It is either not attacked at all, or only very slightly, by oxidising agents, such as nitric and chromic acids ; concentrated sulphuric acid and strong alkalies have no action upon it.] The halogens are exceptions : for example, if chlorine acts upon methane in diffused daylight, one of its hydrogen atoms is substituted by chlorine, and methyl chloride, or chloromethane, is obtained :



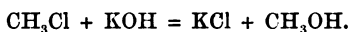
By further action, the remaining hydrogen atoms of methane are replaced by chlorine, and at the same time the boiling point of the product rises as the number of the substituted hydrogen atoms is increased. Methane, in which only one of the hydrogen atoms is substituted by chlorine, is a gas at the ordinary temperature ; but when more than one hydrogen atom is replaced, the substituted products are liquids :

Chloromethane or methyl chloride	. CH_3Cl	. Boiling point - 22° C.
Dichloromethane or methylene chloride	. CH_2Cl_2	. " + 40° C.
Trichloromethane or chloroform	. $CHCl_3$. " + 61° C.
Tetrachloromethane or carbon tetrachloride	CCl_4	. " + 77° C.

Chloroform, or methane in which three hydrogen atoms are replaced by chlorine, is of great importance in medicine. On the

large scale it is not prepared from marsh gas, but from ethyl alcohol, and it will be described later (p. 51).

When methyl chloride is heated for some time with caustic potash at 100° C., an hydroxyl group takes the place of the chlorine atom in the methane, and methyl alcohol and potassium chloride are formed :



Methyl alcohol is a colourless liquid boiling at 66° C., with a specific smell, and has properties very similar to those of ordinary or ethyl alcohol. It is lighter than water with which it mixes in every proportion, its specific gravity being 0.81 ; and it burns with a pale blue, non-luminous flame.

Methyl alcohol has an action upon the animal body similar to that of ethyl alcohol, but its action has been less investigated. According to the prevailing doctrines, the poisonous action of the different alcohols—which can be derived from the members of the methane series in the same way as methyl alcohol from marsh gas—is more intense the higher the molecular weight of the alcohol. Hence methyl alcohol is less poisonous than ethyl alcohol, and this less so than propyl alcohol, and so on.¹

According to the latest investigations, the poisonous effect of methyl alcohol takes place more slowly, but lasts longer than that of ethyl alcohol,² and hence perhaps the symptoms of chronic poisoning produced by methyl alcohol are severer than those produced by ethyl alcohol. As methyl alcohol is now extensively used technically, chronic poisoning by its misuse is no longer of rare occurrence.

Methyl alcohol is used technically as a solvent for fats, oils, resins, etc., and especially in the manufacture of aniline dyes. On a large scale it is not prepared from methane, but is obtained as a bye-product in the dry distillation of wood, therefore it bears the name of wood-spirit. It is separated from the distillate, together with acetic acid and other products, by special methods of purification (p. 57).

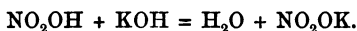
Methyl alcohol—like all alcohols, that is, hydrocarbons in which a hydrogen atom is replaced by an hydroxyl group—has the property of combining with the strongest organic and inorganic acids forming neutral compounds, with the elimination of water. These compounds are called Esters.³ The alcohol plays a similar rôle in the neutralisa-

¹ George Baer, *Studies on Acute Poisoning by Different Alcohols*, Inaug. Dissert. Berlin, 1898. Herein the earlier references are cited.

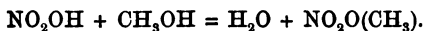
² Hunt, *Johns Hopkins Hosp. Bull.*, August–September 1902, p. 213.

³ These were formerly called compound ethers.

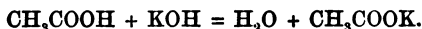
tion of acids to that of the metallic hydroxides (the inorganic bases) in the formation of salts :



[Potassium nitrate.]

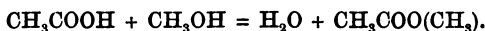


Nitric acid methyl ester [methyl nitrate.]



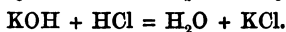
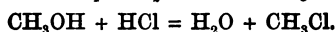
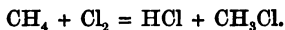
Acetic acid.

Potassium acetate.



Acetic acid methyl ester [methyl acetate.]

If the acid with which the alcohol is combined in an ester be a halogen acid, the compound obtained is the same as that formed by the substitution of a hydrogen atom by a halogen atom in the corresponding hydrocarbon :



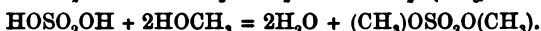
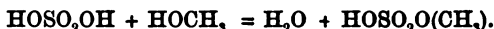
Chloromethane is therefore also the methyl ester of hydrochloric acid, or methyl chloride.

Alcohols differ from the inorganic bases in that they do not react with vegetable colours [litmus], and in that their aqueous solutions do not conduct an electric current. This difference is explained hypothetically, by assuming that the hydroxyl (OH) groups in the solutions of bases are present in the form of ions ; but those of alcohols are not ionised. The facts that bases combine with acids instantaneously, but that the formation of esters takes place slowly, especially at the ordinary temperature, agree with this hypothetical difference between bases and alcohols ; and, further, that the acids in the esters cannot be identified by the formation of insoluble precipitates, as in salts, also bears out this theory ; for example, no precipitate is obtained on adding methyl chloride to a solution of silver nitrate.

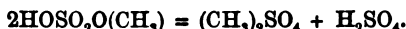
Alcohols give with the dibasic acids two series of esters ; the two hydrogen atoms which can be substituted by metals in these acids can also be substituted by the alcohol, or so-called alkyl, radicals—in the case of methyl alcohol, the methyl (CH_3) radical. Thus, for example, if one of the hydrogen atoms in sulphuric acid be replaced by methyl, the monobasic acid, methyl sulphuric acid is obtained, which gives crystallisable salts with inorganic bases ; if both

D

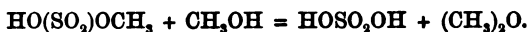
the hydrogen atoms be replaced by methyl groups the methyl ester of sulphuric acid is obtained :



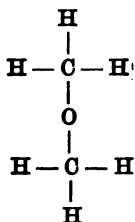
When methyl alcohol is mixed with concentrated sulphuric acid, heat is evolved and methyl sulphuric acid is obtained ; if this mixture be submitted to distillation, the neutral methyl ester of sulphuric acid is formed and distils over, whilst sulphuric acid remains behind :



If a large excess of methyl alcohol be present, two molecules of it combine together, with loss of water, and *methyl ether* is formed :



In methyl ether two monovalent methyl radicals are linked together, by the divalent, oxygen atom :



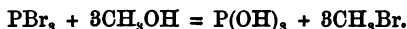
At the ordinary temperature methyl sulphuric acid and the methyl ester of sulphuric acid are liquids, but methyl ether is a gas.

Amongst the esters of methyl alcohol the esters of the halogen acids, or the alkyl halides, are of particular importance, because they serve as the starting-point in the synthesis of more complex compounds. They also serve the purpose of introducing the methyl radical into other compounds. The most important methods of their preparation are the following :

A mixture of methyl alcohol and concentrated hydrochloric acid, or of methyl alcohol, sodium chloride, and sulphuric acid, is heated, and the gas which is evolved is collected over water. The methyl chloride, or chloromethane, so obtained is a colourless gas with an ethereal smell ; it is liquefied at $-22^\circ \text{C}.$, and is soluble with difficulty in water, but more readily in ethyl alcohol. Methyl chloride, liquefied by high pressure, is used in the production of cold by evaporation, especially in Medicine, where it is employed to produce anæsthesia by freezing—e.g. in the treatment of neuralgias, and in small painful

operations. For this purpose liquid methyl chloride can be obtained in metal tubes provided with a special nozzle.

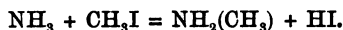
Methyl bromide can be prepared in a similar way to methyl chloride, by saturating methyl alcohol with hydrobromic acid. The following method of preparing it is, however, easier and more advantageous ; it depends upon the following reaction of methyl alcohol with phosphorus tribromide, PBr_3 , phosphorous acid and methyl bromide being formed :



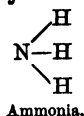
This reaction takes place with great violence, and it is therefore carried out by allowing the phosphorus tribromide to be formed gradually in the presence of methyl alcohol. In order to ensure this, red phosphorus and methyl alcohol are placed in a flask, and the bromine is allowed to fall into it drop by drop. The methyl bromide which is formed is a gas condensing at $4^\circ\text{--}5^\circ\text{C.}$ to a liquid.

Methyl iodide is obtained in an exactly analogous manner from methyl alcohol, phosphorus, and iodine. At the ordinary temperature it is a liquid, boiling at 44°C.

The alkyl halides have manifold uses in synthetical chemistry ; they are used for replacing hydrogen atoms by alkyl groups ; the manner in which methyl iodide is used to replace the hydrogen atoms in ammonia by methyl radicals has already been described (p. 10). If a concentrated aqueous solution of ammonia be heated in a sealed tube with methyl iodide, the following reaction will take place :



The methylamine thus formed is a strong base like ammonia, and therefore is present in combination with the hydriodic acid, which is formed at the same time ; from this salt it can be liberated by distillation with potash. By the further action of methyl iodide upon ammonia, its two remaining hydrogen atoms can be replaced by methyl radicals. The three following substitution products are thereby obtained :



Ammonia.



Methylamine.



Dimethylamine.



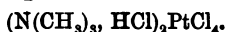
Trimethylamine.

All these three substituted ammonias are gaseous at the ordinary temperature, and are very soluble in water. Methylamine, of all the known gases, is the most soluble in water. It is well known that large volumes of hydrochloric acid and ammonia can be taken up by

water, which at the ordinary temperature absorbs about 450 times its volume of hydrochloric acid, and 600 times its volume of ammonia; at 12°·5 C. water can take up 1150 times its volume of methylamine.

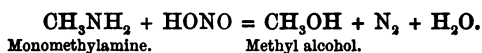
Methylamine will be again met with in connection with the synthesis of sarcosine and creatine. Creatine is a complicated compound rich in nitrogen constantly found in considerable quantities in our tissues, especially in muscle. On heating creatine with soda lime, methylamine is evolved, together with ammonia. Still more important physiologically than methylamine is trimethylamine, which is a decomposition product of choline, this being a decomposition product of lecithin. Lecithin is a constant constituent of every cell of all animal and plant tissues, and on account of its wide distribution in the tissues, trimethylamine often occurs amongst those gases which are evolved in their decomposition; it can be easily identified by its smell. The tissues of fishes, which are especially rich in lecithin, produce this gas at the commencement of putrefaction, and hence the statement that trimethylamine smells like herring brine.

The substituted ammonias form salts with acids which are analogous in constitution to the ammonium salts. The salts formed with hydrochloric acid are analogous to ammonium chloride, and form, like it, beautifully crystalline double salts with platinum chloride. The double salt of platinum chloride with trimethylamine hydrochloride has the composition :



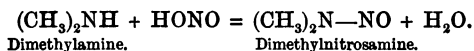
[The substituted ammonias, or amines, can be distinguished by their behaviour to nitrous acid.

Primary amines, such as monomethylamine, which contain the $-NH_2$ group, are converted into the corresponding alcohols with evolution of nitrogen :



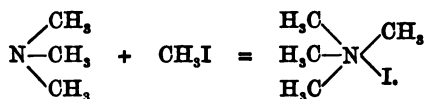
This is a general reaction for converting an $-NH_2$ group into an $-OH$ group, which will often be referred to subsequently.

Secondary amines, such as dimethylamine, contain the $>NH$ group, and are converted into *nitroso* derivatives, which are yellow oils :

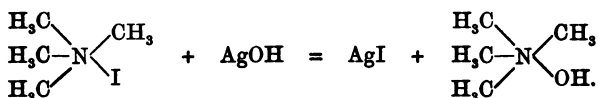


Tertiary amines, such as trimethylamine, in which the three hydrogen atoms of ammonia are replaced by methyl radicals, are not acted upon.]

When, in the preparation of trimethylamine from ammonia and methyl iodide, the latter is present in excess, the trimethylamine which is formed combines with the methyl iodide to a theoretically very interesting compound, in which we must regard the nitrogen as being pentavalent:



This compound, tetramethylammonium iodide, is an ammonium iodide in which all the four hydrogen atoms have been replaced by methyl radicals; it consists of colourless needles or prisms, soluble with difficulty in water. When it is treated with silver hydroxide it behaves differently from the simple ammonium salts; the ammonium hydroxide which is obtained from the latter cannot be isolated, as it decomposes immediately into ammonia and water, but tetramethylammonium hydroxide can be obtained in a crystalline state:

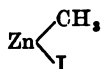


Tetramethylammonium hydroxide is not volatile; its crystals are deliquescent; its aqueous solution is alkaline, and takes up carbonic acid from the air; it behaves in all its reactions in a manner analogous to potassium hydroxide. On heating, it is decomposed into trimethylamine and methyl alcohol. The analogy between the ammonium salts and the potassium salts can thus be demonstrated better in the substituted ammonium salts than in the simple ones.

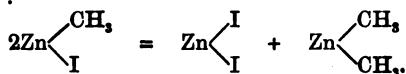
Inorganic chemistry shows that phosphorus, arsenic, and antimony are elements very similar to nitrogen. They are trivalent or pentavalent, and they form compounds with hydrogen analogous to ammonia. In these compounds, just as in ammonia, the hydrogen atoms can be partially, or completely, replaced by alkyl radicals. These compounds have only a theoretical and purely chemical interest, and are of no practical or physiological value; it suffices, therefore, simply to mention them. [Arsenical poisoning from wall-papers made with arsenic compounds is due to the formation of methylarsine, CH_3AsH_2 , by the action of bacteria.]

The methyl compounds with the metals zinc and sodium are more important than the compounds with arsenic and antimony, as they are often used in the synthesis of more complex compounds. When metallic zinc is heated in a sealed tube with methyl

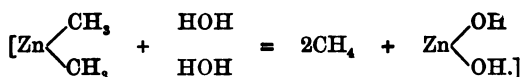
iodide for a long time at 130° C., a non-volatile compound of the composition



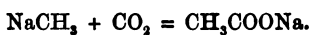
is first formed, which, on further heating, decomposes into zinc iodide and zinc methyl :



Zinc methyl is a colourless liquid with an unpleasant penetrating smell ; it boils at 46° C., takes fire spontaneously in the air, and is violently decomposed by water into methane and zinc hydroxide :

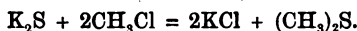


Metallic potassium and sodium dissolve in zinc methyl with the separation of an equivalent quantity of zinc. The potassium and sodium methyl, which are presumably formed, have not yet been isolated ; the solution absorbs carbonic acid, the alkali salt of acetic acid being formed :



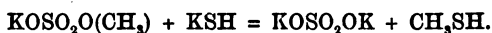
A word must still be said about the compounds of methyl with sulphur, or methyl sulphides. In methyl alcohol, and in methyl ether, the divalent oxygen atom can be replaced by the divalent sulphur atom, and the two compounds methyl mercaptan (CH_3SH) and methyl sulphide ($[(\text{CH}_3)_2\text{S}]$) result ; the former is of physiological interest, as it occurs as a decomposition product of certain proteins.

In order to prepare methyl sulphide, potassium sulphide is simply dissolved in methyl alcohol and gaseous methyl chloride is passed into the heated solution, when methyl sulphide distils over :



This is a disagreeably smelling liquid, which boils at 37° C.

Methyl mercaptan is obtained by distilling potassium methyl sulphate with potassium hydrosulphide :



and it is a liquid with a penetrating nauseous smell, boiling at 6° C. It occurs amongst the gases which are evolved during putrefaction, i.e. in the decomposition of certain proteins by bacteria,¹ and it is

¹ M. Nencki and Sieber, *Monatshefte f. Chem.* 1889, vol. x. p. 526.

found in the large intestine of man,¹ as well as in the urine after eating asparagus or cabbage.² It can be obtained from some proteins, not only by bacterial decomposition, but also by fusing with potash and subsequently distilling the mass with oxalic acid.³

There are very few gases to which our olfactory nerves are so sensitive as to methyl mercaptan. We can perceive it quite distinctly

when only $\frac{1}{23,000,000}$ milligramme is contained in a litre of air.⁴

Our sensitiveness to the smell of this gas finds a teleological explanation in the fact that it is a product of putrefaction; since the most poisonous products of putrefaction, the toxalbumins, are not volatile and are therefore without smell, this evil-smelling gas, which appears at the same time, warns us of their presence.

Amongst the practically important derivatives of methyl alcohol are its oxidation products formaldehyde and formic acid. If oxidising agents be allowed to act upon methyl alcohol, two hydrogen atoms are removed from it by the oxygen with the formation of formaldehyde, CH_2O , and then on further action an atom of oxygen enters the molecule of formaldehyde, producing formic acid, HCOOH . [Cf. Lecture 5.]

The most convenient method of preparing formaldehyde consists in passing the vapours of methyl alcohol through a glass tube containing a platinum spiral, which is at first gently heated with a flame; this commences to glow as the vapours are passed over it, and continues to do so after the flame is removed. This action of platinum has not yet been explained, but it belongs to the so-called 'catalytic' or 'contact' actions, which are met with in inorganic chemistry, e.g. in the form of Döbereiner's lamp.

Formaldehyde is a colourless pungent-smelling gas, which condenses to a liquid at -21°C . The name aldehyde is corrupted from *alcohol dehydrogenatum*, the first syllable—*form*—showing its relation to formic acid.

Formaldehyde is a neutral compound; it does not combine with alcohols or acids to form esters, with loss of water, and therefore it cannot be regarded as a hydroxyl-containing compound; we must

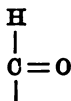
¹ M. Nencki, *ibid.* p. 862.

² M. Nencki, *Arch. f. exper. Pathol. u. Pharmacol.* 1891, vol. xxviii. p. 206; F. Niemann, *Arch. f. Hygiene*, 1893, vol. xix. p. 126; M. Rubner, *ibid.* p. 136.

³ N. Sieber and G. Schoubenko, *Arch. des Sciences biologiques St. Pétersbourg*, 1892, vol. i. p. 314.

⁴ Emil Fischer and Franz Penzoldt, *Liebig's Ann. d. Chem.* 1887, vol. ccxxxix. p. 131.

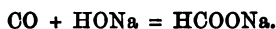
assume that the oxygen atom is bound by two bonds to the carbon atom, and its structural formula is written as follows :



It is absorbed by water, and if its aqueous solution be allowed to evaporate over concentrated sulphuric acid, only a portion of the formaldehyde is evolved with the water vapour; the remainder is polymerised, and remains behind as a white crystalline mass. This polymerisation product is called oxymethylene, and the size of its molecule is unknown; on heating, it is again decomposed into molecules of formaldehyde. The polymerisation of aldehyde, in slightly alkaline solution, to sugar has already been mentioned (p. 3).

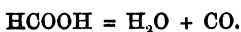
A 40-per-cent. solution of formaldehyde in water is known in commerce under the name of Formol or Formalin; it is used, when considerably diluted, as a disinfecting agent, and also as a preservative for anatomical preparations. Tissues are converted into tough elastic masses by formalin.

Formic acid can be obtained from methyl alcohol by the action of the most various oxidising agents. The intermediate product, formaldehyde, cannot generally be identified in the process. It is only when such weak agents as atmospheric oxygen are used that the process of oxidation can be stopped at the stage of formaldehyde. Formic acid can be also prepared synthetically from carbon monoxide, which is obtained by the direct union of its elements, on heating charcoal in the presence of insufficient oxygen. When carbon monoxide is allowed to act for a long time on potassium hydrate at 100°C ., it is absorbed with the formation of potassium formate. This method has recently been employed in the preparation of formic acid on a large scale; carbon monoxide under a pressure of six to seven atmospheres is completely absorbed by sodium hydrate at $156\text{--}170^{\circ}\text{C}$. in about six hours, and the theoretical quantity of sodium formate expected from the equation is formed :

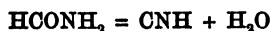
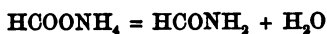


The formic acid is liberated from the salt by a non-volatile acid, such as sulphuric acid, and then distilled; it is a pungent, acid-smelling liquid, boiling at 99°C . and becoming crystalline below 0°C .

When heated with concentrated sulphuric acid, it is decomposed into carbon monoxide and water :



This decomposition corresponds to its synthesis. Ammonium formate, a deliquescent salt, when heated loses water, forming firstly formamide, a colourless liquid, and then hydrocyanic acid:



This reaction is described in detail under the chemistry of the cyanogen compounds. [Cf. Lecture 10.]

In nature, formic acid occurs as a secretion product in ants, and was first prepared by the distillation of crushed ants with water. It is generally believed that the ants make use of this acid as a means of defence against the attacks of their enemies, wounding them first with their mandibles and then discharging the acid into the wounds. It is still questionable whether the inflammation at the bitten spot is really caused by the formic acid, or by a more intense poison. It seems more probable that formic acid is a weapon against those enemies which cannot be reached by the mandibles and stings, namely the bacteria and the moulds. Formic acid is a very energetic disinfecting agent; like all acids it destroys putrefactive micro-organisms, but it possesses this property in a greater degree than do most of the other organic acids. If we consider how many corpses of small animals, and portions of corpses of larger animals, ants drag into their nests, the constant excretion of such a disinfecting agent appears absolutely necessary. The turpentine contained in the pine-needles which ants prefer as the material for the construction of their nests has also a disinfecting action.

According to August Vogel,¹ a small quantity of formic acid is contained in honey, its importance here also consisting in its disinfecting action. Vogel showed that boiled honey fermented more easily than unboiled, and that quite a small addition of formic acid to a solution of grape-sugar prevented its fermentation by yeast.

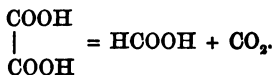
It is often stated that other insects excrete formic acid, and that it occurs in poison glands and stings, as, for example, in the stinging hairs of the 'processionary' caterpillars, and that it is the active principle of the stinging hairs of certain plants, such as the nettle. If we examine these statements more closely we become convinced, firstly, that the presence of formic acid has never yet been definitely demonstrated in these particular stinging organs; and secondly, that it is still less proven that formic acid can cause such an inflammation

¹ A. Vogel, *Sitzungsber. d. math. physikal. Klasse d. Akad. d. W. zu München*, 1882, vol. xii. p. 345.

of the skin. This can only be caused by a much more intense poison, which suggests the toxalbumins (cf. Lecture 17). This assumption is most probable in the case of the poison of the stinging-nettle, as it has been found that boiling destroys its poisonous action; comparative inoculation experiments with boiled and unboiled extracts of stinging-nettles have shown this.¹ It has often been asserted that formic acid occurs in human tissues and secretions, but its presence has never been demonstrated.

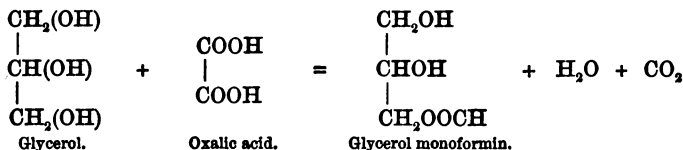
Formic acid has been employed for a very long time as a therapeutic agent; ant-baths have been in use for many centuries. Formerly ants, together with the pine-needles of their nests, were put into the bath, and, if possible, a complete nest; later hot aqueous extracts, sometimes of ants alone, sometimes of these with the pine-needles of their nests, were used as baths. Then ants were distilled with weak alcohol, when formic acid passed over with the alcohol and water vapours into the distillate, which was used as a liniment in skin diseases, in rheumatic affections, and in neuralgia. *Spiritus formicarum* (4 per cent. formic acid, 26 per cent. water, 70 per cent. alcohol) is found in the German Pharmacopœia of to-day, but it is no longer prepared from ants.

Formic acid nowadays is prepared most easily and cheaply from oxalic acid, which is obtained by oxidation from the cheapest carbohydrates (p. 2); when heated with glycerol at 100° C. oxalic acid is decomposed into carbonic acid and formic acid:



[The rôle played by the glycerol is probably as follows.²

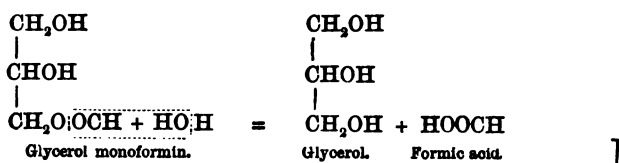
The reaction takes place in two stages. The first stage takes place at 100–110° C., and consists in the evolution of carbon dioxide, and the production of formic acid which combines with the glycerol forming glycerol monoformin—an ester of glycerol with formic acid. The constitution of glycerol is described later (cf. Lecture 7):



¹ G. Haberlandt, *Sitzungsber. d. Wiener Akad. math. natw. Klasse*, 1886, vol. xciii. pt. i., p. 123.

² J. E. Lorin, *Compt. rend.* 1881, vol. xciii. p. 1143; *Bull. Soc. Chim.* 1882, vol. xxxvii. p. 104.

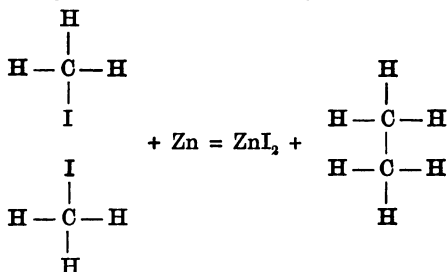
The monoformin is then hydrolysed by excess of oxalic acid into glycerol and formic acid which distils over. The oxalic acid is added in separate portions; each fresh quantity gives rise to another equivalent of formic acid, and the glycerol is recovered again each time, so that a continuous process is established:



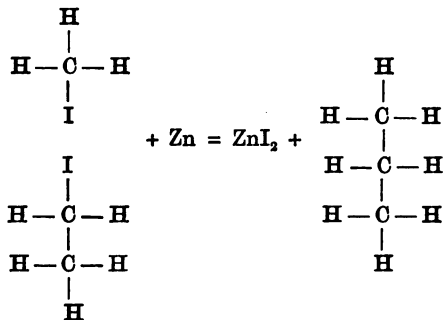
LECTURE IV

ETHANE AND ITS DERIVATIVES

THE second member of the marsh gas series, ethane or dimethyl, is a colourless gas with no smell, and it occurs in nature dissolved in raw petroleum. Its synthetical preparation has been already described (p. 18); starting from acetylene, C_2H_2 , which is prepared by the direct union of its elements, we obtain by the action of nascent hydrogen, firstly ethylene, C_2H_4 , and then ethane, C_2H_6 . A second method of preparing it synthetically consists in linking together two methyl radicals; if we allow zinc or sodium to act upon methyl iodide (synthesis p. 35), the corresponding metallic iodide is formed and the two liberated methyl radicals combine together :



This is a general method of synthetically preparing higher hydrocarbons from lower ones [e.g. methyl iodide and ethyl iodide will give propane, ethyl iodide and propyl iodide pentane :

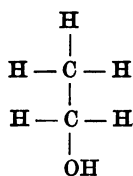


Propane.

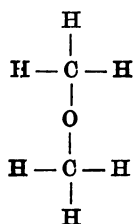
If we wish to prepare the derivatives of ethane synthetically, we can, as in the case of methane, first substitute the hydrogen atoms by halogen atoms, and then substitute these by other elements and radicals. We can, for example, prepare ethyl chloride in an exactly analogous manner to methyl chloride, and then by substituting the chlorine by hydroxyl we can obtain ethyl alcohol (p. 32). A second method of synthesising it by the absorption of ethylene by concentrated sulphuric acid [and the decomposition of the resulting compound by water] has already been described (p. 7). The preparation of ethyl alcohol by the fermentation of carbohydrates will be mentioned later (p. 116).

Ethyl alcohol is a liquid with a characteristic smell, boiling at 78°C . Its specific gravity at the ordinary temperature is less than that of water, $= 0.79$. It mixes with water in all proportions with the evolution of heat, and it is very hygroscopic—i.e. it takes up moisture from the air. Its extensive use as a solvent and preserving agent is well known.

The percentage composition of ethyl alcohol and its molecular weight are the same as that of another compound previously described—methyl ether—which, however, has quite different physical and chemical properties. At the ordinary temperature methyl ether is a gas, ethyl alcohol a liquid. Ethyl alcohol and methyl ether are therefore isomeric compounds; examples of isomerism have been met with amongst the hydrocarbons, but we have here the first very interesting example of this phenomenon in organic compounds containing oxygen:

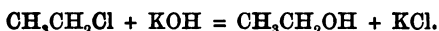


Ethyl alcohol.



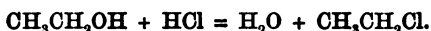
Methyl ether.

That ethyl alcohol is a hydroxyl compound follows from its synthesis:



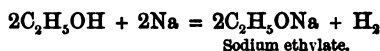
The reverse reaction occurs when ethyl alcohol is saturated with hydrogen chloride and heated; a chlorine atom takes the place of the hydroxyl group and chlorethane, or ethyl chloride,—in which one of the hydrogen atoms of ethane is replaced by chlorine—is formed,

the hydroxyl group of the ethyl alcohol separating as water in combination with the hydrogen atom of the hydrochloric acid :



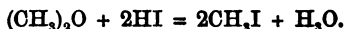
The oxygen atom in ethyl alcohol therefore closely adheres to one of the hydrogen atoms ; it only enters and leaves the molecule at the same time as a hydrogen atom, without any separation of the two carbon atoms.

[Ethyl alcohol, like other alcohols, reacts with metallic sodium ; hydrogen is evolved, and a white mass, sodium alcoholate or ethylate, remains behind upon evaporation. The reaction is analogous to that of sodium with water :



and it shows that one of the hydrogen atoms behaves differently from the others which are contained in the molecule. The oxygen atom is not removed from the molecule, and it can be shown that it is the hydrogen atom attached to the oxygen atom which is replaced by the sodium.]

Methyl ether behaves quite differently. If we wish to remove the oxygen atom from it, e.g. by the action of hydriodic acid, the two carbon atoms are separated, and two molecules of methyl iodide and water are obtained :



[Methyl ether does not react with sodium, and therefore does not contain a hydrogen atom in its molecule which is combined in a different way from the others.]

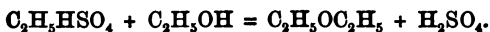
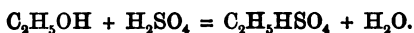
Consequently it must be assumed that the carbon atoms in methyl ether are linked together by an oxygen atom, and this relationship is expressed in the above formula.

The derivatives of ethyl alcohol are exactly analogous to those of methyl alcohol, both in their methods of preparation and in their chemical reactions, and therefore only those of special practical importance will be mentioned.

Ethyl alcohol, like methyl alcohol, combines with acids, with loss of water, forming neutral esters ; by the loss of water from two molecules of ethyl alcohol the practically important ethyl ether, $\text{CH}_3-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_3$, or $(\text{C}_2\text{H}_5)_2\text{O}$, is obtained. It is prepared,

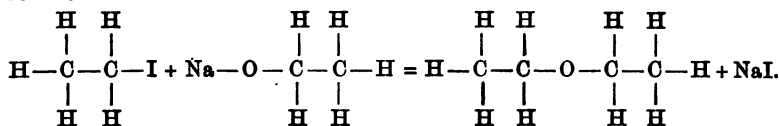
like methyl ether, by the distillation of alcohol with concentrated sulphuric acid (p. 34).

[Ethyl sulphuric acid is first obtained by the action of concentrated sulphuric acid upon ethyl alcohol, and this is then decomposed by excess of alcohol with the formation of ethyl ether :



The sulphuric acid is regenerated ; a small quantity can therefore convert a large quantity of alcohol into ether, and the process is known as the continuous ether process. (As a matter of fact, the sulphuric acid is decomposed by further action—oxidation of the alcohol to carbon dioxide and water, and consequent reduction of the sulphuric acid to sulphur dioxide and water—so that from time to time a fresh supply of sulphuric acid is necessary. Hardly any reaction in organic chemistry is absolutely quantitative ; bye-products are generally formed at the same time.)

The constitution of *ethers* was first demonstrated by Williamson in 1851, who obtained ether by heating sodium ethylate with ethyl iodide :



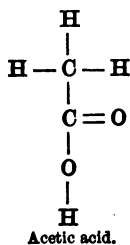
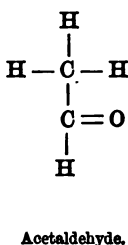
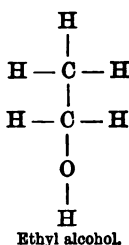
Methyl ether can be obtained in a similar way, as also can mixed ethers, e.g. methyl ethyl ether from methyl iodide and sodium ethylate, or from ethyl iodide and sodium methylate. Ethers correspond to oxides such as $\text{Na}-\text{O}-\text{Na}$.]

From its method of preparation when its constitution was not known, ether obtained the quite inappropriate name of sulphuric ether, which is still used in pharmacy.

Ethyl ether, or shortly, ether, is a colourless liquid boiling at $35\cdot5^\circ\text{C}$. It is lighter than water, with which it mixes, but not in all proportions ; water dissolves a small quantity of ether, and ether dissolves a small quantity of water, and the ether saturated with water floats on the water saturated with ether. The method of 'ether extraction' depends upon this property. It is extensively used in analytical chemistry as a solvent, especially in the separation of substances which are soluble with difficulty in water but easily in ether, from substances which are easily soluble in water but with difficulty in ether. With alcohol it mixes in all proportions.

In Medicine, ether has attained great importance as an anæsthetic; it was used for dental operations in 1846 by the dentist Morton, of Boston, before the introduction of chloroform by Simpson, and nowadays many surgeons prefer it to chloroform in certain operations, chiefly because the danger of heart-failure is less with ether than with chloroform.

From a physiological and medical point of view the oxidation products of ethyl alcohol and its derivatives are of great interest. By the action of oxidising agents, two atoms of hydrogen are first removed from ethyl alcohol with the formation of acetaldehyde, and then an atom of oxygen enters the molecule of aldehyde and acetic acid is obtained :



Acetaldehyde is most conveniently prepared by distilling a mixture of an aqueous solution of potassium bichromate with alcohol and sulphuric acid. The aldehyde, which distils over, must be collected in thoroughly well-cooled receivers, as it boils at 22° C. Acetaldehyde has a great tendency to become further oxidised to acetic acid; it therefore acts as a reducing agent upon compounds which easily give off oxygen; thus, for example, it reduces silver oxide in ammoniacal solution to metallic silver [and an alkaline solution of a cupric salt to cuprous oxide, which separates out as a red precipitate]. By the action of nascent hydrogen, acetaldehyde is reconverted into ethyl alcohol.

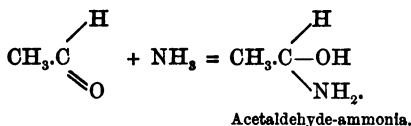
Acetaldehyde, just as formaldehyde (p. 39), is a perfectly neutral compound; it combines neither with acids nor with bases or alcohols, i.e. it cannot combine with compounds containing hydroxyl groups, with elimination of water. The oxygen atom in acetaldehyde is therefore not contained as hydroxyl; this is expressed in the above structural formulæ, where ethyl alcohol and acetic acid both contain hydroxyl groups, but aldehyde contains its oxygen joined to the carbon atom by both its valencies.

If a few drops of concentrated sulphuric acid be added to acetaldehyde, the liquid becomes hot, and often commences to boil violently; when the reaction is over, it can be determined that the boiling-point of the liquid, which has remained colourless, has risen from 22° C. to 124° C. The vapour density of the new compound is three times as great as that of the original one, and therefore it must have a molecular weight three times as high, though elementary analysis gives the same percentage composition for the two compounds. Such compounds having the same percentage composition but different molecular weights, are called *polymers*, in contradistinction to *isomers*, which have the same percentage composition and the same vapour density, and are often called *metamers*.

This polymeric compound of acetaldehyde with three times its molecular weight is called paraldehyde. It is used in medicine as an hypnotic. If paraldehyde be distilled with dilute sulphuric acid, it is again converted into ordinary aldehyde. Those polymeric compounds which can be converted the one into the other are termed true polymers, in contradistinction to those compounds which cannot be converted into one another by such simple reactions, such as formaldehyde (CH_2O), acetic acid ($\text{C}_2\text{H}_4\text{O}_2$), lactic acid ($\text{C}_3\text{H}_6\text{O}_3$). This process of coupling together several molecules with the formation of polymeric compounds is called polymerisation (cf. p. 40).

[The following reactions of acetaldehyde are of great importance :

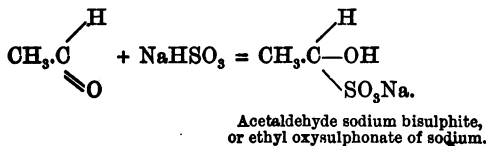
1. With ammonia it forms a colourless crystalline substance known as aldehyde-ammonia; this is obtained by simply passing ammonia gas into an ethereal solution of aldehyde :

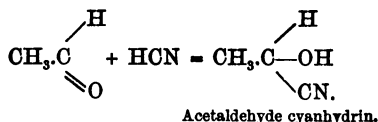


This compound gives the reactions of an aldehyde, and is soluble in water. It is easily decomposed by acids, the aldehyde being regenerated and the ammonium salt of the acid employed being formed.

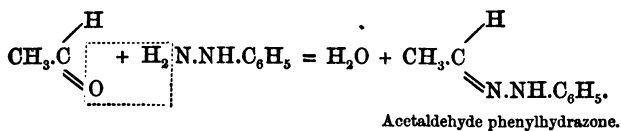
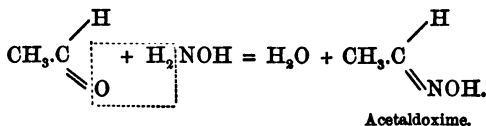
2. With caustic alkalis acetaldehyde is converted into a brown resinous substance, known as aldehyde resin.

3. Acetaldehyde forms addition compounds with sodium bisulphite and with hydrocyanic acid; the latter compound is called acetaldehyde-cyanhydrin :



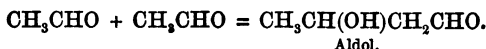


4. The reactions of acetaldehyde with hydroxylamine and the hydrazines, especially phenylhydrazine, are important; oximes and phenylhydrazones respectively are the compounds obtained :

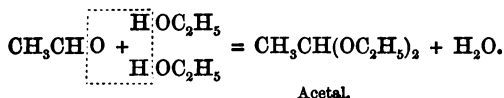


The latter reaction is made much use of in isolating and identifying the carbohydrates.

The 'aldol condensation' which acetaldehyde (and other aldehydes) undergo when concentrated hydrochloric acid is added to well-cooled acetaldehyde and the mixture allowed to stand, is an instance of another condensation which acetaldehyde can undergo; two molecules of acetaldehyde simply combine together :

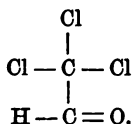


Acetaldehyde can unite with alcohols in the presence of a little hydrochloric acid to form compounds known as acetals :



Formaldehyde unites with methyl alcohol giving methylal.]

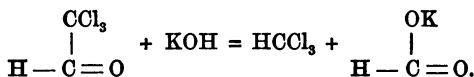
When chlorine is allowed to act upon aldehyde, three of its hydrogen atoms are replaced by chlorine, and trichloraldehyde, generally called chloral, is obtained :



Chloral is a colourless liquid with a penetrating smell ; when kept in a closed vessel it changes into a solid polymeric compound, which, on heating to 180° C., is reconverted into ordinary chloral. It combines

with water forming a hydrate, which is a crystalline stable compound soluble in water. Chloral hydrate, as this compound of chloral with a molecule of water is called, is extensively used as an hypnotic.

The fact that chloral in alkaline solution breaks up into chloroform (p. 31) and formic acid was the reason of its initial use in Medicine.

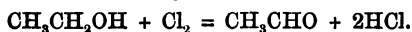


This decomposition was observed in 1832 by Liebig (1803–1873), the discoverer of chloral, but it was only in 1868 that Liebreich suggested the use of chloral as a narcotic in the place of chloroform. He expected that when chloral hydrate was taken, the alkaline fluids of the body—blood, lymph—and of the tissues would liberate chloroform from it; chloral hydrate would thus be preferable to chloroform, which is administered by inhalation, for it would be possible to measure the amount given with greater accuracy. Liebreich's suppositions have not, however, been confirmed. Numerous animal experiments have shown that chloral is not only not decomposed in our tissues, but that it appears in the urine as a more complicated compound. It is reduced in the body to trichloralcohol, which combines with the first oxidation product of sugar, glycuronic acid (cf. Lecture 8), with loss of water, forming the complex compound [urochloralic acid] which is excreted by the kidneys. Nevertheless chloral maintains its position in medicine not as an anæsthetic for surgical operations, but as an hypnotic. The last days of Liebig's life were in fact made easier by his own discovery.

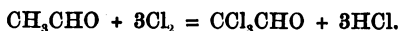
Chloral is now prepared on the large scale by passing dry chlorine into absolute alcohol so long as this is absorbed and hydrochloric acid evolved. Chloral is the substance used in the preparation of the purest chloroform, which is made by heating chloral hydrate with caustic soda. The older method of preparing chloroform, which gives a less pure product, consisted in distilling alcohol with bleaching powder, a mixture of calcium hypochlorite, calcium chloride, and calcium hydrate. This is essentially the same process as the former, chloral being first formed by the action of the calcium hypochlorite upon the alcohol, and then decomposed by the lime into chloroform and calcium formate.

[The process is in reality more complex, and occurs in three stages:

1. The alcohol is oxidised by the chlorine to acetaldehyde:



2. The acetaldehyde is then converted into chloral by chlorine :



3. The chloral is decomposed by the lime into chloroform and calcium formate :



Iodoform, CHI_3 , which has an exactly analogous constitution to chloroform, is prepared by an identical process—by heating alcohol with iodine and caustic potash or potassium carbonate. It consists of yellow hexagonal platelets, which sublime slowly at the ordinary temperature, and it possesses a well-known, unpleasant smell.

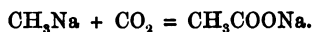
The reaction used in the preparation of iodoform also serves as a qualitative test for alcohol. To the slightly warmed liquid, which is to be tested for alcohol, iodine is added, and then gradually caustic potash until the colour of the iodine just disappears; a yellow precipitate of iodoform is formed. This reaction, called Lieben's reaction, is very delicate, but is apt to be misleading, since many other compounds, e.g. aldehyde, acetone, and in general all compounds containing the group CH_3-C joined to oxygen, give the same reaction. A negative result determines the absence of alcohol, but a positive result alone is not sufficient to indicate its presence. This must be confirmed by distilling off the alcohol and carrying out further tests with the distillate.

Iodoform is widely used as an antiseptic in the treatment of wounds. Its advantages over other disinfecting agents depend upon its being nearly insoluble in water, and upon its being volatile: the first quality prevents any caustic action, as only those substances which penetrate into the tissues can act as caustics; the second quality ensures that the whole neighbourhood of the wound is disinfected. But this latter property has one disadvantage; the unpleasant and persistent smell is irksome to the patient and his surroundings; consequently attempts have been made of recent years to replace iodoform by non-volatile iodine compounds. If iodoform be absorbed in large quantities from wound surfaces, or be taken up by damaged lymph vessels or veins, it may cause very severe toxic symptoms, such as restlessness, general malaise, headache, tremulousness, delirium, and other brain disturbances; it must therefore be used with care as a local antiseptic.

Bromoform, CHBr_3 , an analogous compound to chloroform and iodoform, is a heavy oily liquid, boiling at $150^\circ \text{C}.$; it is very slightly

soluble in water, and has a sweet taste and smell like chloroform. It is sometimes recommended and employed as an internal remedy, but as yet no scientific grounds for its remedial action have been brought forward.

Acetaldehyde, as mentioned above, is an intermediate stage in the oxidation of ethyl alcohol to acetic acid; if an energetic oxidising agent, e.g. manganese dioxide and sulphuric acid, or ozone, be used, ethyl alcohol is completely converted into acetic acid. Ordinary atmospheric oxygen can bring about this reaction if an oxygen carrier, a so-called catalyser such as spongy platinum, be present. Just as there are two methods of preparing ethyl alcohol synthetically (p. 45), so also are there two methods of synthesising acetic acid. A third method was described under the methyl compounds, the synthesis from sodium methyl and carbonic acid (p. 38):



If the sodium acetate so formed be distilled with a non-volatile acid—e.g. sulphuric acid—free acetic acid is obtained. It is a colourless liquid with a characteristic smell, boiling at 118°C . and freezing to a crystalline solid below 17°C .; hence the name glacial acetic acid.

When sodium acetate is heated with an excess of sodium hydrate, marsh gas is evolved, and the residue consists of sodium carbonate:



The same decomposition of acetic acid also takes place under the action of certain ferments, as already stated (p. 30).

This synthesis and decomposition of acetic acid show conclusively that it is a substituted carbonic acid—that is, a carbonic acid in which a hydroxyl group is replaced by the methyl radical:



Carbonic acid.

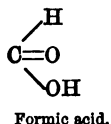
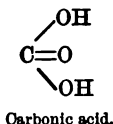


Acetic acid.

Besides the methyl radical, a large number of other radicals can take the place of a hydroxyl group of carbonic acid—e.g. the ethyl radical in propionic acid $(\text{C}_2\text{H}_5)\text{COOH}$, the phenyl radical C_6H_5 in benzoic acid $(\text{C}_6\text{H}_5)\text{COOH}$, etc. All acids thus constituted bear the general name carboxylic acids (carbonic acids). They are all decomposed on heating with excess of alkali into carbonic acid and the

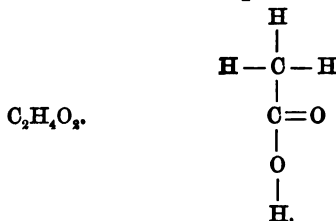
hydrogen compound with the radical, which occupied the position of the hydroxyl group in the carbonic acid. The monovalent radical COOH , which all these acids have in common, is termed *carboxyl*.

Formic acid is also a carboxyl compound ; it is a carbonic acid in which a hydroxyl group is replaced by a hydrogen atom :



Formic acid differs from all the other carboxylic acids by being, at the same time, an aldehyde, and as such it acts as a reducing agent ; it reduces solutions of silver and mercury salts with the separation of metallic silver and mercury.

The structural theory of organic chemistry can be very clearly demonstrated by means of acetic acid. The structural formula of acetic acid is an expression of its synthesis and decomposition, since it shows that it is a carboxyl-containing compound—i.e. a substituted carbonic acid. But this alone does not exhaust the value of structural formulæ, which really express much more. By comparing the empirical formula with the structural formula of acetic acid it can be readily seen how much more the latter expresses :



Acetic acid is a monobasic acid, and therefore only one of its hydrogen atoms can be easily replaced by metals. This is not expressed in its empirical formula, but plainly in its structural formula, where one hydrogen atom has a different position from that of the other three ; this is attached to an oxygen atom, whilst the other three are attached to a carbon atom.

When chlorine acts upon acetic acid in sunlight three hydrogen atoms are successively substituted by chlorine, and the three chlorinated acetic acids, monochloroacetic, dichloroacetic, and trichloroacetic acids are obtained. The fourth hydrogen atom is not directly replaceable by chlorine, which is expressed in the structural formula, where three hydrogen atoms have a different position from that of the

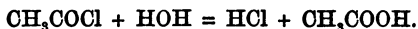
fourth. It can also be shown that the fourth hydrogen atom, which is not directly replaceable by chlorine, is that one which can be replaced by metals, for trichloroacetic acid is also a monobasic acid, containing one hydrogen atom replaceable by metals. The metal in the salts of acetic acid is attached to the oxygen atom, just as the hydrogen atom, which is replaceable by metals, is in the free acid. The metal and the hydrogen atom only separate from, and again enter the compound together with the oxygen atom; when phosphorus pentachloride acts on free acetic acid an atom of chlorine takes the place of the hydroxyl group, forming acetyl chloride CH_3COCl ; acetyl is that complex of atoms which forms the monovalent radical CH_3CO :



When phosphorus pentachloride acts upon sodium acetate a chlorine atom takes the place of the group ONa :



If water be allowed to act on acetyl chloride, a hydrogen atom together with an oxygen atom enters the molecule; i.e. a hydroxyl group takes the place of the chlorine atom:



If sodium hydroxide be allowed to act upon acetyl chloride, the group ONa takes the place of the chlorine atom:



All these reactions are indicated in the structural formula of acetic acid. Structural formulæ are the expressions of syntheses, decompositions, and possibilities of substitution. The more complex the compounds are with which we deal, the more indispensable and valuable do the structural formulæ become.

There are two methods by which acetic acid is prepared on the large scale, namely, by the so-called 'quick vinegar process' and by the dry distillation of wood.

In the quick vinegar process, ethyl alcohol is oxidised to acetic acid by the oxygen of the atmosphere. It has long been known that alcoholic beverages—wine, beer—on standing in the air become sour. Chemical investigation has proved that the alcohol is converted into acetic acid, and comparatively recent microscopical observations have shown that in this conversion certain bacteria, of which we can

already differentiate more than ten varieties, play the rôle of oxygen carriers from the air to the alcohol. The energy set free by the oxidation is presumably used by the bacteria in the discharge of their functions. In order to make use of this process in the preparation of acetic acid on a large scale, alcohol diluted with water—diluted brandy, beer, or wine—is exposed to atmospheric air by as large a surface as possible; therefore a large cask, bored with holes, is filled with wood shavings, and the dilute alcohol is allowed to percolate gradually through the shavings. These serve not only to ensure that as large a surface as possible is exposed to the atmospheric oxygen, but they also guarantee the necessary nutrient material to the bacteria.

The second technical method of preparing acetic acid is by the dry distillation of wood. By dry distillation is meant the decomposition of more complicated organic compounds into simpler ones, by the action of a high temperature in the absence of oxygen. Wood consists chiefly of cellulose, a carbohydrate (cf. Lecture 8); the size of its molecule is unknown, but it has the empirical formula $x(\text{C}_6\text{H}_{10}\text{O}_5)$. When wood is heated in the presence of sufficient air, it is oxidised to the end-products, carbonic acid and water being the last stages in the oxidation; but when it is heated in the absence of oxygen, the hydrogen and oxygen together with a portion of the carbon are split off in the form of volatile compounds, which distil over; part of the distillate condenses in the receivers as a liquid, part escapes as gas, and the remainder of the carbon remains behind in the retort. The dry distillation of wood is often carried out for the purpose of obtaining charcoal or illuminating gas, and in this case, amongst numerous other products of distillation, acetic acid is obtained as a bye-product. In some manufactories the preparation of acetic acid is the chief object, and there the gases evolved on distillation, which consist of hydrogen, carbon monoxide, carbonic acid, marsh gas, acetylene, ethylene and other hydrocarbons, are used for heating the iron retorts, by which means a large amount of fuel is saved, which would have been otherwise necessary to complete the distillation. If the carbonisation be well carried out, the quantity of acetic acid obtained should be 7 to 9 per cent. of the weight of the wood used.

The liquid products of the distillation form two layers in the receivers. One layer, the so-called wood-tar, consists of substances which do not mix with water; they are chiefly benzene, toluene, phenol, naphthalene, paraffin, and many others which will be met with later. The other layer consists of water-dissolved substances,

and this is raw wood vinegar, of which the chief constituent is acetic acid ; it also contains formic acid, propionic acid, butyric acid, valerianic acid, acetone, phenol, and a large amount of 'wood spirit' (methyl alcohol).

The raw wood vinegar is poured off and distilled from copper vessels ; the vapour is carried through milk of lime, which retains the acetic and other acids, whilst the methyl alcohol, acetone, and the other non-acid and easily volatile compounds pass through and are collected in cooled receivers. This forms raw wood spirit, which is first diluted with water, whereby oily impurities are precipitated, and then fractionally distilled over lime.

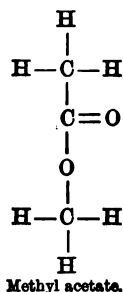
The milk of lime is converted into a solution of calcium acetate, which is evaporated down ; it is then treated with concentrated hydrochloric acid, avoiding an excess, and on distillation the acetic acid passes over. This can be further purified by a very laborious process, which consists in preparing and crystallising out the sodium salt, recrystallising it, and then again distilling it with concentrated sulphuric acid. As acetic acid is very resistant to oxidising agents, it can also be purified by distillation with potassium bichromate or permanganate.

Impure wood vinegar has been used in medicine under the name of *acetum pyrolignosum* (pyrolignic acid) as a disinfectant ; though now out of date, it is yet found in some pharmacopœias, but it is still made use of as a preservative agent for woodwork, ropes, meat, etc.

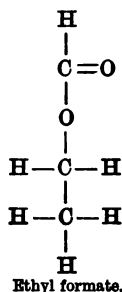
Both the acetic acid prepared by the quick vinegar process and that prepared by the dry distillation of wood are used as table vinegar ; an aqueous solution containing 3 to 6 per cent. acetic acid is generally employed for this purpose.

Of the esters of acetic acid, the ethyl or acetic ester, *æther aceticus*, is officinal, and is used as a flavouring agent in pharmacy. It is prepared by distilling sodium acetate with alcohol and concentrated sulphuric acid on the water bath. Sulphuric acid in this reaction plays a similar rôle to that mentioned under the preparation of ether (p. 34). Acetic ester is specifically lighter than water, with which it only partially mixes ; it boils at 75° C., and is used as a solvent in analytical chemistry.

The methyl ester of acetic acid is an interesting example of isomerism ; it has the same vapour density as the ethyl ester of formic acid and therefore the same molecular weight, and also the same percentage composition $C_3H_6O_2$:



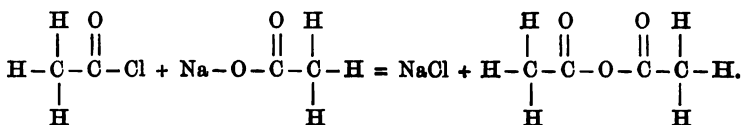
Methyl acetate.



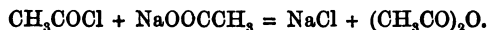
Ethyl formate.

The physical properties, e.g. the boiling-points, of the two esters are different, but their difference is not determinable only by their physical properties. Their action on the olfactory nerves is different; they both have a pleasant, but quite different, odour. Both esters are prepared in an exactly analogous manner to acetic ester.

Just as acetic acid can combine with alcohols with loss of water to form neutral compounds, so also two molecules of acetic acid can combine together with loss of water to form the neutral compound, acetic anhydride. This is best prepared by the action of acetyl chloride¹ (p. 55) upon sodium acetate:

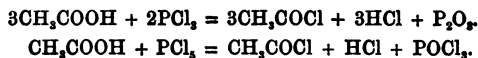


The formulæ are written in this complicated manner in order to show the valencies of the atoms, and the manner of their linking; they can be written more simply as follows:

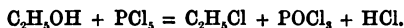


Acetic anhydride is a mobile pungent-smelling liquid, boiling at 137° C.

¹ [Acetyl chloride is prepared by the action of phosphorus trichloride, or pentachloride, upon acetic acid:

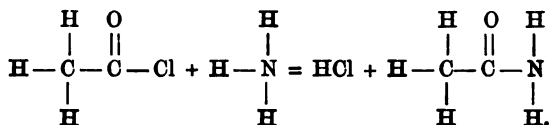


All compounds containing a hydroxyl group, e.g. the alcohols, are acted upon in the same way by phosphorus trichloride, or pentachloride:

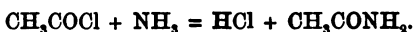


the hydroxyl group being replaced by a chlorine atom.]

By the action of ammonia upon acetyl chloride acetamide is formed :

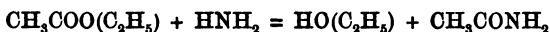


or more simply :

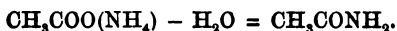


Acetamide forms crystals, which melt at 82°C . and boil at 222°C .

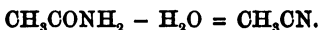
A second method of preparing it consists in allowing ammonia to act upon acetic ester :



and a third method by submitting ammonium acetate to distillation, when it loses a molecule of water, and acetamide distils over :



When acetamide is heated with a dehydrating agent, such as phosphoric acid anhydride (phosphorus pentoxide), it loses a second molecule of water, and acetonitrile, a colourless liquid, boiling at 82°C ., is obtained :



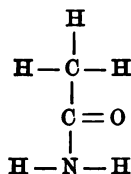
This compound, together with the isomeric isonitrile, will be referred to in greater detail under the cyanogen compounds (cf. Lecture 10).

Acetamide has no direct physiological interest, as it does not occur in our bodies. Its three methods of preparation were mentioned because by these same methods urea, the most important nitrogenous end-product of our metabolism, can be artificially prepared by synthesis, from which it follows that urea must also be an acid amide (cf. Lecture 11).

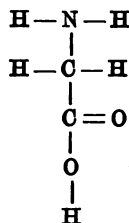
[Acid amides are derivatives of ammonia, in which one or more of its hydrogen atoms are replaced by acid radicals. Amines are derivatives of ammonia, in which the hydrogen atoms are replaced by alkyl radicals, compare methylamine.]

Acetamide must not be confounded with the very important physiological compound amino-acetic acid, glycocoll, or glycine. Amino-acetic acid is also derived, like acetamide, from acetic acid by the introduction of the amino radical NH_2 ; in the formation of acetamide the amino radical takes the place of hydroxyl in the carboxyl

group, whilst in the formation of amino-acetic acid it takes the place of a hydrogen atom in the methyl group :

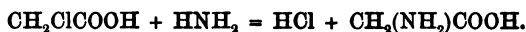


Acetamide.

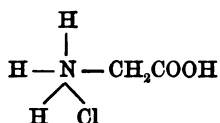
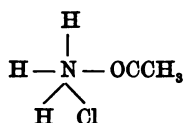
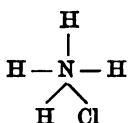
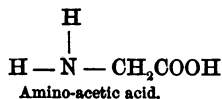
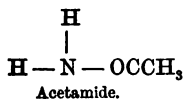
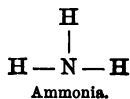


Amino-acetic acid or glycocoll.

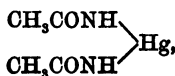
Glycocoll is prepared synthetically by heating monochloroacetic acid with ammonia :



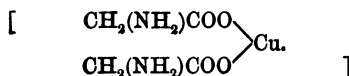
Acetamide has a neutral, amino-acetic acid or glycocoll a slightly acid, reaction ; both compounds behave as bases, forming, for example, with hydrochloric acid, substituted ammonium chlorides ; they are able to add themselves to hydrochloric acid because they are substituted ammonias :



Acetamide is not an acid, although one hydrogen atom of its amino-group can be substituted by certain metals, e.g. mercury, forming the compound



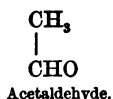
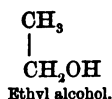
but glycocoll is both an acid and an amine, since it contains a carboxyl group with a hydrogen atom capable of substitution by metals, e.g. it forms a beautifully crystalline copper salt :



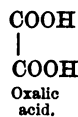
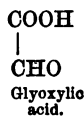
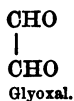
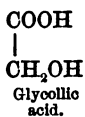
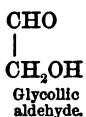
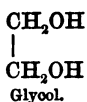
Glycocoll (glycine) consists of colourless crystals which are easily

soluble in water, but insoluble in alcohol. It occurs, combined with benzoic acid, in the animal organism as hippuric acid (cf. Lectures 13 and 1) in the urine, and combined with cholalic, or cholic, acid in the bile as glycocholic acid. It is without doubt a hydrolytic decomposition product of proteins. It can be prepared in large quantities by the hydrolysis of gelatin (cf. Lecture 17), the chief constituent of bones and connective tissue, hence its name glycocoll (sweet glue). It is probably one of the precursors of urea in our body, for, when glycocoll is introduced into the stomach a corresponding increase of urea is found in the urine.

[The oxidation products of ethane so far described, namely ethyl alcohol, acetaldehyde, and acetic acid, are formed by the replacement of the hydrogen atoms attached to one of its two carbon atoms by the hydroxyl group :

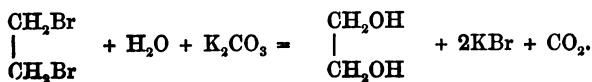


If we replace the hydrogen atoms attached to both the carbon atoms by hydroxyl groups, we obtain the following long series of compounds :



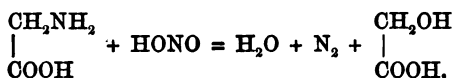
These compounds are no longer simply an alcohol, an aldehyde, or an acid, but they are either alcohol plus alcohol, alcohol plus aldehyde, alcohol plus acid, aldehyde plus aldehyde, aldehyde plus acid, or acid plus acid at the same time, i.e. they have either two kinds of properties (cf. glycocoll) or a reduplication of one property.

Glycol is a dihydric alcohol, i.e. a compound containing two hydroxyl groups, the terminal syllable -ol being given to all alcohols. It was prepared in 1859 by Wurtz, and like most compounds containing two or more hydroxyl groups, has a sweet taste, hence its name from *γλυκύς*, sweet. It can be obtained by boiling ethylene bromide with water and potassium carbonate (p. 10) :



Glycollic aldehyde is a hydroxyaldehyde, and can be obtained directly from glycol by oxidation : its empirical formula is $C_2H_4O_2$, and it is therefore an isomer of acetic acid. It is the first representative of the series of carbohydrates, the most important of which are those containing six atoms of carbon (cf. Lecture 8).]

Glycollic acid, also called hydroxyacetic acid, can be prepared by boiling monochloroacetic acid with potassium or silver hydroxide, or by the action of nitrous acid upon amino-acetic acid, or glycine. This latter is the typical reaction which is generally used for replacing the NH_2 radical by the hydroxyl radical :



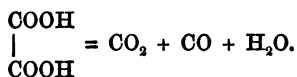
Glycollic acid forms colourless crystals ; it does not occur in the animal body, and is of no physiological interest.

[Glyoxal is the dialdehyde of glycol, and is prepared by the oxidation of acetaldehyde with nitric acid ; as it is a dialdehyde it can unite with two molecules of hydroxylamine and phenylhydrazine, and react with two molecules of hydrocyanic acid.

Glyoxylic acid is best prepared by reducing oxalic acid with sodium amalgam. It is of importance, as it is now employed as a reagent in testing for proteins.^{1]}

Oxalic acid is very widely distributed in the animal and vegetable kingdoms, and is of great physiological and pathological interest. A method of synthesising it has been described (p. 3), and also its preparation by the oxidation of carbohydrates with nitric acid (pp. 2 and 42).

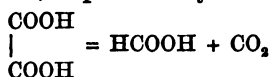
Oxalic acid crystallises from water, with two molecules of water of crystallisation, in colourless monoclinic prisms. It loses its water of crystallisation when the crystals are dried at $100^\circ C.$, or at the ordinary temperature over sulphuric acid. It is important to remember this, as oxalic acid is often used in the preparation of standard solutions. Anhydrous oxalic acid, when gently heated, can be sublimed without charring or separation of carbon, but with partial decomposition. On further heating it breaks down into carbonic acid, carbon monoxide, and water :



At the same time a small quantity of formic acid is formed, which is

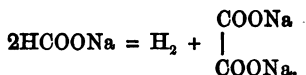
¹ [Hopkins and Cole, *Proc. Roy. Soc.* 1901, vol. lxxiii. p. 21.]

probably to be regarded as an intermediate stage in the complete process of decomposition; it presumably takes place as follows:

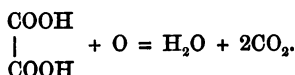


the formic acid then breaking down further into water and carbon monoxide. When oxalic acid is heated with glycerol, the decomposition ceases at the stage of formic acid (p. 42).

Oxalic acid can be also synthetically prepared from formic acid by heating sodium formate rapidly above 400°C . in the absence of air; sodium oxalate is formed and hydrogen evolved:



When heated with concentrated sulphuric acid, oxalic acid is decomposed into carbon dioxide, carbon monoxide, and water. If manganese dioxide be added to a cold aqueous solution of oxalic acid, an effervescence of carbonic acid takes place, and the oxalic acid is completely oxidised to carbonic acid:



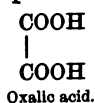
The neutral salts which oxalic acid forms with the alkalies are soluble in water, those with the other inorganic bases are almost all insoluble, whereas the acid salts are soluble. In analytical chemistry oxalic acid is used in the separation of calcium and magnesium; calcium oxalate, even in the presence of ammonium chloride, is not soluble in water or in acetic acid, whereas magnesium oxalate in the presence of ammonium chloride is easily soluble both in water and in acetic acid. When calcium oxalate is rapidly precipitated from a concentrated solution, it forms very minute crystals, most of which will pass through filter-paper, but if it separates slowly it forms beautiful quadratic octahedra, whose principal axes are shortened, so that under the microscope they have the appearance of the so-called 'envelope' crystals. In this form it is deposited in the cells of plants, and in human urinary sediments.

Oxalic acid is very widely distributed in the vegetable kingdom; it circulates through the tissues either as the free acid, or as the alkali or acid calcium salt, but it is deposited as the neutral calcium salt. It is still a point of controversy whether the oxalic acid, taken into the animal body with the vegetable food, is converted by oxidation into carbonic acid and water, or whether it is excreted

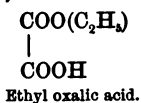
unchanged. It is not improbable that oxalic acid appears in the urine as the end-product of the incomplete decomposition and oxidation of some of our foodstuffs, and that it occurs under pathological conditions in increased quantities. This may give rise to the danger of the formation of insoluble concretions of calcium oxalate in the urinary passages, in the pelves of the kidneys or in the bladder; the question of the conditions of the formation, solution, and separation of calcium oxalate forms an important chapter of pathological chemistry.

The quantity of oxalic acid which enters the body with vegetable food, or which arises by metabolism, is always very small. If large quantities of artificially prepared oxalic acid be introduced into the animal body, it acts as a deadly poison. Cases of poisoning in man, resulting in death, often occur; in one case it was determined that 15 grammes caused the death of an adult man in fifteen minutes; in some cases calcium carbonate has been successfully used as an antidote.

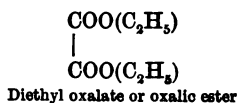
Oxalic acid combines with alcohols, with elimination of water, forming esters in the same way as do formic and acetic acids, as already described; the only difference is that oxalic acid, which is dibasic, forms two series of esters, of which the one series are monobasic acids and the other series neutral compounds, just as in the case of sulphuric acid (p. 33):



Oxalic acid.



Ethyl oxalic acid.



Diethyl oxalate or oxalic ester

In the same way oxalic acid forms two amides:



Oxalic acid.

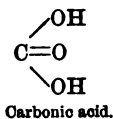


Oxamic acid.

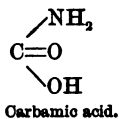


Oxamide.

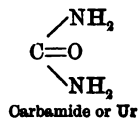
These are prepared in an analogous way to acetamide; oxamic acid is formed, by the loss of one molecule of water, on heating acid ammonium oxalate; oxamide on heating neutral ammonium oxalate. The amides of oxalic acid are of no practical or physiological interest, but they are completely analogous to the physiologically important amides of carbonic acid, which are described in detail later (cf. Lecture 11).



Carbonic acid.



Carbamio acid.



Carbamide or Ur

LECTURE V

THE HOMOLOGUES AND ISOMERS OF THE METHANE SERIES

The Derivatives of Propane. Part I.

IN the second lecture mention was made of the homologous series of the saturated hydrocarbons, the so-called methane series, and the conception of homology was defined. From all the members of the hydrocarbons analogous compounds can be derived—alcohols, aldehydes, acids, ethers, mercaptans, amines, etc. All these analogous derivatives, again, form homologous series in which the next member can be regarded as having arisen from the preceding member by the substitution of one of the hydrogen atoms attached to the carbon atoms, by a methyl radical. Every subsequent member thus contains an atom of carbon and two atoms of hydrogen more than the preceding one, as can be seen from the following table :

HYDROCARBONS		ALCOHOLS		ACIDS	
C_nH_{2n+2}		$C_nH_{2n+2}O$		$C_nH_{2n}O_2$	
CH_4	Methane	CH_3O	Methyl alcohol	CH_2O_2	Formic acid
C_2H_6	Ethane	C_2H_5O	Ethyl alcohol	$C_2H_4O_2$	Acetic acid
C_3H_8	Propane	C_3H_7O	Propyl alcohol	$C_3H_6O_2$	Propionic acid
C_4H_{10}	Butane	C_4H_9O	Butyl alcohol	$C_4H_8O_2$	Butyric acid
C_5H_{12}	Pentane	$C_5H_{11}O$	Amyl alcohol	$C_5H_{10}O_2$	Valerianic acid
C_6H_{14}	Hexane	$C_6H_{13}O$	Hexyl alcohol	$C_6H_{12}O_2$	Caproic acid
C_7H_{16}	Heptane	$C_7H_{15}O$	Heptyl alcohol	$C_7H_{14}O_2$	Oenanthylic acid
C_8H_{18}	Octane	$C_8H_{17}O$	Octyl alcohol	$C_8H_{16}O_2$	Caprylic acid
C_9H_{20}	Nonane	$C_9H_{19}O$	Nonyl alcohol	$C_9H_{18}O_2$	Pelargonic acid
$C_{10}H_{22}$	Decane	$C_{10}H_{21}O$	Decyl alcohol	$C_{10}H_{20}O_2$	Capric acid
$C_{11}H_{24}$	Undecane			$C_{11}H_{22}O_2$	Undecylic acid
$C_{12}H_{26}$	Dodecane	$C_{12}H_{25}O$	Dodecyl alcohol	$C_{12}H_{24}O_2$	Lauric acid
$C_{13}H_{28}$	Tridecane			$C_{13}H_{26}O_2$	Tridecylic acid
$C_{14}H_{30}$	Tetradecane	$C_{14}H_{29}O$	Tetradecyl alcohol	$C_{14}H_{28}O_2$	Myristic acid
$C_{15}H_{32}$	Pentadecane			$C_{15}H_{30}O_2$	Pentadecylic acid
$C_{16}H_{34}$	Hexadecane	$C_{16}H_{33}O$	Cetyl alcohol	$C_{16}H_{32}O_2$	Palmitic acid
$C_{17}H_{36}$	Heptadecane			$C_{17}H_{34}O_2$	Margaric acid
$C_{18}H_{38}$	Octadecane	$C_{18}H_{37}O$	Octadecyl alcohol	$C_{18}H_{36}O_2$	Stearic acid
$C_{19}H_{40}$	Nonadecane			$C_{19}H_{38}O_2$	Nondecylic acid
$C_{20}H_{42}$	Eicosane			$C_{20}H_{40}O_2$	Arachic acid
$C_{21}H_{44}$	Heneicosane				
$C_{22}H_{46}$	Docosane			$C_{22}H_{44}O_2$	Behenic acid
$C_{23}H_{48}$	Tricosane				
$C_{24}H_{50}$	Tetracosane			$C_{24}H_{48}O_2$	Lignoceric acid
		$C_{26}H_{54}O$	Ceryl alcohol	$C_{26}H_{52}O_2$	Cerotic acid
$C_{27}H_{56}$	Heptacosane			$C_{30}H_{60}O_2$	Melissic acid
		$C_{30}H_{62}O$	Myricyl alcohol		
$C_{51}H_{104}$	Hentriacontane				
$C_{52}H_{106}$	Dotriacontane				
$C_{55}H_{112}$	Pentatriacontane				
$C_{60}H_{122}$	Hexacontane				

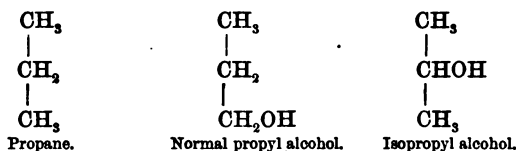
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Just as the alcohols and acids form homologous series, so also do the aldehydes, ethers, mercaptans, etc. The physical properties of the individual members, their melting points, boiling points, specific gravities, solubilities, etc., vary with the number of carbon atoms by regular increments, as already noticed in the hydrocarbons (p. 21).

The majority of the members of the same homologous series have essentially the same chemical properties; they react in the same way, form the same compounds, and possess the same capacity for substitution. Hence it is unnecessary in an elementary text-book to describe the chemical properties of the derivatives of each member of a series of hydrocarbons; and it is sufficient to describe the variations from the general rules which occur in the practically important compounds, as has been done in the lectures on the methane and ethane derivatives.

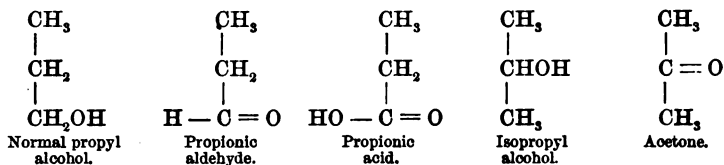
Amongst the higher members of the methane series we meet with the difficult phenomenon of isomerism, which has been already mentioned when discussing the saturated hydrocarbons with six carbon atoms, in which five isomers are possible (p. 19). Not only does isomerism exist amongst the hydrocarbons themselves, but also amongst all their derivatives.

The first three members of the hydrocarbons show no isomerism. A different arrangement of the carbon and hydrogen atoms is *a priori* not conceivable presuming that there is complete saturation. Amongst the derivatives, on the other hand, isomerism commences with the third member; if a hydroxyl group substitute a hydrogen atom in propane, two arrangements are conceivable:



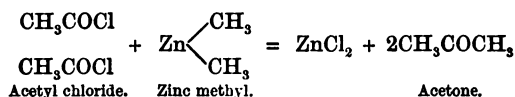
The hydroxyl group can either take the place of one of the three hydrogen atoms attached to either of the *end* carbon atoms, or it can take the place of one of the two hydrogen atoms attached to the *middle* carbon atom. The two propyl alcohols mentioned above have actually been, and no more can be, prepared; the one boils at 97° C. and has a specific gravity 0.804, the other boils at 81° C. and has a specific gravity 0.789. Now, that propyl alcohol in which the hydroxyl group and two hydrogen atoms are attached to the same carbon atom, gives, on oxidation, an aldehyde and then an acid, the other gives acetone; experiment has shown that the alcohol with the

higher boiling point gives the acid, and that the other gives acetone. The former alcohol is called normal propyl alcohol, the latter isopropyl alcohol. This latter is obtained by the action of nascent hydrogen upon acetone, into which it is reconverted on oxidation :

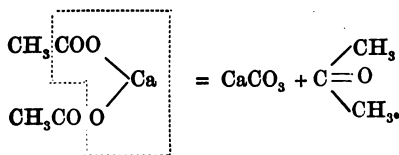


Normal propyl alcohol is a constituent of the so-called 'fusel oil,' which consists chiefly of the higher members of the homologous series of alcohols; they are formed in small quantities together with ethyl alcohol in the fermentation of sugar; they have a higher boiling point, and therefore they remain behind after distilling off the ethyl alcohol in the rectification of the raw spirit. Fusel oil contains propyl-, butyl-, and amyl- alcohols. The normal propyl alcohol is obtained from it by fractional distillation.

Acetone is a very important compound, as it is the first member of the homologous series of ketones, and it bears the name also of dimethylketone. Ketones are compounds of the divalent radical carbonyl >CO with two monovalent alkyl radicals; e.g. diethylketone $(\text{C}_2\text{H}_5)_2\text{CO}$, methylpropylketone $(\text{CH}_3)\text{CO}(\text{C}_3\text{H}_7)$ etc. A general method of preparing ketones consists in allowing the acid chlorides to act upon zinc alkyl compounds :



When calcium acetate is heated in a retort, calcium carbonate is formed and acetone distils over, which can be collected in a well-cooled receiver :

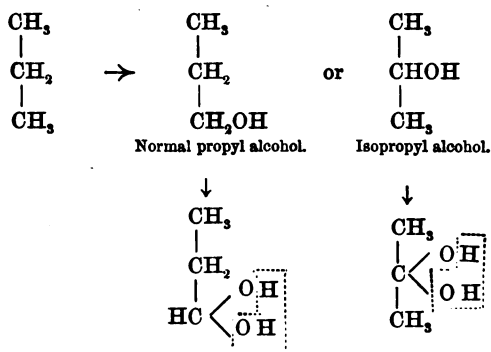


[Acetone is one of the products obtained in the dry distillation of

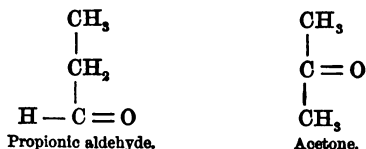
wood (p. 56), by which method it is prepared on the large scale ; it occurs in the distillate with the methyl alcohol from which it is separated.]

Acetone is a light, volatile, aromatic smelling liquid which is miscible with water, alcohol, and ether, and boils at 56°C ; from its aqueous solution it can be separated by saturation with salts. It often occurs in small quantities in normal urine. In certain anomalies of metabolism, especially in diabetes mellitus, it appears in some quantity in the blood, from which it passes into the urine and also into the expired air.

[Oxidation may be regarded as the replacement of a hydrogen atom by the hydroxyl group OH ; e.g. a hydrogen atom of propane can be replaced by the hydroxyl group OH, giving normal propyl alcohol or isopropyl alcohol ; these are therefore the first oxidation products of propane. On further oxidation another hydrogen atom is replaced by the hydroxyl group, and this occurs at that carbon atom to which oxygen is already attached, thus :



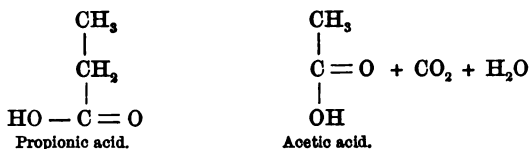
These hypothetical compounds do not exist ; they immediately lose a molecule of water forming propionic aldehyde and acetone respectively :



In general, two OH groups cannot exist attached to one and the same carbon atom.

On further oxidation the same process occurs, namely, replacement of H by OH ; propionic aldehyde is converted into propionic

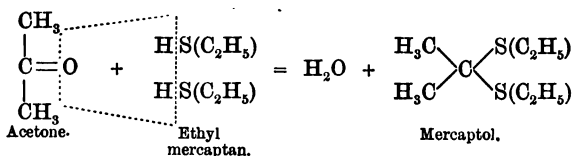
acid, but acetone is broken down into acetic acid, carbonic acid and water :



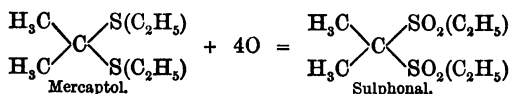
Primary alcohols such as normal propyl alcohol, are thus distinguished from secondary alcohols, such as isopropyl alcohol : primary alcohols on oxidation give first aldehydes, and then acids ; secondary alcohols give ketones, which, on oxidation, lose carbonic acid yielding an acid containing fewer carbon atoms than are contained in the original alcohol.]

It may be well here to insist upon the following general principle of organic chemistry : The first carbon atom in a molecule which is attacked by oxygen is that one to which an oxygen atom is already attached.

From acetone sulphonal, which is an important pharmacological compound, is prepared ; it was discovered by Baumann,¹ and is much used, and still more misused, as a hypnotic. Ethyl mercaptan, $\text{C}_2\text{H}_5\text{HS}$, which is analogous to methyl mercaptan in preparation and composition, and like it a nauseous smelling liquid, boiling at 36°C. , is mixed with anhydrous acetone and gaseous hydrogen chloride is passed into the mixture. This acts as a dehydrating agent, and the following compound, mercaptol, which may be regarded as a substituted methane, is obtained :



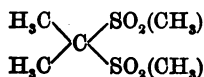
When this compound is oxidised with potassium permanganate at the ordinary temperature, four oxygen atoms enter the molecule and sulphonal is formed :



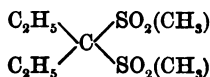
[The sulphur atoms are here hexavalent.]

¹ E. Baumann, *Ber. d. d. chem. Gesellsch.* 1886, vol. xix. p. 2808.

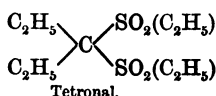
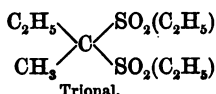
Sulphonal forms crystals which are soluble with difficulty in water; upon this insolubility perhaps depends its slow and long-maintained action. The hypnotic action of sulphonal appears to be bound up with the ethyl radicals, for the methyl compound



does not produce sleep, whereas the compound

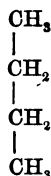


does. Hence it has been supposed that the analogous compounds with three (trional), and four (tetronal), ethyl radicals

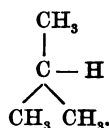


would act more strongly as inducers of sleep than sulphonal. This supposition seems to be confirmed by experience.¹

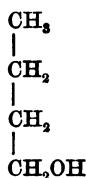
In the case of butane, the fourth member of the marsh gas series, two isomeric hydrocarbons are theoretically possible:



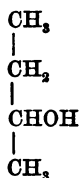
and



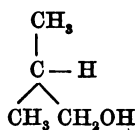
More hydrocarbons of the composition C_4H_{10} are not conceivable, and only two have actually been prepared. The number of alcohols which can be derived from them is four, and four only are actually known:



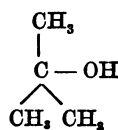
I.



II.



III.



IV.

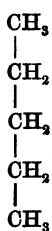
¹ See E. Baumann and A. Kast 'On the Relations between Chemical Constitution and Physiological Action in Certain Sulphones,' *Z. f. physiol. Chem.* 1889, vol. xiv. p. 52.

Two of these four alcohols (I. and III.) on oxidation should give aldehydes and then acids, the third (II.) should give methylethylketone, and the fourth (IV.) should break down on oxidation into smaller molecules; for, according to the above rule, oxygen will attack that particular carbon atom to which the hydroxyl group is already attached. This carbon atom has its other three valencies satisfied by other carbon atoms, and if more oxygen linkings are to be attached to it, this can only take place after the previous separation of a neighbouring carbon atom. All these theoretical assumptions have been actually confirmed by experiment, and these examples serve to demonstrate the inestimable value of the structural theory.

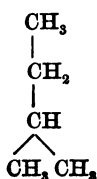
An alcohol which contains the hydroxyl group and *two* hydrogen atoms attached to the same carbon atom, that is, contains the monovalent radical CH_2OH , which on oxidation is converted firstly into the aldehyde radical CHO , and on further oxidation into the acid, or carboxyl radical, COOH , is called a *primary* alcohol.

An alcohol which contains the hydroxyl group and *one* hydrogen atom attached to the same carbon atom, that is, contains the divalent radical >CHOH , which on oxidation is converted into a ketone radical >CO , is called a *secondary* alcohol. Finally, an alcohol which contains the trivalent radical $\equiv\text{C}-\text{OH}$, which, on oxidation, breaks down into smaller molecules, is called a *tertiary* alcohol.

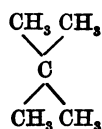
In the case of pentane, the fifth member of the methane series, three isomers are possible, all of which have been actually prepared :



I.



II.



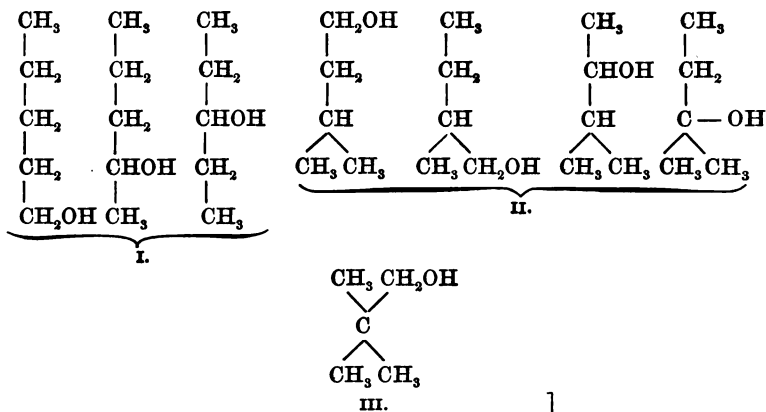
III.

The first of these three hydrocarbons, called normal pentane, yields three alcohols—one primary and two secondary—according as the hydroxyl group is attached to one of the carbon atoms next to the methyl groups, or to the carbon atom in the middle.

The second hydrocarbon gives two primary, one secondary and one

tertiary alcohol, and the third one gives only a primary alcohol, since all the four methyl radicals have the same position with regard to the middle carbon atom.

[The following formulæ make this clear :



Upon oxidation these eight alcohols will yield four different aldehydes, and then four acids, and three ketones, but the eighth or tertiary alcohol will break down on oxidation into molecules containing fewer carbon atoms.

All these suppositions have been experimentally proved ; eight amyl alcohols and four valerianic acids, [as the alcohols and acids derived from these pentanes are called], have been prepared.

A carbon atom which has all its four valencies satisfied by other carbon atoms, as in the third isomer of pentane, is known as a *quaternary* carbon atom.

A *tertiary* carbon atom is one which has three of its valencies satisfied by carbon atoms, and its fourth saturated by a hydrogen atom ; this forms the trivalent radical methine $\equiv\text{CH}$, and if a hydroxyl group takes the place of the hydrogen atom, the tertiary alcohol group, $\equiv\text{C}-\text{OH}$, is formed, which by oxidation is separated from the neighbouring carbon atoms.

A *secondary* carbon atom is one which is united to two other carbon atoms ; when two hydrogen atoms satisfy the other valencies of this carbon atom it gives the divalent radical methylene $=\text{CH}_2$, and when one of these hydrogen atoms is replaced by hydroxyl, the secondary alcohol radical $=\text{CHOH}$ is formed, which on oxidation is converted into the ketone, or *carbonyl*, group $=\text{C}=\text{O}$.

A *primary* carbon atom is one which is attached to only one other carbon atom, and must stand at the end of a chain; it forms the monovalent radical methyl —CH_3 , when three hydrogen atoms are attached to it, and if one of these hydrogen atoms be replaced by a hydroxyl group, the primary alcohol group $\text{—CH}_2\text{OH}$ is formed; this, on oxidation, gives the aldehyde group —CHO , and then the carboxyl group —COOH .

A chain of carbon atoms, as in the first of the three pentanes, in which no one carbon atom is attached to more than two others, is called *normal*, the other carbon chains *branched*, or *iso*-compounds. These designations are sometimes indicated by placing *n*- or *i*- [or better *iso*-, e.g. *iso*-pentane] before the name.

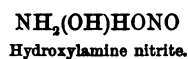
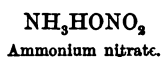
The five isomers of hexane, the sixth member of the methane series, have been already mentioned (p. 19); it can easily be determined that seventeen isomeric alcohols can be derived from them, and of these eleven are already known.

The number of isomers in the higher members of the methane series increases very rapidly with the number of the carbon atoms. The possible number of isomers of the compounds having the composition C_7H_{16} is 9; of C_8H_{18} is 18; of C_9H_{20} is 35; of $\text{C}_{10}\text{H}_{22}$ is 75; of $\text{C}_{11}\text{H}_{24}$ is 159; of $\text{C}_{12}\text{H}_{26}$ is 355; and of $\text{C}_{13}\text{H}_{28}$ is 802. Attempts to prepare all these possible isomers have naturally not yet been made, but in order to give an idea of the unceasing labour which has overcome the experimental difficulties in the preparation of isomers, both of the methane series and of other series and groups of hydrocarbons and their derivatives, it may be stated that fifty-five isomers of the compound $\text{C}_9\text{H}_{10}\text{O}_3$ have been already prepared and investigated; the number of its possible isomers is still greater.

In face of these facts we can realise how great are the difficulties which confront physiological chemistry, one of the chief objects of which is the study of the proteins, with at least 700 carbon atoms in their molecule! The protein molecule, however, does not consist of long chains of carbon atoms, but is made up of a large number of small chains which are linked together by oxygen, by sulphur, or by nitrogen atoms. No chain with more than twelve carbon atoms is at present known in the protein molecule. So many isomers are possible from the manner of the linking of these chains that, at the present time, the establishment of a structural formula for a protein cannot be thought of.

The formation of so many isomers is not only the chief difficulty, but it is also the essential characteristic, of organic chemistry.

Inorganic chemistry furnishes us with scarcely any examples of isomerism; that of ammonium nitrate and hydroxylamine nitrite is one of the few instances known :



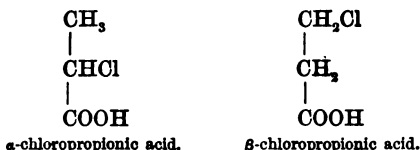
[It will be seen that each of these two substances has the empirical formula $\text{H}_4\text{N}_2\text{O}_3$.]

LECTURE VI

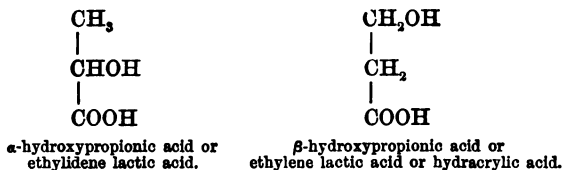
THE DERIVATIVES OF PROPANE AND BUTANE AND STEREOISOMERISM

A. *The Derivatives of Propane, continued. Stereoisomerism.*

ON oxidation, normal propyl alcohol, as previously described (p. 66), yields firstly an aldehyde and then an acid, propionic acid, which is a liquid very similar to acetic acid. Just as in acetic acid, so also in propionic acid, one of its hydrogen atoms can be easily substituted by chlorine, but in the case of acetic acid only one monochloroacetic acid is possible, whereas in the case of propionic acid two isomeric monochloropropionic acids can be obtained:



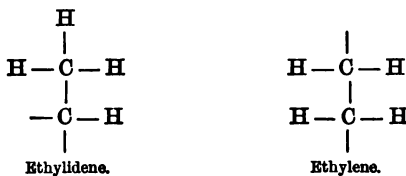
Similarly, two bromo- and two iodo-propionic acids can be obtained. By the action of silver hydroxide, the halogen atom in these compounds can be replaced by a hydroxyl group, and the two corresponding isomeric hydroxypropionic acids, or lactic acids, are obtained:¹



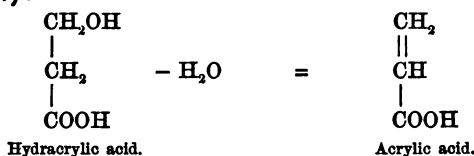
The α - and β -hydroxypropionic acids are called ethylidene and

¹ The pioneer work of Joh. Wislicenus upon the lactic acids should be read before all others, *Liebig's Ann. d. Chem.* 1873, vols. clxvi. p. 3, clxvii. pp. 302 and 346.

ethylene lactic acids, because they contain the isomeric divalent radicals ethylidene and ethylene:



Ethylene lactic acid also bears the name hydracrylic acid, because, on heating, it loses a molecule of water and is converted into the unsaturated acid, acrylic acid, in which we assume a double bond (cf. Lecture 7):



These two hydroxypropionic acids, ethylidene and ethylene lactic acids, are distinguished by their oxidation products; ethylidene lactic acid yields on oxidation acetic and carbonic acids; ethylene lactic acid, on the other hand, yields oxalic and carbonic acids; it does not yield acetic acid, since it does not contain the methyl radical.

Ethylene lactic acid does not occur in the animal body, and is only of theoretical interest. Ethylidene lactic acid, [known generally as lactic acid], is, however, of great physiological interest; it is widely distributed in the animal body, and occurs as a metabolic product of many micro-organisms.

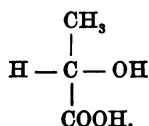
Lactic acid is a syrupy liquid, which mixes with water in all proportions, and volatilises with it in considerable quantities when the water is boiled. At a pressure of 1 mm. it can be completely distilled without decomposition at 109–125° C. The distillate solidifies in a freezing mixture to a crystalline solid, which begins to melt at +18° C.¹

In the investigation of lactic acid we come upon a new difficulty. The lactic acids which arise as a result of the metabolism of different cells are not identical, although the structural formula allows of only one ethylidene lactic acid, and although these ethylidene lactic acids

¹ F. Krafft and W. A. Dyes, *Ber. d. d. chem. Gesellsch.* 1895, vol. xxviii. p. 2589.

behave alike in all their chemical reactions. The difference is in their physical properties, chiefly in their optical behaviour. The lactic acid, which is isolated from the muscular tissue of mammals,¹ has the property of rotating the plane of polarised light to the right; by the decomposition of cane sugar by certain bacteria a lactic acid is obtained, which rotates the plane of polarised light to the left,² and further by the fermentation of the milk sugar in milk an optically inactive lactic acid is formed.

This peculiarity, namely the existence of optically different substances which possess the same chemical structure, is found only in those compounds which have a so-called *asymmetric carbon atom*, i.e. a carbon atom whose four valencies are saturated by four different elements or radicals; a carbon atom of this kind is contained in ethylidene lactic acid:



This fact, that an asymmetric carbon atom determines certain physical properties, particularly the above-mentioned optical behaviour, was demonstrated independently and at the same time, in 1874, by Le Bel,³ and van 't Hoff.⁴ Their hypothetical explanation of this phenomenon was that the four radicals attached to the carbon atoms did not lie in one plane, but were arranged in three dimensions of space and in a quite definite order round the carbon atom.

If we imagine the four radicals to be arranged in one plane round a carbon atom, an isomerism must occur when any *two* radicals are different from the other two: we should, for example, have met with isomerism already in dichloromethane—



—but only one dichloromethane actually exists.

If we imagine the four radicals to be arranged at different distances

¹ [This has been called sarcosolactic acid, but the name only refers to its origin, and its use should be discontinued.]

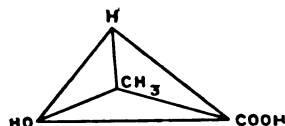
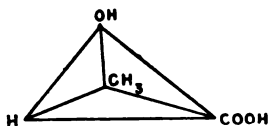
² F. Schardinger, *Monatshefte f. Chem.* 1890, vol. xi. p. 545.

³ J. A. Le Bel, *Bull. Soc. Chim.* 1874, vol. xxii. p. 337.

⁴ J. H. van 't Hoff, *The Arrangement of Atoms in Space.* (Longmans: London.)

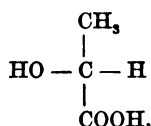
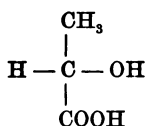
from the carbon atom, isomerism must occur when *one* radical differs from the other three.

But if we imagine that the four radicals are placed at the same distance from the carbon atom and from each other, but not in *one* plane, isomerism can only occur when all the four radicals are different. This is the case, if we imagine the carbon atom to be in the centre of a regular tetrahedron, and the four radicals to be situated at the four corners. When the four radicals are different, as e.g. in lactic acid, two arrangements are possible, which cannot be made to coincide by any rotation whatsoever :



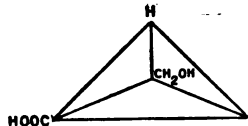
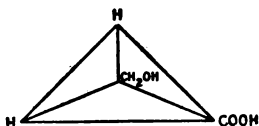
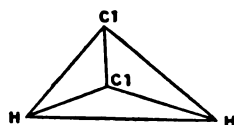
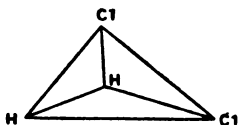
The one figure is in fact the mirror image of the other ; the order of the radicals H, OH, COOH, in the left-hand figure is clockwise, that in the right-hand figure is counter-clockwise.

[The following formulæ represent the projections on a plane surface :



]

If, however, the two radicals or elements attached to the carbon atom be the same, as in dichloromethane or in *ethylene* lactic acid, the two figures on rotation can be made to coincide :



Thus, the existence of only one dichloromethane and only one ethylene lactic acid, but of two isomeric ethylidene lactic acids,

the one dextro-rotatory, the other lævo-rotatory, can be hypothetically explained.

The third modification of lactic acid, which is optically inactive, is nothing but a mixture of the same number of molecules of dextro- and of lævo-lactic acid. The one rotates the plane of polarisation the same number of degrees to the right as the other does to the left, so that their effects exactly balance one another. This can be shown in two ways : firstly, the solubility of certain compounds of the dextro- and lævo-acids, e.g. the strychnine salts, is different, and therefore they can be separated by fractional crystallisation.¹ Secondly, certain micro-organisms have the power of decomposing only one of the two isomers, leaving the other unattacked, or they decompose the one more quickly than the other. Thus, for example, *Penicillium glaucum* decomposes the lævo- more quickly than it does the dextro-acid, and consequently dextro-lactic acid remains behind.

This phenomenon occurs in all compounds which contain an asymmetric carbon atom, a large number of which will be met with later. The dextro-rotatory compounds are designated by the prefix *d*-, the lævo-rotatory by *l*-, and the optically inactive mixture by *i*- or [*dl*].² This kind of isomerism, in contradistinction to that of chemical structure which only explains chemical decomposition and synthesis, is called physical isomerism or *stereoisomerism* [στερεός, solid], as it can only be hypothetically explained by the stereometric arrangement of the atoms, i.e. by their arrangement in three dimensions of space.

If a compound containing an asymmetric carbon atom be synthetically prepared only the optically inactive mixture is obtained, because the possibility of the formation of one arrangement is as likely as that of the other. By certain definite means the *d*- and the *l*- compounds can be prepared from this mixture. It is still an enigma to us under what conditions the activity of the living plant or animal cells produces one modification only, either the *d*- or the *l*- compound ; in spite of many experiments,³ no one has yet succeeded in obtaining *directly* by synthesis either a *d*- or an *l*- compound ; the synthetic preparation has only been attained by the separation of the previously synthesised inactive mixture.⁴

¹ Thomas Purdie and W. Walker, *Jour. Chem. Soc.* 1892, vol. lxi. p. 754.

² [E. Fischer prefers to designate the inactive mixture of the active compounds by the prefix *dl*-, as *i*- is already used for iso- ; it also denotes the facts better. *Ber. d. d. chem. Gesellsch.* 1907, vol. xl. p. 102.]

³ E. Fischer and M. Slimmer, 'Experiments on Asymmetric Synthesis,' *Ber. d. d. chem. Gesellsch.* 1903, vol. xxxvi. p. 2575.

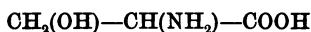
⁴ [Marckwald and also Mackenzie have recently prepared optically active compounds by synthesis, but the methods employed do not as yet give any clue as to how the living organism almost always produces the optically active compound.]

The optical difference of these two isomers depends upon a different arrangement of the atoms inside the molecule and not upon a different arrangement of the molecules themselves, because substances having an asymmetric carbon atom still retain their optical properties in solution, and also, as in the case of certain terpenes and camphors, in the gaseous state if they can be volatilised undecomposed; for there are optically active substances, whose activity depends upon the arrangement of their molecules, such as the dextro- and lævo-rotatory crystals of quartz and sodium chlorate; if either the dextro- or lævo-rotatory crystals of this latter salt be dissolved in water, in both cases the solution is optically inactive.

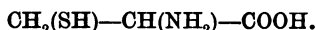
The lactic acids are not the only important substitution products of propionic acid. The three following substitution products—alanine, serine, and cysteine—are of great physiological interest. Alanine is a propionic acid in which a hydrogen atom in the α -position (see p. 83) is replaced by the amino radical NH_2 , i.e. it is α -aminopropionic acid:



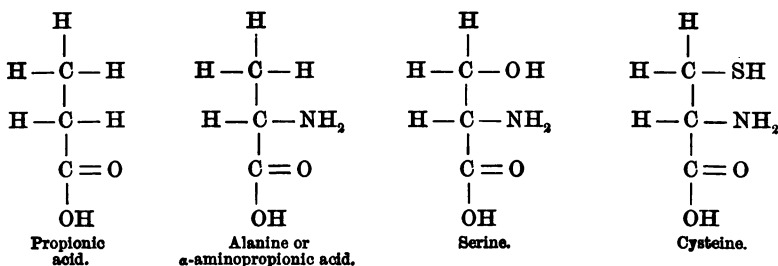
Serine is derived from alanine by the replacement of a hydrogen atom in the β -position by a hydroxyl group:



and cysteine is serine in which the divalent oxygen atom of the hydroxyl group in the β -position is replaced by a divalent sulphur atom:



Each of these three substitution products contains an asymmetric carbon atom, and is therefore optically active:



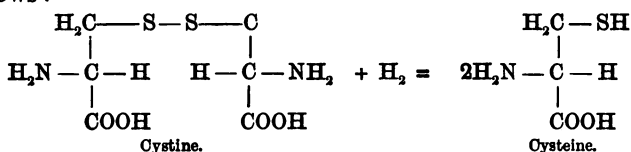
Alanine is found amongst the 'hydrolytic' decomposition products of gelatin, silk and horn (keratin); these are proteins (cf. Lecture 17), all of which can be broken up with absorption of water when boiled

with acids or alkalis, or by the action of ferments, into a large number of compounds, which will be described later. This kind of decomposition, with absorption of water, is called hydrolytic decomposition. Amongst the decomposition products which result on boiling gelatin,¹ silk,² horn,³ and certain other proteins with acids, alanine is found, always in its dextro-rotatory modification, as well as substituted alanines, in which a hydrogen atom is replaced by the aromatic radicals phenyl, or hydroxyphenyl, as in phenylalanine and hydroxyphenylalanine (or tyrosine) respectively; the former is found in considerable quantities amongst the decomposition products of all proteins; these latter compounds will be described under the 'aromatic group.' (Cf. Lectures 11, 12, 13.)

Alanine has been prepared synthetically by several methods—e.g. by the action of ammonia on α -chloropropionic acid. It consists of colourless crystals, easily soluble in water. By the action of nitrous acid it is converted into lactic acid, and if dextro-rotatory alanine be used, dextro-rotatory lactic acid is obtained.

Until some years ago serine had only been identified with certainty amongst the products of the hydrolysis of silk⁴ and horn⁵; Emil Fischer then supposed that it would also occur amongst the decomposition products of all other proteins, such as gelatin, caseinogen, etc., and this has now been definitely proven.

Cysteine arises by decomposition and reduction—by the action of tin and hydrochloric acid⁶—from cystine, whose constitution is as follows:



By oxidation—by the action of atmospheric oxygen, of iodine, or of ferric chloride—cystine is again converted into cystine.

Cystine⁷ occurs amongst the hydrolytic decomposition products

¹ E. Fischer, Levene and Aders, *Z. f. physiol. Chem.* 1902, vol. xxxv. p. 70.

² Weyl, *Ber. d. d. chem. Gesellsch.* 1888, vol. xxi. p. 1529, and E. Fischer and A. Skita, *Z. f. physiol. Chem.* 1901, vol. xxxiii. p. 177.

³ E. Fischer and Th. Dörpninghaus, *Z. f. physiol. Chem.* 1902, vol. xxxvi. p. 462.

⁴ Emil Cramer, *Journ. f. prakt. Chem.* 1875, vol. xvi. p. 76.

⁵ Emil Fischer, *Ber. d. d. chem. Gesellsch.* 1902, vol. xxxv. p. 2660; E. Fischer and Dörpninghaus, *Z. f. physiol. Chem.* 1902, vol. xxxvi. p. 462.

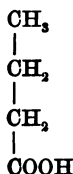
⁶ Baumann, *Z. f. physiol. Chem.* 1884, vol. viii. p. 299; *Ber. d. d. chem. Gesellsch.* 1885, vol. xviii. p. 258.

⁷ The most recent work on cystine is by K. A. H. Mörner, *Z. f. physiol. Chem.* 1899, vol. xxviii. p. 595; 1901, vol. xxxiv. p. 207. G. Embden, *ibid.* 1900, vol. xxxii.

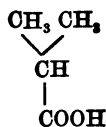
of proteins (especially horn or keratin). In certain rare anomalies of metabolism it appears in the urine, and it sometimes forms stones in the bladder, since it is with difficulty soluble in water.

B. The Derivatives of Butane, and Stereoisomerism continued.

Just as from propionic acid, so also from butyric acid, the next member of the homologous series of acids, some important physiological substances are derived. From the fourth member of the marsh gas series four butyl alcohols are obtainable (p. 70), and the two acids, normal butyric and isobutyric acids :



Normal butyric acid.



Isobutyric acid.

Isobutyric acid has as yet been found only a few times amongst the products of the putrefaction of proteins, and in human excrement.¹ It does not occur in our food or tissues, and therefore has at present no physiological interest.

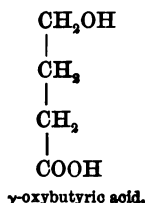
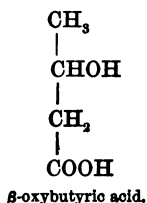
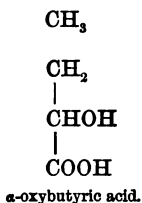
Normal butyric acid on the other hand is constantly formed in large amounts in the fermentation of carbohydrates (cf. Lecture 8) in our alimentary canal. Combined with glycerol it forms a constituent of the fat of the milk of mammals (cf. Lecture 7). The free acid has a nauseous smell, and is the substance which renders rancid butter uneatable. The glycerol compound is not volatile, but when butter becomes rancid butyric acid, which is volatile, is set free. This acid is excreted by ground-beetles (*Carabidæ*), and serves them as a protection against their enemies.

When in normal butyric acid a hydroxyl group takes the place of a hydrogen atom three isomers are possible ; these are :²

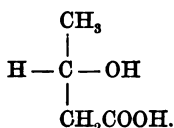
p. 94. E. Friedmann, *Hofmeister's Beitr. z. chem. Physiol. u. Path.* 1902, vol. ii. p. 433 ; 1902, vol. iii. p. 1 and p. 184 ; 1903, vol. iv. p. 486. A. J. Patten, *Z. f. physiol. Chem.* 1903, vol. xxxix. p. 350. In these papers the large amount of work on cystine and cysteine is quoted.

¹ L. Brieger, *Ber. d. d. chem. Gesellsch.* 1877, vol. x. p. 1027.

² [Oxy- is an abbreviation, used for purposes of convenience, of hydroxy-, which is the more accurate terminology.]

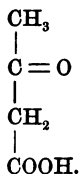


The substitution products of acids are designated by the Greek letters α , β , γ , and so on, according as the substituting element, or radical, is attached to the carbon atom next to the carboxyl group, or the following, or the next following, etc. Of the three isomeric butyric acids, the β -compound is of physiological and pathological interest. It occurs in the urine as a product of the incomplete oxidation of food in diabetes, and in other metabolic disturbances. When isolated from the urine it generally consists of a syrupy liquid, but, by repeated recrystallisation of its salts, it can be purified and obtained in plate-like crystals.¹ It contains an asymmetric carbon atom—



—and therefore can be obtained in a *d*- and *l*- form. In the human body, in the urine and blood² of diabetic patients, the *l*-acid is that which is always found.

As β -oxybutyric acid contains the secondary alcohol group CHOH , this must yield on oxidation a ketone group CO , forming a so-called ketone-acid :



This acid bears the name aceto-acetic acid [diacetic acid], and it can be regarded as being derived from acetic acid, by the replacement of a hydrogen atom of the methyl group by the monovalent acetyl radical, CH_3CO . Aceto-acetic acid is often found in the urine

¹ Magnus-Levy, *Arch. f. exper. Pathol. u. Pharmacol.* 1901, vol. xlv. p. 389.

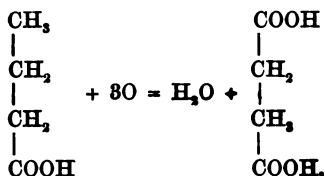
² Hugounenq, *Compt. rend. Soc. Biol.* 1887, p. 161. O. Minkowski, *Investigations on Diabetes mellitus after Extirpation of the Pancreas* (Vogel : Leipzig, 1893).

accompanying oxybutyric acid, and it is detected by the wine-red colour which it gives with ferric chloride. It breaks down easily into acetone (p. 67) and carbonic acid :

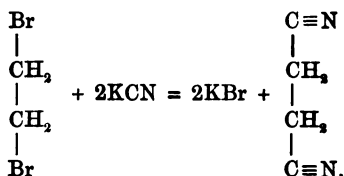


Acetone is often found together with oxybutyric acid and acetoacetic acid in the urine, where it is revealed by its smell. It is also found in the blood of diabetic patients, from which, on account of its volatility, it passes into the expired air.

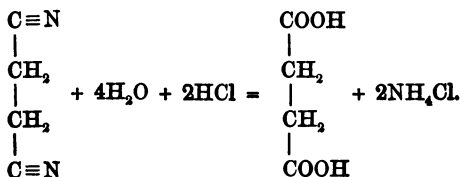
If energetic oxidising agents, e.g. nitric acid, be allowed to act on normal butyric acid, this is oxidised to an acid with two carboxyl groups, i.e. to the dibasic succinic acid :



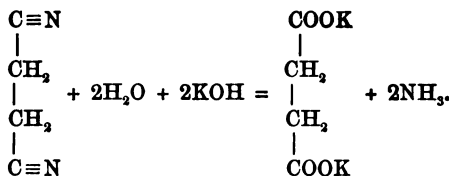
Succinic acid can also be synthesised atom by atom from its elements. The building up of ethylene from its elements, and its combination with bromine to form ethylene dibromide, has been described (pp. 7 and 10); ethylene dibromide, when heated with potassium cyanide in alcoholic solution,¹ is converted into ethylene dicyanide and potassium bromide :



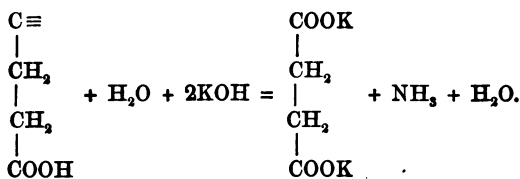
After the alcohol has evaporated ethylene dicyanide remains as a solid crystalline mass, which, when boiled with caustic potash or strong hydrochloric acid, is decomposed, with absorption of four molecules of water, into succinic acid and ammonia :



¹ On the synthesis of potassium cyanide see Lecture 10.

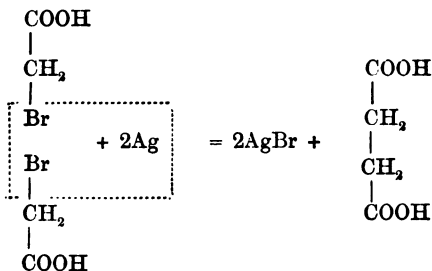


A second method of synthesis consists in converting β -chloropropionic acid into β -cyanopropionic acid, by boiling it with potassium cyanide, and then, on boiling this compound with potash, potassium succinate is formed :



The action of potassium cyanide upon the halogen compounds constitutes a general and useful method of introducing another carbon atom into a chain of carbon atoms, and of rising from simpler to more complicated molecules.

A third method of synthesising succinic acid is by the action of silver powder upon monobromacetic acid in a sealed tube at 130°C . :



From the three methods of preparing succinic acid cited above, its structure, as well as that of normal butyric acid, is unequivocally proved.

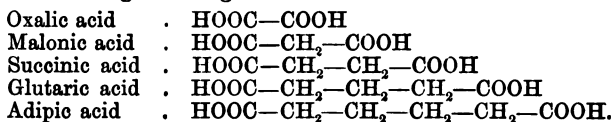
Succinic acid was first obtained from amber (*succinum*), hence its name. When amber is submitted to dry distillation, a brown acid liquid distils over, from which on evaporation succinic acid, deeply coloured, crystallises out; after treatment with nitric acid and recrystallisation, it is obtained in the form of colourless crystals, which melt at 182°C . and boil without decomposition at 235°C . Its vapours have a suffocating smell, and provoke an irresistible desire to cough.

Succinic acid is of interest physiologically: it is a metabolic

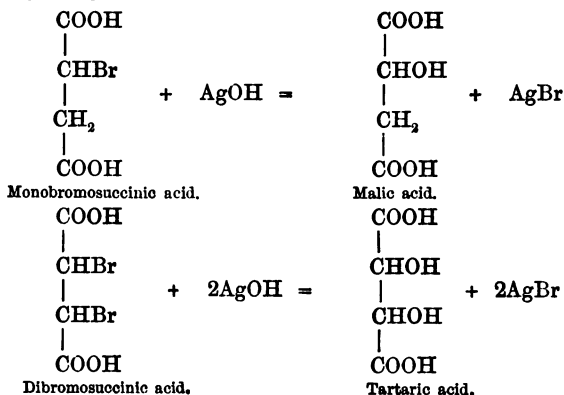
product of yeast; after alcohol and carbonic acid, it is one of the chief products of the alcoholic fermentation of sugar, its amount being exceeded only by that of glycerol (cf. Lecture 8). It also occurs during the bacterial decomposition of carbohydrates and proteins, and in the vegetable kingdom it has been found in lettuce, in worm-wood, in the poppy, in unripe grapes, and in other unripe fruits.

Succinic acid appears to be very widely distributed in the higher animals and man; it has been found in the spleen, the thymus, the thyroid, in wool-fat or lanoline, in hydrocephalic and hydrocele fluids, and it is especially abundant in the fluid contents of Echinococcus cysts. It is of further physiological interest in that it stands in very close relationship to malic and tartaric acids, which are contained in many of our foodstuffs, especially in all acid fruits and berries.

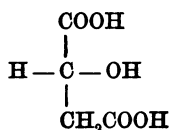
[Succinic acid belongs to the series of dibasic acids, the first member of which is oxalic acid (p. 62). The next member is malonic acid, a compound often used in synthesis in organic chemistry. Then comes succinic acid with its important derivatives, and the next two members are glutaric and adipic acids. We have therefore the following homologous series :



By submitting an aqueous solution of succinic acid and bromine in a sealed tube to a high temperature and great pressure, two substitution products are formed, namely, monobromosuccinic acid and dibromosuccinic acid, and by boiling the aqueous solutions of these acids with silver hydroxide, monohydroxysuccinic acid or malic acid, and dihydroxysuccinic acid or tartaric acid are obtained :

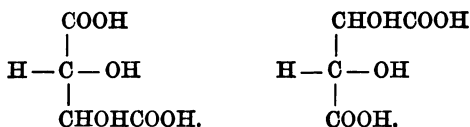


Malic acid contains an asymmetric carbon atom—



—and we therefore expect it to exist in a dextro- as well as in a lævo-rotatory modification, and also as the optically inactive mixture of the two. Malic acid, as it occurs in nature in apples and other fruits, is always lævo-rotatory, crystallising with difficulty and forming warty masses of deliquescent, incompletely formed crystals. The synthetically prepared malic acid, like all synthetically prepared compounds, is optically inactive (p. 79); it can be resolved, by the fractional crystallisation of its cinchonine salts, into its dextro- and lævo-components.

Tartaric acid contains two asymmetric carbon atoms, each of them with the same four radicals—



—and we must therefore expect *a priori* that it must exist in four different modifications, as follows:

1. The arrangement of the four radicals round the two asymmetric carbon atoms is the same, and causes the dextro-rotation of both. This will be dextro-tartaric acid.

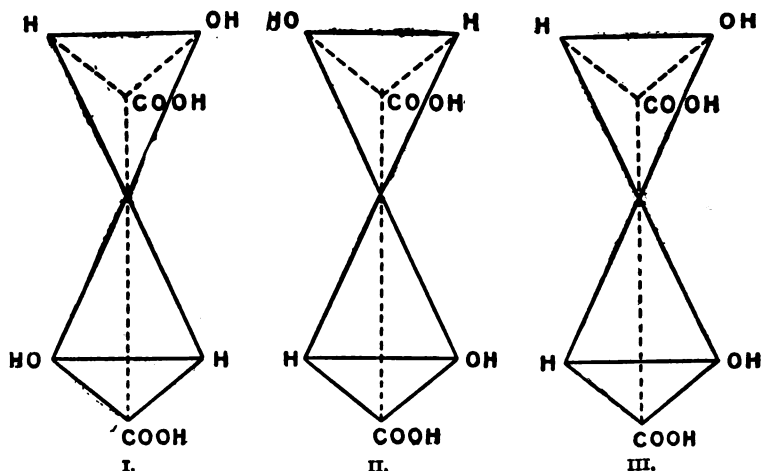
2. The arrangement of the four radicals round the two asymmetric carbon atoms is the same, and causes the lævo-rotation of both. This will be lævo-tartaric acid.

3. The arrangement round one of the asymmetric carbon atoms causes dextro-rotation; that round the other causes lævo-rotation; the two actions inhibit each other within the molecule, i.e. intramolecularly, and therefore this will form an optically inactive acid, which cannot be separated by fractional crystallisation into a dextro- and a lævo-rotatory modification.

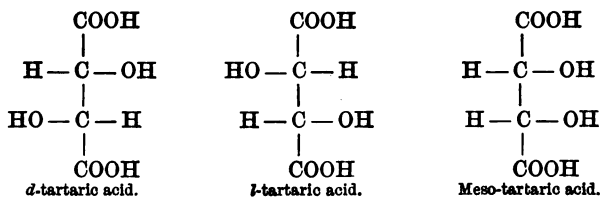
4. A mixture of the same number of molecules of modifications 1 and 2. This will be an optically inactive acid, which can be separated by fractional crystallisation into modifications 1 and 2, i.e. into *d*- and *l*-tartaric acids.

[These modifications can be more easily understood if they are

represented by models, and the following diagrams may therefore help to make the conception of the stereoisomerism of the tartaric acids quite clear:



or projected on to a plane surface:



All these four modifications are known. The dextro-tartaric acid occurs as the free acid, and as its acid potassium salt, in grapes, and in many other berries and fruits. An optically inactive tartaric acid is often found in grapes, and is called paratartaric acid or racemic acid, after the Latin word *racemus*, grape. Pasteur (1822-1895) showed that this inactive acid could be separated into a dextro- and a lævo-rotatory tartaric acid by either of the three following methods, which he discovered:

1. If a salt of tartaric acid be allowed to crystallise slowly, two kinds of crystals separate out from the solution, which can be differentiated by their shape, and separated by mechanically picking out the individual crystals. It was by means of the double salt of tartaric acid with sodium and ammonium that Pasteur succeeded in effecting their separation; the hemihedrally formed facets of these

two kinds of crystals had a different position, the one kind being the mirror image of the other. From the one he prepared lævo-tartaric acid, from the other dextro-tartaric acid.¹ On account of this property of racemic tartaric acid, all other optically inactive compounds with asymmetric carbon atoms, which can be separated into a dextro- and a lævo-rotatory modification, are called 'racemic,' or shortly, *r*- [or *dl*-, vide p. 79] compounds.

2. His second method of separating racemic acid depended upon the fact that the dextro- and lævo-rotatory acids form salts with optically active bases which have a different solubility, so that they can be separated by fractional crystallisation. Racemic lactic acid, as we have seen, can be separated by the fractional crystallisation of its strychnine salts, but the cinchonine salt is the one which is especially useful for the separation of racemic tartaric acid.

3. His third method of separation² rested upon his discovery that certain moulds, such as *Penicillium glaucum*, only decompose the dextro-rotatory tartaric acid. If the mould be allowed to grow upon a dilute solution of racemic tartaric acid the solution becomes lævo-rotatory.

The optically inactive tartaric acid which cannot be separated into two 'optical antipodes' is called anti-tartaric, or more frequently mesotartaric, acid. This is formed from *d*-tartaric acid by boiling it for a long time with excess of caustic soda, or with dilute hydrochloric acid. [Method of racemising optically active substances.]

The synthetically prepared tartaric acid was first separated into its *d*- and *l*-components by the French chemist, Emile Cl. Jungfleisch,³ in 1873. This discovery caused a great sensation, since it was the first artificial preparation of an optically active compound, for up to that time many chemists thought that optically active compounds could only be formed by the living cell. We can now prepare a large number of such compounds synthetically; we cannot, however, *directly* prepare a lævo- or dextro-rotatory compound, but only the mixture from which the two acids can be subsequently separated by any one of the above methods. [Cf. note 4, p. 79.]

On a large scale tartaric acid is obtained from tartar, or impure acid potassium tartrate. It will be remembered that tartaric acid is a reagent used in the differentiation of potassium from sodium,

¹ Louis Pasteur, *Ann. de Chim. et de Phys.* 1849 (iii.), vol. xxviii. p. 56.

² L. Pasteur, *Compt. rend.* 1860, vol. li. p. 298.

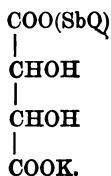
³ E. Cl. Jungfleisch, *Compt. rend.* 1863, vol. lxxvi. p. 286; or *Bull. Soc. Chim.* 1873 (ii.), vol. xix. p. 194.

because the acid potassium salt is soluble with difficulty in water, whereas the sodium salt is easily soluble. Acid potassium tartrate is still more insoluble in dilute alcohol than in water. When, therefore, grape juice ferments, acid potassium tartrate settles on the sides of the casks, and, mixed with calcium salts and colouring matters which are present, forms a brown crust, the so-called raw tartar. Pure acid potassium tartrate is obtained from this by recrystallisation, and under the pharmaceutical name of cream of tartar is used as a purgative.

In order to prepare the pure acid from tartar, the acid potassium salt is boiled with water and chalk, whereby half the tartaric acid is precipitated as calcium salt, the other half remaining in solution as neutral potassium salt. Calcium chloride is then added to the solution, when all the tartaric acid is precipitated as calcium salt. This is washed and decomposed with sulphuric acid; the solution of tartaric acid so obtained is filtered from the calcium sulphate, decolourised with animal charcoal, and evaporated down, when the free acid crystallises out in large colourless prisms.

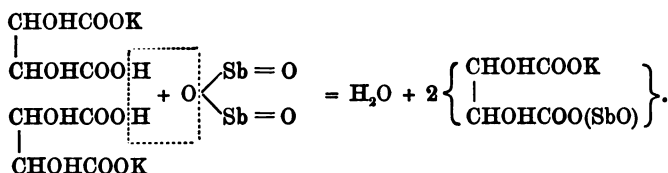
Tartaric acid is largely employed in the preparation of various lemonades and effervescent powders. It may be well to state here that all these artificial lemonades should be discarded, as those prepared from boiled fruits are always preferable, because these contain colloidal substances—carbohydrates and proteins—which moderate the irritating action of the acid and salt solution upon the mucous membrane of the stomach and intestines.

Tartar emetic is a double salt of tartaric acid with antimony and potassium: it is prepared by dissolving antimonious oxide Sb_2O_3 in a hot solution of acid potassium tartrate; on cooling, tartar emetic crystallises out. Antimony is a trivalent element, and if two of its valencies are saturated by a divalent oxygen atom, a univalent radical results. This group (SbO) takes the place of the hydrogen atom in one of the two carboxyl groups of tartaric acid, the hydrogen atom of the other carboxyl group being replaced by potassium:



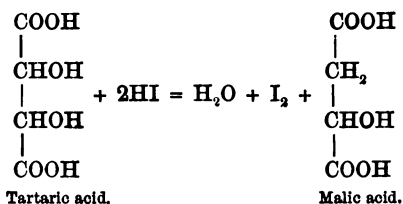
Two molecules of this compound crystallise with one molecule of

water of crystallisation. The process of its formation is therefore the following :—



The radical SbO bears the name antimonyl, and tartar emetic is therefore also called potassium antimonyl tartrate; like all antimony compounds it is poisonous. It is soluble in seventeen parts of water, and in small doses it has been much used in therapeutics; in doses of 0·1–0·2 gramme as an emetic, in the much smaller doses of 0·005–0·02 gramme as an expectorant, and finally, like arsenic, it has been given for skin diseases.

Tartaric acid when reduced with hydriodic acid is converted firstly into malic acid, and then into succinic acid. Hydriodic acid acts like nascent hydrogen; in hydriodic acid the hydrogen atom is more loosely bound to the iodine atom than it is to its fellow hydrogen atom in a hydrogen molecule; atmospheric oxygen at the ordinary temperature does not attack the hydrogen molecule, but it attacks the hydriodic acid molecule; on allowing a colourless aqueous solution of hydriodic acid to stand exposed to the air it gradually becomes darker and darker in colour, and finally iodine separates in beautiful crystals. When, therefore, hydriodic acid acts upon the hydroxyl group of tartaric acid, water is formed and eliminated, and a hydrogen atom takes the place of the hydroxyl group:



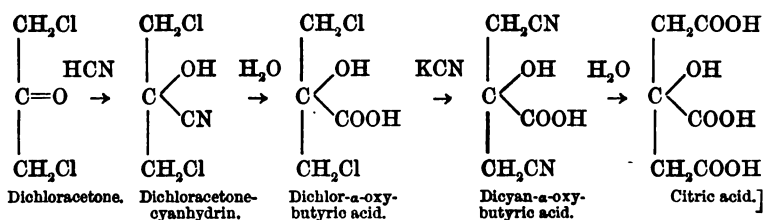
On further reduction succinic acid is formed from malic acid in the same way. If the tartaric acid be dextro-rotatory the malic acid, formed by reduction, is also dextro-rotatory; if lævo-rotatory, the resulting malic acid is lævo-rotatory.

In many acid berries and fruits malic and tartaric acids are often accompanied by citric acid, which has a more complicated structure than that of these two simple derivatives of succinic acid. The acid

taste of berries and fruits is due to these three acids, and their acid potassium salts. In the animal body these acids are oxidised to carbonic acid and water, and their acid salts are converted into alkaline potassium carbonate; hence, after eating too freely of sour berries and fruits, the urine becomes alkaline and effervesces upon the addition of an acid.

The synthesis of citric acid has been carried out by several methods¹ and its structure determined.

[The following synthesis from dichloracetone demonstrates clearly the two methods, previously described, of introducing a carbon atom into a simple molecule with the production of a more complicated one (pp. 49 and 85):



Citric acid is a tribasic acid. Its tricalcium salt has the curious property of being soluble easily in cold water, but with difficulty in boiling water, and upon this fact its separation from lemon-juice and its preparation on a large scale depends.

A very striking and interesting phenomenon is the constant occurrence of considerable quantities of citric acid in the milk of man, and of all those mammals in which it has so far been investigated.² Its occurrence here is striking, since it has so far only been met with in the vegetable kingdom, and it is still a question what importance is to be attached to its presence in milk. It is supposed that it is concerned in the solution of the calcium salts, as its amount is proportional to the amount of calcium in the milk of the various animals.³ It may be assumed that it arises in the animal body from the carbohydrates which contain six atoms of carbon, and as a matter of fact, two moulds—*Citromyces Pfefferianus* and *C. glaber*—form such large quantities of citric acid from carbohydrates, that this method of its preparation is now made use of technically.⁴

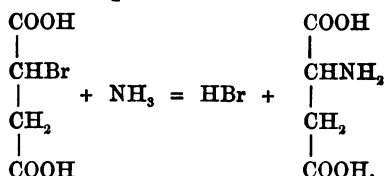
¹ E. Grimaux and P. Adam, *Ann. de Chim. et de Phys.* 1881 (v.), vol. xxiii. p. 356.

² Th. Henkel, *Molkenseitung*, 1888, vol. ii. p. 259; *Landw. Versuchstationen*, 1891, vol. xxxix. p. 143; A. Scheibe, *ibid.* p. 153.

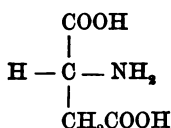
³ L. Vaudin, *Ann. de l'Institut Pasteur*, 1894, vol. viii. p. 502; cf. also G. v. Bunge, *Z. f. Biologie*, 1904, vol. xlv. p. 537.

⁴ C. Wehmer, *Sitzungsber. d. k. preuss. Akad. d. W. zu Berlin*, 1898, p. 519.

Amongst the ammonium derivatives of succinic acid amino-succinic acid, or aspartic acid, is of very great physiological interest. This amino-acid can be prepared synthetically by several means, e.g. by the action of ammonia upon monobromosuccinic acid :



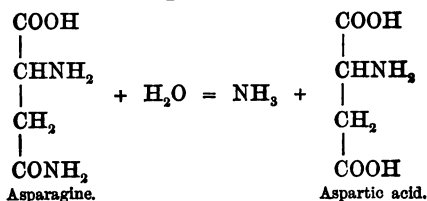
Aspartic acid is of importance physiologically because it occurs in considerable quantities amongst the hydrolytic decomposition products of all the proteins which have been hitherto examined. Aspartic acid contains an asymmetric carbon atom :



That acid, which arises from the decomposition of proteins, is lævo-rotatory, and the synthetically prepared 'racemic' aspartic acid has been separated into its two optical antipodes by Emil Fischer.¹

Aspartic acid crystallises in rhombic plates and prisms, which are soluble with difficulty in cold water, but fairly easily in hot. It is converted by nitrous acid, according to the typical reaction (pp. 62 and 81), into malic acid.

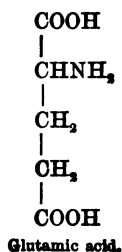
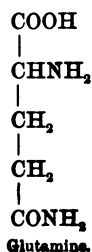
The amide of aspartic acid, called asparagine, is found very widely distributed in the vegetable kingdom; it has been identified in beetroot, in potatoes, in the young leaves of plants, in the sprouts of peas, beans and vetches, and is especially abundant in asparagus, in which it was first found, hence its name. It is converted when boiled with water, or more easily with acids and alkalis, into aspartic acid and ammonia, with absorption of water :



¹ Emil Fischer, *Ber. d. d. chem. Gesellsch.* 1899, vol. xxxii. p. 2451.

[This structural formula shows very clearly the difference between an amide and an amine, as asparagine is a compound exhibiting both these properties (p. 59).

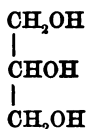
Glutamic acid, the next homologue to aspartic acid, also occurs as a hydrolytic decomposition product of proteins. It occurs in the vegetable kingdom, together with its amide, generally in association with aspartic acid and asparagine :



LECTURE VII

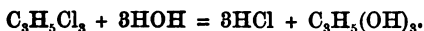
GLYCEROL AND THE FATS

AMONGST the derivatives of propane one very important physiological compound—glycerol or glycerine¹—has not yet been described; in the first lecture, in recounting the achievements of synthetical chemistry, a method of preparing it synthetically was mentioned (p. 5), and the structural formula—



—was given to it.

The correctness of this formula can now be established. The empirical formula of glycerol is $\text{C}_3\text{H}_8\text{O}_3$. The presence of three hydroxyl groups in its molecule is shown by its preparation from trichlorhydrin, by heating this with water (p. 5):



[It is therefore a trihydric alcohol, i.e. a compound containing three hydroxyl groups. The three hydroxyl groups must be attached one to each carbon atom, and this is proved by its preparation from trichlorhydrin, and by its products of oxidation; for, as previously stated, if two hydroxyl groups be attached to one carbon atom, a molecule of water is eliminated and an aldehyde or ketone results.]

By careful oxidation glycerol yields a monobasic acid, glyceric acid $\text{C}_2\text{H}_3(\text{OH})_2\text{COOH}$, and on further oxidation a dibasic acid, tartronic acid $\text{CHOH}(\text{COOH})_2$. From this it follows that glycerol must contain two primary alcohol groups, CH_2OH (p. 71), and one secondary alcohol group, CHOH . The carbon atoms of the primary alcohol groups must form the two end members of the chain of carbon atoms, and the secondary alcohol group must lie in the middle.

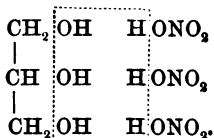
¹ [The termination *-ol* denotes an alcohol, that of *-ine* an amine, i.e. a base. Consequently, the term glycerine is inaccurate; it is not a base but an alcohol, and therefore the word glycerol should be always used.]

As glycerol is a trihydric alcohol, it can combine with three molecules of a monobasic acid, with the loss of three molecules of water, to form a neutral ester. In this form, as the ester of fatty acids, glycerol is a constituent of all plant and animal tissues.

Glycerol is an oily, colourless, odourless liquid with a sweet taste, hence its name. It is heavier than water, and has a specific gravity of 1.3. If glycerol be kept for some time at a temperature of $0^{\circ}\text{C}.$, it forms crystals belonging to the rhombic system, which melt first at $+17^{\circ}\text{C}.$ It distils almost without decomposition at $290^{\circ}\text{C}.$

Glycerol mixes with water in all proportions; it is very hygroscopic, and takes up water from the air; when mixed with water a contraction in volume occurs, and heat is evolved. Upon this property the use of glycerol as a preservative for anatomical and histological preparations depends; and upon its dehydrating action, and high boiling point, also depends its use as an adjunct to external remedies. A drug dissolved in water, or alcohol, can have no lasting action upon the skin, as the solvent evaporates at once, and the drug then dries and falls off. If, e.g., *Pityriasis versicolor* is to be treated with sublimate, it does not suffice to allow an aqueous solution of sublimate to act upon the portions of the skin affected by the mould, as the greater part of the solution rolls off the skin at once, and the remainder evaporates as quickly as water, and in consequence the sublimate cannot penetrate into the skin. If, however, a dilute solution of sublimate be mixed with glycerol and be rubbed into the skin, the solvent not only does not evaporate, but it continually takes up water from the air. The solution, therefore, continues active, and the sublimate can penetrate into the deeper layers of the epidermis, and kill the mould (*Microsporon furfur*), the mycelia of which are there proliferating. Glycerol, however, must not be brought into contact with inflamed areas, as it has an irritating action and produces pain, probably on account of its hygroscopic properties. Solutions made with glycerol have this advantage over ointments made with fats, oils, vaseline, etc., that they can be readily washed off with water, as glycerol mixes with water in every proportion.

Technically, the most important use of glycerol is in the preparation of nitroglycerine, which is its neutral ester with nitric acid, and is formed by the combination of one molecule of glycerol with three molecules of nitric acid, with the loss of three molecules of water:



In the preparation of nitroglycerine, glycerol is slowly and cautiously brought into contact with a mixture of concentrated nitric and sulphuric acids, which must be kept cool; after some time the mixture is poured into water, when the nitroglycerine, which is not miscible with water, separates as a heavy oil, and is purified by washing with water and soda solution.

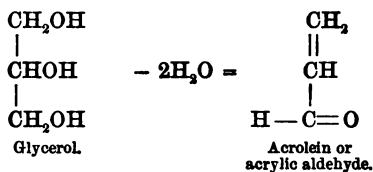
The most striking property of nitroglycerine is its explosiveness, which is a common property of all the esters of nitric acid. The oxygen in these compounds is in a labile condition, being only loosely attached to the nitrogen atom. Nitrogen has only very slight affinity for other elements, and herein lies the reason why nitrogen is found in nature chiefly in the free state, in which condition it constitutes four-fifths of the atmosphere. Carbon and hydrogen on the other hand have a great affinity for oxygen, and therefore a rise in temperature, or a blow, suffices to bring about a rearrangement, and to change the oxygen from a labile into a stable condition of equilibrium. Heat is evolved in this process and many gaseous products, carbonic acid, steam, nitrogen are formed; these gases expanded by the heat occupy a volume 10,000 times greater than that of the nitroglycerine, and this sudden increase in volume explains its enormous explosive power.

The transport of nitroglycerine is fraught with great danger. This was overcome by the Swedish engineer, A. Nobel, who succeeded in obtaining a mixture which is transportable without danger, by allowing dry, indifferent powders to soak up the nitroglycerine. Such preparations are known as dynamite, and the powder generally used is the so-called 'Kieselguhr,' which is a diatomaceous earth. Ordinary dynamite is a mixture of 75 per cent. nitroglycerine and 25 per cent. kieselguhr; it forms a plastic mass which cannot be easily exploded by pressure and blows, but is very easily exploded by small quantities of mercury fulminate (cf. Lecture 10). In order to explode dynamite cartridges a small capsule filled with fulminate is placed in them, and this is made to explode by means of a percussion cap or by an electric spark.

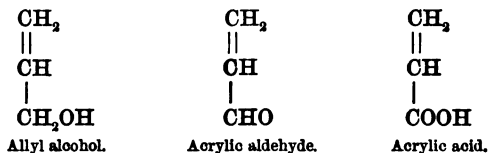
When pure glycerol is gradually and carefully heated, it distils almost without decomposition at 290°C ., but when it is rapidly heated various decomposition products are formed. Among these is found acrylic aldehyde or acrolein, the vapours of which have a very penetrating smell and are very irritating to the eyes; it is a colourless liquid boiling at 52°C . The unpleasant smell of acrolein is known to everyone who has smelt the fumes which arise from a tallow candle just extinguished, or which are formed by the incomplete

H

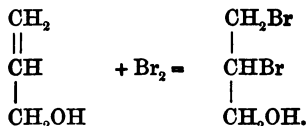
combustion of fats. Glycerol is almost completely converted into acrolein when it is distilled with dehydrating agents—e.g. with acid potassium sulphate. The most delicate method of qualitatively detecting glycerol depends upon this. Acrolein is formed from glycerol by the loss of two molecules of water :



The aldehyde nature of acrolein follows from the facts that it is converted by nascent hydrogen into the primary alcohol, allyl alcohol, and by oxidation into the monobasic acrylic acid :



As the two carbon atoms, which acrylic aldehyde contains with the aldehyde group, have only three atoms of hydrogen attached to them, we must assume a double linking between them, as also in the cases of allyl alcohol and acrylic acid. The presence of the double linking in these three compounds is further shown by the fact that at the ordinary temperature they 'add' on two atoms of bromine—i.e. they combine with bromine without the separation of hydrobromic acid, and, at the same time, the unsaturated becomes transformed into a saturated compound :



The radical C_3H_5 is called allyl because its sulphide $(\text{C}_3\text{H}_5)_2\text{S}$, a volatile liquid with a very penetrating smell, is contained in garlic, *Allium sativum*, to which it imparts the characteristic odour. The allyl ester of sulphocyanic acid $\text{CNS}(\text{C}_3\text{H}_5)$ forms that constituent of mustard which gives it its pungent smell ; it arises by the decomposition of the glucoside myronic acid, which is contained in the mustard seeds (cf. Lectures 9 and 10).

Acrylic acid has been previously mentioned ; hydracrylic acid,

which is the isomer of lactic acid, when heated, loses water and is converted into acrylic acid (p. 76).

Glycerol is found in nature chiefly in the neutral esters of the fatty acids. The oils and fats which are present in all animal and plant tissues consist of triglycerol esters, or glycerides. The fatty acids which have a share in the formation of these glycerides belong for the most part to the homologous series of fatty acids (p. 65), the first members of which, formic, acetic, propionic and butyric acids, have been already described.

SERIES OF FATTY ACIDS $C_nH_{2n}O_2$

		Melting point	Boiling point
Formic acid	$HCOOH$	+ 8° C.	101° C.
Acetic acid	CH_3COOH	+ 17° C.	118° C.
Propionic acid	C_2H_5COOH	- 24° C.	141° C.
Butyric acid (normal)	C_3H_7COOH	- 2° C.	162° C.
Valerianic acid (normal)	C_4H_9COOH	- 59° C.	185° C.
Caproic acid (normal)	$C_5H_{11}COOH$	- 2° C.	205° C.
Oenanthalic acid	$C_6H_{13}COOH$	- 11° C.	233° C.
Caprylic acid	$C_7H_{15}COOH$	+ 17° C.	236° C.
Pelargonic acid	$C_8H_{17}COOH$	+ 18° C.	
Capric acid	$C_9H_{19}COOH$	+ 31° C.	
Undecylic acid	$C_{10}H_{21}COOH$	+ 28° C.	
Lauric acid	$C_{11}H_{23}COOH$	+ 44° C.	
Tridecylic acid	$C_{12}H_{25}COOH$	+ 41° C.	
Myristic acid	$C_{13}H_{27}COOH$	+ 54° C.	
Pentadecylic acid	$C_{14}H_{29}COOH$	+ 51° C.	
Palmitic acid	$C_{15}H_{31}COOH$	+ 62° C.	
Margaric acid	$C_{16}H_{33}COOH$	+ 60° C.	
Stearic acid	$C_{17}H_{35}COOH$	+ 68° C.	
Nondecylic acid	$C_{18}H_{37}COOH$	+ 67° C.	
Arachic acid	$C_{19}H_{39}COOH$	+ 75° C.	
Behenic acid	$C_{21}H_{43}COOH$	+ 75° C.	
Lignoceric acid	$C_{23}H_{47}COOH$	+ 80° C.	
Cerotic acid	$C_{25}H_{51}COOH$	+ 78° C.	
Melissic acid	$C_{29}H_{59}COOH$	+ 90° C.	

The first nine members of this series are liquids at the ordinary temperature, the remainder solids, capable of crystallisation. The first three members are mobile liquids, with a pungent, acid smell; the next six are oily, with very unpleasant smells. The first three members and normal butyric acid mix with water in every proportion; isobutyric acid and the five following acids only mix with certain definite proportions of water. The higher members from capric acid with ten carbon atoms and upwards, are insoluble in water, but soluble in alcohol, and more easily so in ether. The lower members can be

distilled without decomposition, and are easily volatile with steam, although their boiling points are higher than that of water. The higher members—from the twelfth upwards—can only be distilled without decomposition *in vacuo*. [On this account these acids are divided into the volatile and non-volatile fatty acids.]

The lower acids which mix with water have a strongly acid reaction to litmus: in order to determine the acid reaction of the higher acids, which are insoluble in water, another colouring matter must be chosen, as the acid reaction can only appear when both the acid and the colouring matter have a common solvent. Litmus is soluble in water, but not in alcohol; the higher fatty acids, conversely, are soluble in alcohol, but not in water, and therefore they cannot react with litmus. The beautiful alkanet colouring matter, however, which is soluble in alcohol, gives a fine red colour with an alcoholic solution of the higher fatty acids; on adding an alcoholic solution of soda, a blue colour appears as soon as the quantity of soda equivalent to the acid is exceeded. In this way, by titration, the amount of free fatty acid which is mixed with neutral glycerides can be quantitatively determined. This method is often made use of in physiological chemistry.

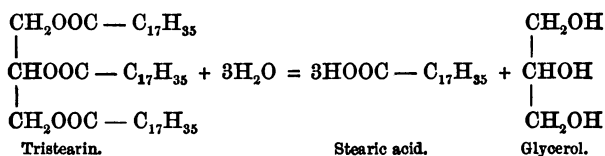
The members of the series of fatty acids which are concerned in the formation of the fat of our body and of our food, are chiefly palmitic acid with sixteen, and stearic acid with eighteen carbon atoms. In certain fats such as butter, butyric, caproic, caprylic and capric acids are found in small quantities.

In addition to these acids, all the fats of our body contain large quantities of another acid belonging to another series. This is oleic acid, which contains eighteen carbon atoms like stearic acid, but two atoms of hydrogen less; it is an unsaturated acid like acrylic acid, which, as above mentioned, is the first member of this series, the so-called acrylic acid or oleic acid series. At the ordinary temperature oleic acid is a colourless, oily liquid, without smell or taste, insoluble in water, but soluble in alcohol and ether.

The triglycerides of palmitic acid and of stearic acid are solid and crystalline at the ordinary temperature; the triglyceride of oleic acid is liquid. These compounds can be prepared synthetically by heating glycerol with the respective acid. The tristearic acid ester of glycerol is called tristearin, or more shortly stearin; the glycerol ester of tripalmitic acid, tripalmitin or palmitin; the glycerol ester of trioleic acid, triolein or olein. The melting point of stearin is 72° C., of palmitin 62° C.; olein at the ordinary temperature is a liquid, and solidifies at -6° C. The physical state of a fat depends on the

relative quantities of the three glycerol esters which it contains. Olive oil, for instance, contains about 75 per cent. olein, and is liquid at the ordinary temperature; beef suet, with about 25 per cent. olein, is solid. Between these two in their content of olein are pig's fat and human fat,¹ which at the ordinary temperature are softer than beef suet. At the body temperature human fat is liquid. The fat of cold-blooded animals contains more olein than human fat; it is a liquid at the ordinary temperature like fish oil; this is understandable on teleological grounds.

The simplest method of decomposing a fat into its constituents is by means of superheated steam; the triglycerides then take up three molecules of water, and break down into glycerol and three molecules of fatty acid:



This method is used on the large scale in the manufacture of candles, and for the preparation of glycerol. The fats, together with water, are placed in large retorts, and submitted to a temperature of 290 to 315° C., by passing steam heated to 315° C. through the retorts for twenty-four hours. Both the glycerol and the liberated fatty acids distil over, and two layers are formed in the receivers. The upper layer consists of a mixture of the three acids, and if this liquid be allowed to cool slowly, the stearic and palmitic acids gradually crystallise out and are separated from the liquid oleic acid by pressure. The mixture of stearic and palmitic acids is used in the manufacture of candles, and the oleic acid finds its chief use in the manufacture of soap. The lower layer in the receiver consists of a solution of glycerol in water; this is concentrated, purified by filtration through animal charcoal, and further evaporated *in vacuo*. In order to prepare specially pure glycerol, this is again submitted to distillation with superheated steam, and the pure glycerol is collected in receivers kept at a temperature above 100° C., whilst the water, with a small portion of the glycerol, is collected in other and cooler receivers.

The decomposition of fats by water alone is chemically the simplest process, but in most works it is not employed. Their decomposition is

¹ On the chemical composition of human fat see L. Langer, *Monatshefte f. Chem.* 1881, vol. ii. p. 382; A. Lebedeff, *Z. f. physiol. Chem.* 1882, vol. vi. p. 139; C. A. Mitchell, *The Analyst*, 1896, vol. xxi. p. 171.

effected by heating with bases—alkalies, lime, magnesia—or with dilute sulphuric acid. If the chief object be the preparation of soap, caustic soda is used; on boiling the fats with caustic soda the triglycerides break down into one molecule of glycerol and three molecules of the sodium salts of the fatty acids. These sodium salts are soluble in water, and when common salt is added to the still boiling solution, which now consists of the alkali salts of the fatty acids, glycerol, water and excess of soda, the salts of the fatty acids separate out and rise to the surface as a compact mass, since they are insoluble in concentrated salt solution. The salts of the fatty acids are removed from the vessel and pressed into shape, and form the so-called curd soap. The under layer, consisting of an aqueous solution of glycerol, common salt and excess of soda, can be used for the preparation of glycerol. If the quantity of common salt added be insufficient, no separation of the soap from the aqueous solution occurs; the contents of the vessel remain homogeneous and solidify on cooling, and the soap so obtained is called 'compressed soap.'

When potash is used in the process of saponification instead of caustic soda, a soft mass, the so-called soft soap, is obtained on evaporation of the solution. Soft soap, which is used in medicine as an external application, contains, like the compressed soaps, glycerol and an excess of alkali, together with the alkali salts of the fatty acids.

When lime is used for the saponification, the insoluble calcium salts of the fatty acids are formed; these are decomposed with sulphuric acid in order to liberate the fatty acids, which are then employed for the preparation of candles by the above method.

If the fats be decomposed by boiling with water and lead oxide, glycerol and the lead salts of the fatty acids are formed; at the ordinary temperature they form dough-like masses, the so-called lead plaster, and are used, with additions of various kinds, as external applications.

The action of soap as a cleansing agent depends upon the fact that the alkali salt of the fatty acid is partially decomposed by a large quantity of water, i.e. by mass action, into free fatty acid and free alkali. The resulting dilute alkaline solution is an excellent solvent for many substances which are not soluble in water alone; the still undecomposed soap solution is able to mix intimately with all kinds of fat, which may contaminate the dirty object, forming emulsions (p. 103); the soap lather loosens the impurities of all sorts, and conduces to their removal.

No lather is formed when a water rich in calcium salts is used;

white flakes result consisting of the calcium salts of the fatty acids, which are insoluble in water; the alkali also has no action, since it combines with the acids of the calcium salts, sulphuric acid and carbonic acid. Water rich in calcium—the so-called hard water—is not therefore suitable for washing purposes; the amount of soap used has to be much larger, and can only act as a cleansing agent after an amount equivalent to that of the calcium salts in the water has been used up.

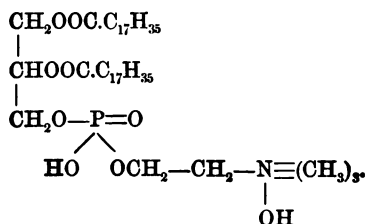
Physiologically it is important to know that fats are only saponified by caustic alkalis, and not by alkali carbonates; the neutral glycerides of the fatty acids and sodium carbonate have no action upon one another. Sodium carbonate, however, is decomposed by the free fatty acids, carbon dioxide being given off and the sodium salt of the fatty acid, or soap, being formed. Our normal fresh food contains only neutral fats, but in the blood and lymph soaps occur. How, then, is the saponification of the fat effected? Free alkalies do not occur in our alimentary tract or in our tissues, and they cannot arise there, since all tissues contain carbonic acid. But the ferments of the pancreas decompose fats, with absorption of water, into glycerol and fatty acids; these form soaps with the sodium carbonate which is contained in the pancreatic juice, in the intestinal juice, and in the bile, and this soap solution converts the remaining undecomposed fat into a fine emulsion.

When commercial olive oil, which is never quite neutral, but always somewhat rancid—i.e. contains some free fatty acid together with the neutral glycerides—is shaken up with a dilute soda solution, at the first shake the whole mass of oil is broken up into microscopically small drops; it is changed into a fine emulsion. The molecules of free fatty acid were distributed amongst the molecules of the neutral fat, and according to the quantity in which the fatty acid molecules form soaps with the molecules of sodium carbonate, so will carbonic acid be liberated, and the neutral fat molecules will be separated from each other [by a layer of soap]. In a similar way the fats of the food are partially split up by the pancreatic ferment and with the sodium carbonate, which is being continually secreted, forms an emulsion of the finest fat droplets on the wall of the intestine, which droplets pass through the intestinal wall and reach the beginning of the chyle vessels.

How fat outside the organism becomes rancid is not yet sufficiently explained; bacteria are supposed to yield a ferment which breaks up the fat, but some authors maintain that fatty acids are set free simply by the action of the oxygen of the air on the

glycerol, without the presence of bacteria. Even the term 'rancid' is disputed; some authors do not call every fat which contains free fatty acids rancid, but only those which evolve evil-smelling volatile products. These products are not volatile fatty acids at all, but substances of the nature of esters, or aldehydes, of unknown origin. There is much literature on this question, but no unity of opinion.

The fats are not the only glycerol compounds occurring in our body; in all animal and vegetable tissues, and in every cell, other compounds of glycerol are found; in these only two of the three hydroxyl groups of the glycerol are esterified by fatty acids, the third by the tribasic phosphoric acid. One of the two remaining hydroxyl groups of the phosphoric acid is esterified by the organic base choline, the synthesis and constitution of which has been described (p. 11). This very complicated compound is called lecithin, as it was first prepared from egg-yolk (λέκιθος). The fatty acids which take part in the formation of the various lecithins are either stearic, palmitic, or oleic acid, and we therefore differentiate between distearyl-, dipalmityl-, and dioleyl-lecithin. The constitutional formula for distearyl-lecithin is :



The constitution¹ is shown by the following reactions. Lecithin is decomposed by boiling with baryta water into two molecules of the barium salt of the fatty acid which are precipitated, and one molecule each of barium glycerophosphate, which is soluble, and of choline. As the choline is only slowly split off, it must be assumed that this base is not combined in the form of a salt with the substituted phosphoric acid, since it is not the hydroxyl group which is attached directly to the nitrogen atom, but it is the hydroxyl group of the oxyethyl radical which is concerned in the formation of the ester.

Lecithins are not really soluble in water, but they swell up into gelatinous masses; under the microscope these appear as character-

¹ On the constitution and chemical properties of lecithins see C. Diakonow, *Hoppe-Seyler's med. chem. Untersuchungen*, 1867, Heft ii. p. 221, and 1868, Heft iii. p. 405; *Centralbl. f. d. med. Wissensch.* 1868, No. 1, 7, 28; A. Strecker, *Ann. Chem. Pharm.* 1868, vol. cxlviii. p. 77; Hundeshagen, *On the synthesis of Lecithins*. Inaug. Diss. Leipzig, 1883; E. Gilson, *Z. f. physiol. Chem.* 1888, vol. xii. p. 585.

istic slimy threads and rosettes, the so-called myelin forms; they are soluble in alcohol, ether, chloroform, benzene and carbon disulphide, and they crystallise only with difficulty; they are soft, waxy masses, and crystals will separate from a concentrated alcoholic solution when it is kept for a long time below 0°C .

Upon the importance of the lecithins in the functions of life we know scarcely anything with certainty. No tissue is so rich in them as the nervous tissue, in which they form the chief constituent of the medullary sheaths of nerves; it is supposed that they form a store of food for the functions of the axis cylinders. That they are indispensable for our nourishment follows from the fact that they form a constant constituent of milk. The milk of the various kinds of mammals is so much the richer in lecithin, the greater the relative weight of the brain of the suckling.

In connection with the fats the waxes must be shortly described; they are not compounds of glycerol, but they are esters of the higher members of the series of fatty acids. The chief constituent of bees' wax is the ester of palmitic acid with myricyl alcohol, $\text{C}_{30}\text{H}_{61}\text{OH}$, together with free cerotic acid, $\text{C}_{26}\text{H}_{52}\text{O}_2$.

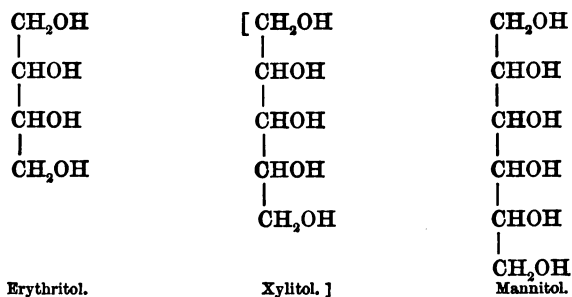
Spermaceti is a compound similar to the waxes, which is found in the skull cavities of various whales, dissolved in the liquid fats, from which it crystallises out on the death of the animal. Its chief constituent is the palmitic acid ester of cetyl alcohol, $\text{C}_{16}\text{H}_{33}\text{OH}$.

Spermaceti and the waxes are used in medicine as additions to external applications, to ointments and plasters, to which they impart the desired consistency.

LECTURE VIII

THE CARBOHYDRATES

THE dihydric glycol (p. 61), and the trihydric glycerol (p. 95), which have been already described, are examples of polyhydric alcohols; the tetrahydric erythritol, [the pentahydric xylitol,] and the hexahydric mannitol are examples of compounds containing four, [five,] and six hydroxyl groups in their molecule respectively:



Erythritol and mannitol are beautifully crystalline compounds with a sweet taste, soluble in water. They contain a normal chain of carbon atoms, as shown by their reduction with hydriodic acid, [which gives respectively normal butane and normal hexane]. Both compounds are found in nature: erythritol either in the free state, or combined as ester with an aromatic acid in many lichens and algæ; and mannitol very widely distributed in the vegetable kingdom. The various mannitols obtained from different plants are not identical, because mannitol contains four asymmetric carbon atoms, and numerous stereoisomeric compounds are therefore conceivable, many of which have been prepared. The mannitol which has been known longest was prepared in 1806 by Joseph Louis Proust (1755–1826); it was found in manna, and was obtained from the dried juice which exudes from the cut bark of the manna ash, *Fraxinus ornus*, a tree cultivated in Sicily. This manna contains from 30 to 60 per

cent. mannitol, which is separated from the other constituents by extracting it with hot water and allowing it to crystallise out. Mannitol is also found in large quantities in certain pileated mushrooms, and it forms 20 per cent. by weight of the dried *Agaricus integer*. It is also found in celery, in olives, in the leaves of syringa, and in many other plants and portions of plants.

If mild oxidising agents be allowed to act upon the polyhydric alcohols, either a primary alcohol group is first oxidised to an aldehyde group, when we obtain a so-called aldose, or a secondary alcohol group is oxidised to a ketone group, when we obtain a so-called ketose.

These first oxidation products of the polyhydric alcohols are of the utmost physiological importance, as to this group of compounds the so-called carbohydrates belong. These substances constitute part of the chief food material of man, and are the principal constituents of all plants, and they form, generally speaking, the greater portion of all the organic matter of our earth.

[The oxidation products of ethane have been already described; glycollic aldehyde—

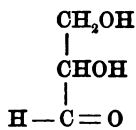


—is the first oxidation product of glycol, and it is an aldose and represents the simplest carbohydrate.]

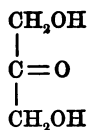
The first products of the oxidation of glycerol, namely, glyceric aldehyde and dioxyacetone (p. 5), are examples respectively of aldoses and ketoses:



Glycerol.



Glyceric aldehyde.



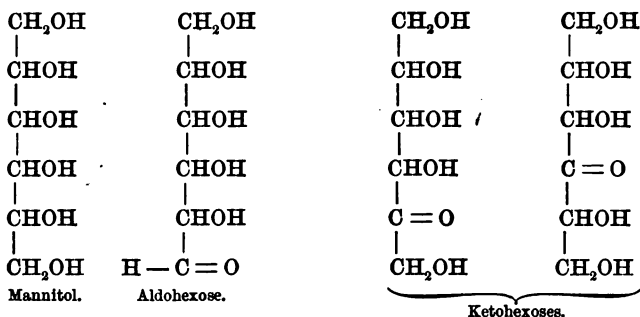
Dioxyacetone.

[In the formation of glyceric aldehyde, a primary alcohol group has been oxidised; in dioxyacetone, the secondary alcohol group; and this represents the first ketose of the series. They are trioses. In just the same way the compound erythritol can yield aldoses and ketoses, i.e. tetroses.

The pentoses, derived from the next member of the series, are of importance physiologically, as they are constituents of nucleic

acid, which is contained in the nuclei of cells, and they are also obtained from gums and wood. The chief examples are arabinose and xylose; they are both aldoses, differing only in the arrangement of the groups attached to their three asymmetric carbon atoms.]

The carbohydrates [proper, i.e. those to which the name was formerly given, and which contain six carbon atoms only in their molecule,] bear the same relationship to mannitol as glyceric aldehyde and dioxyacetone do to glycerol. The first products of oxidation of mannitol are one aldose and two ketoses:

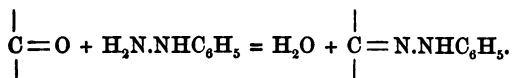


This aldohexose and the two ketohexoses were formerly considered to be the simplest carbohydrates, and they were called sugars. The newer chemical nomenclature designates as sugars not only the hexoses, but also all those aldoses and ketoses which contain less or more than six atoms of carbon in their molecules. The Greek numeral placed before the termination -ose shows the number of carbon atoms in the sugar, and hence the names aldohexose and ketohexose, [pentose etc.].

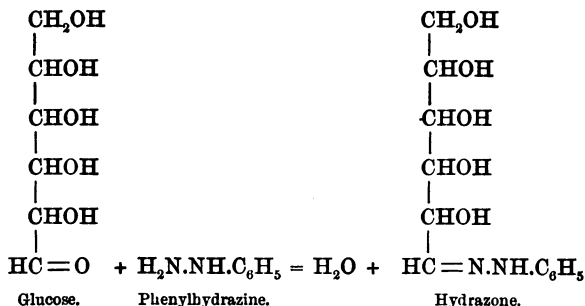
All aldoses and ketoses, i.e. all sugars in the widest sense, have a great tendency to become further oxidised, and upon this the following general reactions depend:—On warming with an alkaline silver solution, a mirror of metallic silver is formed, which is due to the reduction of the silver oxide; on heating with a blue alkaline solution of copper oxide this is reduced and red cuprous oxide is precipitated; on warming with caustic potash oxygen is taken up from the air and the solution turns first yellow, then brown, and finally becomes resinous. [These three reactions are due to the presence of the aldehyde group, or the ketone-alcohol group, in their molecule.¹]

¹ [Acetone does not reduce, as it contains no alcohol group, but monooxyacetone, which contains an alcohol group, does.]

The following reaction, which is given by all aldoses and ketoses, does not depend upon their oxidation, but, on the contrary, on their reduction. When heated with an excess of phenylhydrazine, which is an aromatic compound, in acetic acid solution, they give a yellow crystalline precipitate which is insoluble in water. Phenylhydrazine is an important and sensitive reagent for aldehydes (p. 50) and ketones, and for all compounds which contain an oxygen atom attached to a carbon atom by both its valencies. It removes the oxygen atom from all these compounds, and loses itself the two hydrogen atoms attached to the nitrogen atom; water is formed and the nitrogen atom attaches itself to the carbon atom by these two valencies, in the position in which the oxygen atom was contained in the ketone or aldehyde:

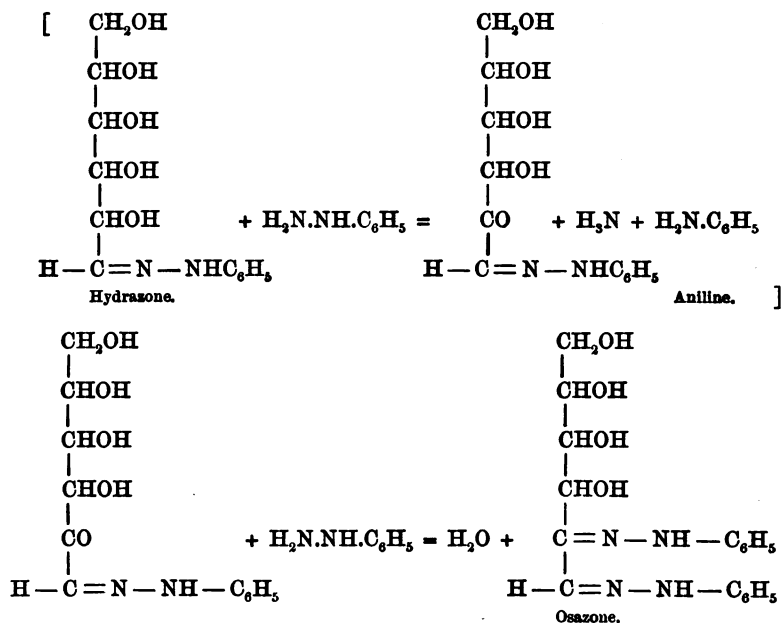


As the sugars contain either a ketone or an aldehyde group, these compounds consequently also react with phenylhydrazine in a similar way:



The compound which is formed is called a hydrazone, and the hydrazones of the various sugars are soluble in water. If an excess of phenylhydrazine act upon the sugar in acetic acid solution, a second molecule of phenylhydrazine is taken up, and an insoluble compound, an *osazone*, separates out in the form of yellow crystals. A second molecule of phenylhydrazine acts upon one of the secondary alcohol groups, upon that CHOH group [next to the aldehyde group, which is oxidised to a ketone group], and the two atoms of hydrogen, which separate, reduce the phenylhydrazine to aniline and ammonia, whilst a third molecule of phenylhydrazine combines with the ketone group

giving the osazone. The process of the formation of an osazone from the hydrazone occurs as follows :



This formation of osazones is of the greatest importance in the chemistry of the sugars. Emil Fischer's¹ brilliant success in the study of the sugars is largely due to his discovery of this reaction. The sugars are hygroscopic and very soluble in water, from which they are often very difficult to crystallise when the solutions contain other substances, but by the help of the formation of the osazones their isolation becomes easy. By the preparation of the osazones Fischer definitely showed that the solution of sugar synthetically prepared by Butlerow in 1861 really contained sugar² (p. 3). The osazones of the various monosaccharides have different melting points, and different solubilities ; it can therefore sometimes be decided, by determining the melting point, which osazone of the thirty-two possible hexoses has been prepared. Further, the preparation of the osazone is one of the most reliable qualitative reactions for determining the presence of sugar in the urine.

The most important, practically and physiologically, of all aldoses

¹ E. Fischer, *Ber. d. d. chem. Gesellsch.* 1884, vol. xvii. p. 579.

² E. Fischer, *ibid.* 1888, vol. xxi. p. 989 ; 1890, vol. xxiii. p. 2125.

and ketoses are those containing six atoms of carbon, the hexoses, which belong to the so-called group of carbohydrates. The hexoses, however, are not the only carbohydrates, for to this group belong numerous compounds which can be regarded as anhydrides, or products of polymerisation of the simple hexoses or monosaccharides. The best-known representatives of the monosaccharides are grape sugar [and fruit sugar]. When two monosaccharides, whose empirical formula is $C_6H_{12}O_6$, combine together, with loss of water, a so-called disaccharide with the empirical formula $C_{12}H_{22}O_{11}$ is obtained; the best-known examples of the disaccharides are cane sugar, milk sugar, and malt sugar (maltose). When more than two molecules of a monosaccharide combine together, with the loss of a molecule of water for every molecule of monosaccharide, we obtain the polysaccharides, of which the best known representatives are starch, cellulose, and glycogen. These have the empirical formula $(C_6H_{10}O_5)_x$. All these carbohydrates in their empirical composition consist of carbon, hydrogen and oxygen in the proportion in which these two latter elements compose water, and hence the name carbohydrate.

[The following list tabulates the most important carbohydrates :¹

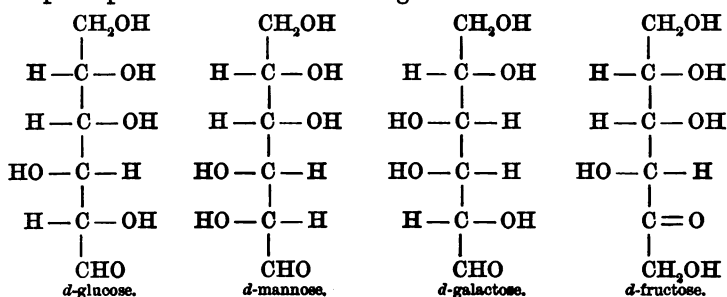
Monosaccharides.	Disaccharides.	Polysaccharides.
A. <i>Trioses</i> .	Cane sugar or saccharose.	Starch.
Glyceric aldehyde.	Milk sugar or lactose.	Glycogen.
Dioxyacetone.	Malt sugar or maltose.	Cellulose.
B. <i>Pentoses</i> .		Inulin.
Arabinose.		Dextrin.
Xylose.	Trisaccharides.	(Gums.)
C. <i>Hexoses</i> .	Raffinose.	
Grape sugar or glucose.		
Fruit sugar or fructose.		
Galactose.		
Mannose.		

We will now study the individual carbohydrates more closely. As we have seen, the hexoses have three chemical isomers, as well as numerous stereoisomers. The aldohexoses have four asymmetric carbon atoms, and for each of these atoms two isomers are possible. Each of these two isomers, on account of the second asymmetric carbon atom, can again form two isomers, and so on, and simple calculation shows that $2^4=16$ stereoisomeric aldohexoses are possible. Each of the two-ketohexoses contains three asymmetric carbon

¹ [The terms monosaccharose, disaccharose, etc., are now more frequently used than monosaccharide, etc., and they are sometimes abbreviated to monose, diose, polyose. This is misleading, as diose, triose, pentose indicate carbohydrates with 2, 3, 5 atoms of carbon. It is better, therefore, in this place to retain the terminal -ose for the simple carbohydrates, and, saccharide for the more complex.]

atoms, and, in consequence, each of them can form $2^3=8$ isomers, that is, together sixteen isomers. Altogether, therefore, thirty-two stereoisomeric monosaccharides are conceivable, and the majority of these thirty-two sugars have been prepared, and their structure definitely determined;¹ many of them occur in nature.

[The stereoisomerism, or arrangement of the hydrogen atoms and hydroxyl groups attached to the four asymmetric carbon atoms, in the four principal hexoses is the following :



Only these four hexoses are fermented by yeast, and they show the close relationship between the structure of a compound and its decomposition by ferments, which are specific in their action.]

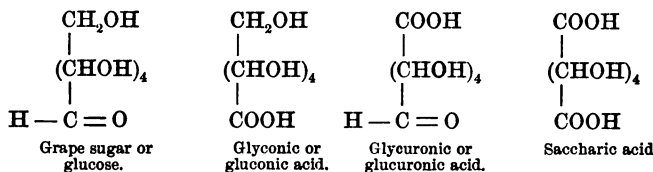
Physiologically, the most important sugar is grape sugar or glucose, glycose, *d*-glucose, or dextrose. It is found in grapes and in many sweet fruits, and it is also formed by the hydrolytic decomposition of the most diverse carbohydrates, e.g. from starch and cellulose. From starch, which is the most important carbohydrate of our food, and the chief constituent of cereals, leguminous plants, and potatoes, grape sugar is formed by hydrolytic ferments in our alimentary tract and in our tissues. In diabetes, where the capability of oxidising the carbohydrates in the tissues is lost, all the carbohydrates taken in the food appear in the urine as grape sugar.

Grape sugar is very easily soluble in water, also in hot alcohol; from its aqueous solution it crystallises with a molecule of water of crystallisation, but from its alcoholic solution without water of crystallisation. The solution rotates the plane of polarised light to the right [its specific rotation² being $[\alpha]_D^{20} = +52\cdot5$], and upon its optical behaviour depends a method for its quantitative estimation, which is especially used in the analysis of diabetic urine.

¹ A summary of the latest results of the investigation of the structure of sugars is given in Emil Fischer's lecture, 'Syntheses in the Sugar Group,' *Ber. d. d. chem. Gesellsch.* 1890, vol. xxiii. p. 2114.

² [The specific rotation is the deviation of the plane of polarised light produced by a layer of a 100 per cent. solution 1 decimetre in thickness.]

Grape sugar is an aldose; on oxidation it yields three acids: the monobasic gluconic, and glycuronic acids, and the dibasic saccharic acid:



Of these acids, glycuronic acid is of physiological interest, as it occurs as a product of the commencement of oxidation of grape sugar in the body. When the oxidation of sugar has once commenced in our tissues, it continues rapidly and without cessation to the end-products, carbonic acid and water. Only occasionally, therefore, is glycuronic acid met with, and especially when substances combustible with difficulty, such as chlorinated fatty compounds [e.g. chloral], or aromatic compounds [e.g. camphor], are allowed to enter the organism; by their combination with glycuronic acid this is prevented from being oxidised, and the product of their combination passes into the urine; glycuronic acid can be obtained from them by hydrolytic decomposition.¹ The synthesis of glycuronic acid has been accomplished by E. Fischer² [and according to him the origin of the glycuronic acid is as follows:—The chloral or camphor being poisons are removed from the body by combination with glucose, and this occurs with the aldehyde group; the primary alcohol group of the glucose is then oxidised to the carboxyl group, and in this form, as a glycuronic acid compound, it is excreted in the urine. The organism protects itself against the poison in this way].

Among the decompositions of grape sugar, those fermentations brought about by moulds and bacteria are of particular physiological interest. The lactic acid fermentation has been described (p. 77); but the butyric acid fermentation (p. 82), and also the alcoholic fermentation, require further description.

Butyric acid fermentation is brought about by the ferments produced by certain bacteria,³ and already more than twenty varieties of bacteria have been described which can produce this change.

¹ M. Jaffe, *Z. f. physiol. Chem.* 1878, vol. ii. p. 47; O. Schmeideberg and H. Meyer, *ibid.* 1879, vol. iii. p. 422; v. Mering, *ibid.* 1882, vol. vi. p. 480.

² E. Fischer and O. Piloty, *Ber. d. d. chem. Gesellsch.* 1891, vol. xxiv. p. 521.

³ Among the latest investigations on butyric acid fermentation, see A. Schatzenfroth and R. Grassberger, *Arch. f. Hygiene*, 1900, vol. xxxvii. p. 54.

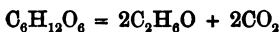
The decomposition produced by some varieties closely follows the equation :



Equal volumes of carbonic acid and hydrogen are evolved. Other species of bacteria produce, together with these three decomposition products, lactic acid, butyl alcohol, acetic acid, propionic acid, caproic acid, etc. Some authors suppose that the butyric acid fermentation always consists, firstly, in a decomposition of the sugar molecule into two molecules of lactic acid, as certain bacteria actually convert calcium lactate into butyric acid;¹ in this case a synthetical process must be assumed.

As the butyric acid bacteria are anaerobic, certain species of them grow in the intestine of man, and the contents of the intestine always contain butyric acid. If the contents of the intestine be placed in a suitable vessel over mercury, the evolution of carbonic acid and hydrogen can be observed. The occurrence of nascent hydrogen accounts for the numerous energetic reduction processes which take place in the intestine, and it is important to know that hydrogen is a very troublesome intestinal gas on account of its very low coefficient of absorption—fifty times smaller than that of carbonic acid—and consequently it is not, like carbonic acid, quickly absorbed by the walls of the intestine, and expired through the lungs.² It should therefore be the aim of the physician to take care that patients who suffer from chronic intestinal troubles, and are disposed to flatulency, should only take easily absorbable carbohydrates, which will not reach the lower portions of the intestine, where the decrease in the acid reaction is conducive to butyric acid fermentation. The carbohydrates, which are taken in with acid fruits, do not easily undergo butyric acid fermentation, because the free acids, and the aromatic constituents in them, prevent the growth of the butyric acid bacteria, but the carbohydrates of cereals and leguminous plants easily undergo it. In many people butyric acid fermentation is encouraged by taking milk.³

The alcoholic fermentation of sugar takes place in the organisms of a whole series of various yeasts, moulds, and bacteria. The process of decomposition never exactly follows the equation—



¹ V. Paschutin, *Pflüger's Arch.* 1873, vol. viii. p. 352; Alb. Fitz, *Ber. d. d. chem. Gesellsch.* 1884, vol. xvii. p. 1188.

² Cf. Bunge, *Textbook of Human Physiology*, 2nd edition, 1905, vol. ii. p. 419 (Vogel, Leipzig).

³ E. Ruge, *Sitzungsber. d. k. Akad. d. W. zu Wien*, 1862, vol. xlv. p. 739.

—since bye-products are always formed in small quantities, the greater part of which consist of glycerol and succinic acid (p. 84): the higher alcohols (p. 67), propyl, butyl, and amyl alcohols, which constitute fusel oil, only form a small portion of the bye-products [and they probably arise from the hydrolytic decomposition products of proteins¹].

The heat of combustion of ethyl alcohol is only nine-tenths of that of the sugar from which it is formed, according to the above equation; one-tenth of the chemical energy contained in the sugar is therefore converted into vital energy during the process of fermentation by the yeast organism, this energy being evidently utilised in the performance of its functions; probably, however, only a portion of it is actually needed for this purpose. The evolution of such large amounts of alcohol has evidently another significance in the life of the yeast; it serves as a weapon against its competitors in the fight for existence, i.e. against other micro-organisms, for when fresh grape-must commences to ferment it teems with micro-organisms, moulds, and bacteria of all kinds. According to the rate at which the alcohol content rises, so do the other species of micro-organisms die out one after another, whilst the yeast, multiplying very rapidly, outlives all the others and remains victor in the fight. It withstands the poisonous action of its own excreta better than most of its competitors. Direct experiments have shown that yeast can withstand as much as 10–18 per cent. of alcohol in its nutrient medium, whilst most of its rival micro-organisms are killed, or at least inhibited in their growth, when the amount of alcohol in their nutrient material reaches 4–10 per cent.

The life-process of the yeast cell is not essential to the production of the alcoholic fermentation of sugar. It has been shown by Edward Buchner² that the expressed juice of yeast cells, [i.e. quite free from any living cells], possesses the power of decomposing sugar into alcohol and carbonic acid; he was also able to obtain an aqueous glycerine extract of the dried and crushed, [and therefore dead,] yeast, which could induce the alcoholic fermentation of sugar.

In the technical utilisation of alcoholic fermentation for the preparation of alcoholic liquors and of pure alcohol, it would be too expensive to start from grape sugar, and therefore either cereals rich in starch, or potatoes, or berries and fruits, rich in grape sugar, are

¹ [F. Ehrlich, *Ber. d. d. chem. Gesellsch.* 1906, vol. xxxix. p. 4072; 1907, vol. xl. p. 1027.]

² Ed. Buchner, *ibid.* 1897, vol. xxx. p. 117, and 1900, vol. xxxiii. p. 3307.

employed. The starch is converted into the simpler carbohydrates, dextrin and maltose, by the hydrolytic action of certain ferments, and the solution of these carbohydrates is then fermented by the yeast.

~ Yeast contains ferments which convert dextrin and maltose into grape sugar, and also the ferment which decomposes grape sugar into alcohol and carbonic acid, [but it does not contain the ferment called diastase, or amylase, which is present in the cereal, and which converts the starch into dextrin and maltose.

There are thus three stages in the decomposition of the starch :

1. The conversion of the starch into dextrin and maltose by the diastase in the cereal.
2. The conversion of the dextrin and maltose into glucose by the ferment maltase in the yeast.
3. The conversion of glucose into alcohol and carbonic acid by the ferment zymase in the yeast.

All polysaccharides are first converted into monosaccharides by special ferments before they can undergo alcoholic fermentation. Cane sugar, the other polysaccharide which is often employed, is first hydrolysed into glucose and fructose by the ferment invertase, and the two monosaccharides are then converted into alcohol and carbonic acid.]

In the preparation of alcoholic liquors from grapes and fruits the process is simpler, as the yeast is already present on the surface of the berries and fruits, and, after they are pressed out, it at once sets the pre-formed grape sugar into fermentation. Pure alcohol is prepared by distillation after the fermentation process is over.

Upon the alcoholic fermentation of grape sugar depends one of the most reliable methods for the qualitative and quantitative determination of sugar in urine.

[Fructose and galactose, the other common monosaccharides, are generally obtained from the disaccharides cane sugar and milk sugar (see below).

Arabinose and xylose, the two pentoses, are obtained by boiling gum arabic and straw, in which they are contained as polysaccharides, with dilute acids.]

We will now consider the more complicated carbohydrates, the disaccharides, the best known of which are cane sugar, milk sugar, and malt sugar, or maltose.

Cane sugar is very widely distributed in the vegetable kingdom, being especially abundant in the sugar-cane and the beet-root, from which it is obtained on the large scale. It forms beautiful crystals,

very easily soluble in water, with a much sweeter taste than grape sugar. It rotates the plane of polarisation to the right [its specific rotation being $[\alpha]_D = +66.5$]; on hydrolysis it is converted into two molecules of simple hexoses, or monosaccharides :



These two hexose molecules are not identical; they themselves, and their compounds, possess different solubilities and therefore they can be separated. One of these two hexoses is identical with grape sugar and the other, as shown by its oxidation and decomposition products, is a ketose, namely, fruit sugar or fructose. This is also found very widely distributed in the free state in the vegetable kingdom, and forms, together with grape sugar and cane sugar, a constituent of honey. Fructose rotates the plane of polarisation to the left, and to a greater degree than grape sugar does to the right, [its specific rotation¹ being $[\alpha]_D = -92^\circ$]; therefore, the mixture of grape sugar and fruit sugar in equivalent proportions, as obtained by the hydrolysis of cane sugar, is lævo-rotatory. When a dextro-rotatory cane-sugar solution becomes by hydrolysis lævo-rotatory the sugar solution is said to be inverted, i.e. its rotatory power has been reversed. On this account a ferment, which exists in yeast and also very widely in animal and plant tissues, and which splits this disaccharide into the two monosaccharides, is called invertin, or invertase.

Milk sugar, or lactose, the representative carbohydrate in the food of suckling mammals, is also a disaccharide; by hydrolysis [by acids or by the ferment lactase] it is decomposed into glucose and galactose. Galactose is a dextro-rotatory aldose, [specific rotation $[\alpha]_D = +82^\circ$,] which does not occur in the free state in the animal body; but it is found in combination in cerebrin,² one of the constituents of nervous tissue (cf. Lecture 9).

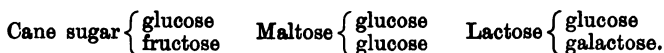
Glucose is much less soluble in water than cane sugar, and p. 80. Its less sweet taste may depend on this. It can be easily crystallised, and forms with a molecule of water of crystallisation large, hard, rhombic prisms. It is insoluble in alcohol, and thus differs from other sugars.

[Maltose, $[\alpha]_D = +140^\circ$, is, as above described, obtained by the hydrolysis of starch by the ferment diastase. It crystallises in fine needles; and it is converted by hydrolysis, by acids, or by the ferment maltase, into two molecules of glucose.

¹ [Tollens, *Ber. d. d. chem. Gesellsch.* 1891, vol. xxiv. p. 2000.]

² Thierfelder, *Z. f. physiol. Chem.* 1890, vol. xiv. p. 209.

The three disaccharides are therefore constituted as follows :



The trisaccharide raffinose $\text{C}_{16}\text{H}_{32}\text{O}_{16}$ is obtained from beet-sugar residues. It is also dextro-rotatory $[\alpha]_D = +104.4^\circ$. It is made up of one molecule of each of the monosaccharides, glucose, fructose, and galactose, into which it is decomposed by hydrolysis by acids. The enzyme invertase splits off fructose, leaving a disaccharide composed of glucose and galactose, which is not identical with lactose, but is an isomer, and the enzyme emulsin splits off galactose, leaving the disaccharide cane sugar.^{1]}

Of the large number of polysaccharides found in the vegetable and animal kingdoms starch is the most important, as it is the chief carbohydrate of our food. It makes up 60 per cent. of the dry substance of leguminous plants, about 70 per cent. of the dry substance of grain, and up to 80 per cent. of the dry substance of potatoes.

The starch grains which occur in various plants, and in various parts of plants, have very different forms and sizes when examined under the microscope; they consist of concentric layers, with a nucleus, placed sometimes in the centre, and sometimes excentrically. Starch grains are found, especially abundantly as reserve material, in the roots, tubers, and seeds of many plants; for example, in the tubers of potatoes, and in the seeds of grain, and in leguminous plants.

The starch grains are not changed at all by cold water, and therefore they can be isolated by mechanically crushing the plant material, passing this through a sieve, decanting, and washing with cold water. This process is carried out in works on a large scale, and pure starch meal, called shortly starch or amyllum, is obtained as a white powder.

In hot water starch swells up to a paste, and this, when mixed with much water, forms an apparent solution, which is opaque; it is never really in solution, as it does not diffuse through dialoidal membranes, and it belongs, therefore, to the so-called colloids.

By dilute iodine solution starch is coloured deep blue; not only is iodine a very sensitive reagent for starch, but starch paste is a very delicate reagent for iodine, and for all substances which liberate iodine from its compounds; starch paste is therefore much used in qualitative analysis, and in quantitative methods of titration.

When starch is boiled with dilute acids, the starch molecule,

¹ [C. Neuberg, *Biochem. Z.* 1907, vol. iii. p. 519.]

whose size is unknown, is completely broken down into simple glucose molecules :



Its hydrolysis by the ferments, which are contained in growing seedlings and in the secretions of the salivary glands and the pancreas, is not such a simple process. The starch is broken down into dextrin—a colloidal carbohydrate—and maltose—a disaccharide—which is decomposed, on hydrolysis by acids, into two molecules of grape sugar. Dextrin is by no means a simple body ; several dextrans can be distinguished, one of which is coloured red by iodine, whilst the other is not. It is still undecided whether the two dextrans arise at the same time, or one after the other, according as more and more maltose molecules are split off from the starch molecule. Another colloidal carbohydrate occurs as an intermediate stage between starch and the dextrans ; it is coloured blue by iodine, and is therefore called 'soluble starch.' Finally, it has been shown that the original starch grain is not a chemical individual, and that the concentric layers consist of different carbohydrates in various proportions.

Glycogen is a carbohydrate very similar to starch ; it is deposited in the tissues of nearly all animals as a reserve material, where it plays a similar part to that of starch in plants. Glycogen and starch are those forms in which the excess of carbohydrate is stored up in the tissues, whether as the reserve material for the later development of the embryo, as e.g. the starch in the tubers and seeds, or as the source of energy for functions to be developed later, as e.g. the glycogen in the liver and in the muscles of man.

Glycogen and starch have another property in common : both are decomposed into a number of glucose molecules on boiling with acids, or into dextrans and maltose by the action of ferments. They differ from one another in that the former dissolves in cold water, giving an opalescent solution, which is not coloured blue, but red-brown, by iodine solution.

In the roots and tubers of many plants belonging to the family of the Compositæ—*Inula*, *Dahlia*, *Helianthus*, *Cichorium*, *Taraxacum*—a carbohydrate is found which plays in them the same part as starch does in the potato tubers, but which differs from starch as it is not split up by hydrolysis into glucose molecules, but into lævo-rotatory fructose molecules. This carbohydrate is called Inulin, from its occurrence in the tubers of *Inula Helenium*, and is of therapeutical interest. Many diabetic patients who have lost the capability of destroying dextro-rotatory grape sugar can still split up and oxidise

— the lævo-rotatory fruit sugar. It was therefore hoped that the inulin-containing tubers would provide them with a substitute for food materials, rich in starch and grape sugar, but its use is inadvisable, because patients soon lose their power of tolerating fruit sugar.

Cellulose is probably a still more complex carbohydrate than starch, and it forms the chief constituent of the cell membranes in plant tissues; it is characterised by its insolubility, and can therefore be obtained from all plant tissues, after they have been successively extracted with the ordinary solvents, i.e. by boiling with dilute alkalis and acids, alcohol, and ether; what remains behind is moderately pure cellulose, which retains the structure of the original tissue. Linen, cotton wool, and filter-paper are nearly pure cellulose. When these substances are treated first with concentrated sulphuric acid at the ordinary temperature, and then boiled with dilute sulphuric acid, cellulose is broken down into a number of grape-sugar molecules. In the treatment with the concentrated sulphuric acid, cellulose passes into a colloidal modification, which is coloured blue by iodine and is called 'amyloid';¹ upon which a reaction for detecting cellulose depends. Technical use is made of this conversion of cellulose into a colloidal substance in the preparation of parchment paper. When ungelatinised paper is acted upon for a short time by concentrated sulphuric acid and is then washed with water, vegetable parchment is obtained; the paper now no longer consists of a felt composed of separate threads of cellulose, nor does it contain pores through which filtration is possible, but it consists of a continuous colloidal mass. Filtration through such parchment paper is not possible, but diffusion is, i.e. when different substances are present in the same solution, all these do not pass through it in proportional quantities, but some pass through more quickly than others.

Cellulose dissolves entirely without decomposition in ammoniacal copper oxide solution, from which it is again precipitated by acids and salts as an amorphous powder.

When cellulose is treated with a mixture of nitric and sulphuric acids, nitric acid esters are formed, the hydroxyl groups of the cellulose combining with the nitric acid, with elimination of water, in the same way as in the formation of nitroglycerine (p. 96); these nitric acid esters of cellulose are also explosive compounds. According to the concentration of the acids and the duration of their

¹ This must not be confounded with the pathological amyloid degeneration of tissues, which gives a similar iodine reaction; nothing more is known about this substance, except that it contains nitrogen. See N. P. Krawkow, *Arch. f. exper. Pathol. u. Pharmacol.* 1898, vol. xl. p. 195, where the earlier literature is cited.

action upon it, one to three NO_2 radicals to every six carbon atoms enter the molecule of cellulose. If cotton wool be used in the preparation, and the highest nitrate containing three NO_2 groups to every six atoms of carbon be formed, guncotton is obtained, which still retains the appearance of the cotton wool. The lower nitrates with one and two NO_2 groups, when dissolved in a mixture of alcohol and ether, constitute collodion, which is used in surgery and photography; in histology collodion is used for embedding microscopical preparations, the very pure collodion, which is specially prepared for this purpose, being called celloidin. Celluloid is a solution of slightly nitrated cotton wool in molten camphor; it is used as an imitation for vulcanite and horn, but has the great disadvantage of being very easily inflammable.

Cellulose also occurs in the animal kingdom. Carl Schmidt¹ (1822-1894) in 1844 made the discovery that the tunica of the *Ascidia* contain cellulose as their chief constituent. This statement has been repeatedly confirmed by later investigations, and recently by the accurate researches of E. Winterstein.²

¹ Carl Schmidt, *The Comparative Physiology of the Lower Animals* (Vieweg & Son: Brunswick, 1845), pp. 1-65. [O. v. Fürth, *Comparative Chemical Physiology of the Lower Animals* (Fischer: Jena, 1903), p. 467.]

² E. Winterstein, *Z. f. physiol. Chem.* 1893, vol. xviii. p. 43. Here the other literature upon animal cellulose is summarised.

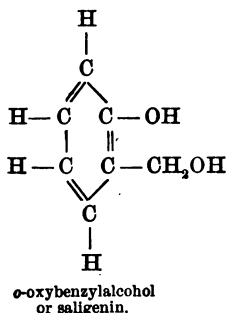
LECTURE IX

THE GLUCOSIDES

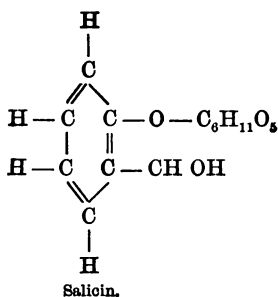
MENTION has been frequently made of the glucosides, bodies which on hydrolysis are broken down into a monosaccharide, and one or more other compounds. The hydrolysis, i.e. decomposition with absorption of water, is produced both by ferments and by boiling with acids. The monosaccharide is, in most cases, grape sugar, but certain glucosides yield another variety of sugar. The substances combined with the sugar belong to the most varied classes of organic compounds. The glucosides are very widely distributed in the vegetable kingdom, and as our knowledge of plant chemistry increases, new ones are continually being discovered; more than a hundred different glucosides have already been investigated and described, but only a few of this large number are of interest medically. The glucosides are generally divided into those free from nitrogen, and those containing nitrogen.

A pharmacologically interesting glucoside is found in the bark of the willow; infusions of willow bark were used in olden times as remedies; at the time of Napoleon's march over the continent of Europe quinine bark was very expensive, and willow bark, which has the same bitter taste as quinine bark, was used in its place. It was found that an extract of willow bark had a good effect upon the course of many feverish illnesses, though it had not the specific action of quinine in intermittent fever; later, the active constituent was isolated from aqueous extracts of willow bark. If the bark be extracted with boiling water, and the concentrated extract digested with lead oxide and filtered, and the dissolved lead then removed with hydrogen sulphide and filtered off, rhombic leaflets and prisms, which have an intensely bitter taste, separate out from the concentrated filtrate. This compound was called salicin, after the botanical name of the willow, *Salix*. Exact chemical investigation showed that by ferments, or by boiling with acids, salicin was decomposed with absorption of water into glucose and a crystalline nitrogen-

free compound, saligenin, the elementary analysis of which gave it the empirical formula $C_7H_8O_2$.¹ More exact study of the structure of saligenin showed that it was ortho-oxybenzylalcohol (p. 176), a compound which can also be obtained by synthesis :



Salicin, the compound of saligenin with glucose, has the composition :²



The remedial action of willow bark was thus explained : Saligenin is a primary alcohol, which on oxidation must yield salicylic acid (p. 181), and consequently salicin must possess all the pharmacological actions known to be possessed by salicylic acid.

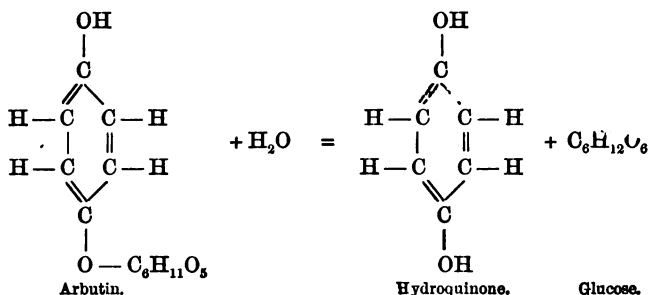
Salicin is decomposed into sugar and saligenin by the ferments of the alimentary secretions and of the tissues, and the saligenin is then oxidised to salicylic acid. Saligenin has the advantage over salicylic acid and its salts in that it does not irritate the mucous membrane of the stomach, and hence does not so easily produce digestive dis-

¹ R. Piria, *Liebig's Ann. d. Chem.* 1845, vol. lvi, p. 35.

² [The constitution of the various aromatic constituents combined with glucose in the glucosides will be easily understood after the aromatic compounds have been studied. It is better to discuss the glucosides after the carbohydrates, as many have been synthetically prepared (see later) which do not contain aromatic constituents, and are of importance on account of the constitution of glucose.]

turbances. The pharmacologist Marmé¹ has, however, warned us against the use of salicin, as saligenin is not completely oxidised to salicylic acid in the body, since a portion is oxidised only to salicylic aldehyde, which is poisonous.

Like the decoction of willow bark, a decoction of the leaves of bear-berries, *Arbutus uva ursi*, one of the Ericaceæ growing wild in Central and North Europe, has been greatly prized as a remedy for centuries; it has been used with success in the treatment of cystitis. Its therapeutic power was only explained when the preparation of the crystalline glucoside arbutin from the aqueous extract of the leaves of the bear-berry had been accomplished, and it had been shown that this glucoside broke down into glucose and hydroquinone (p. 172):



Hydroquinone is an energetic antiseptic; a small quantity of it added to urine outside the body prevents its alkaline fermentation (p. 151), which occurs in cystitis in the urinary passages.

[Phloridzin is another glucoside, which breaks down on hydrolysis into glucose and phloretin. When taken internally it produces diabetes.]

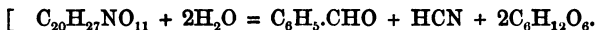
The active constituents of digitalis belong partly to the nitrogen-free glucosides, but as yet all these have not been separated in a satisfactory manner, and the chemical composition of the various components of the active glucoside still remain uninvestigated.²

Amygdalin is an example of the glucosides which contain nitrogen; it is found in large quantities in the bitter almond, in small quantities in the sweet almond, and also in the kernels of apples,

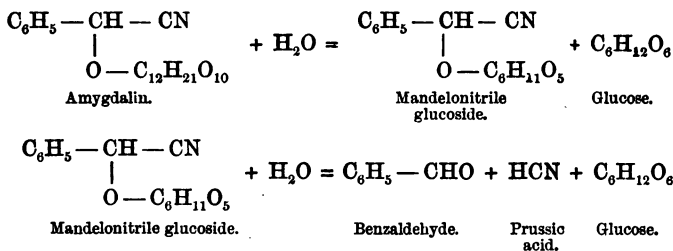
¹ W. Marmé, *Nachrichten von d. k. Gesellsch. d. W. Göttingen*, 1878, pp. 229, 372. Cf. also A. Buchwald, *On the Action and Therapeutic Value of Salicin*, Dissert. Breslau, 1878.

² O. Schmiedeberg, *Arch. f. exper. Pathol. u. Pharmacol.* 1874, vol. iii. p. 16; 1883, vol. xvi. p. 149. H. Kiliani, *Ber. d. d. chem. Gesellsch.* 1891, vol. xxiv. p. 339, and 1898, vol. xxxi. p. 2454; *Arch. d. Pharmacie*, 1892, vol. ccxxx. p. 250, and 1893, vol. ccxxxi. p. 448. In these papers all the literature on digitalis is collected together.

pears, apricots, peaches, plums, cherries, and other fruits belonging to the family of the Rosaceæ, especially in the bark of the bird-cherry, *Prunus padus*, and in the leaves of the cherry-laurel tree, *Prunus laurocerasus*. Amygdalin can be extracted with alcohol from these portions of the plants, and made to crystallise; the crystals are easily soluble in water, and are decomposed on hydrolysis into grape sugar, benzaldehyde (p. 177), and prussic acid (p. 132), with the absorption of two molecules of water :



From this equation it is seen that two molecules of glucose are obtained from amygdalin. These two molecules of glucose are combined together in the form of a disaccharide, and amygdalin is therefore not a simple glucoside, like salicin and arbutin. It has been supposed that the two glucose molecules were combined together in the form of maltose, and that amygdalin was therefore a maltoside. Recent work¹ does not confirm this view, and the mode of combination of the two glucose molecules remains undecided. By the action of dilute acid, or by the yeast enzyme amygdalase, only one molecule of glucose is split off, and another glucoside, mandelonitrile glucoside, is obtained, which can then be hydrolysed to glucose, benzaldehyde and prussic acid :



The hydrolysis of all natural glucosides is effected by boiling with dilute acids, or by the ferment emulsin, which is contained in almonds whether bitter or sweet, together with amygdalin. Like all the ferments occurring in the animal and vegetable kingdoms, it probably belongs to the group of the proteins. (Cf. Lecture 17.)

If we enquire what is the significance of amygdalin in the development and life of the plants in which it is found, the question may be answered by the following facts : The constituents which are liberated

¹ [Caldwell and Courtauld, *Jour. Chem. Soc.* 1907, vol. xci. pp. 666, 671; *Proc. Roy. Soc.* 1907, vol. lxxix. B, p. 350. H. E. Armstrong and E. F. Armstrong, *Proc. Roy. Soc.* 1907, vol. lxxix. B, p. 360.]

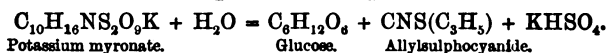
with the sugar on hydrolysis, serve as a weapon against the attacks of micro-organisms, moulds, and bacteria; benzaldehyde, like most aromatic compounds, is an antiseptic and therefore bactericidal, and prussic acid, as we have seen (p. 132) is apparently a general protoplasmic poison which inhibits the life of every cell. In almonds, and generally in the seeds of plants, the most important food-stuffs—proteins, fats, carbohydrates—are stored up as material for the later growth of the seedling, and these reserve stores form the most favourable media for the growth of all kinds of micro-organisms. As soon as moulds or bacteria penetrate the seed, the amygdalin comes into contact with the emulsin, which was previously separated from it by a histological arrangement, and the poisons are set free and kill all the micro-organisms. Amygdalin plays the same important rôle in the bark of the bird-cherry; whenever the integument of the plant is wounded, an antiseptic treatment of the wound is immediately ensured. It appears as if every plant contains a glucoside in its bark which acts as a defence against the invasion of micro-organisms, and it is very remarkable that the constituents of glucosides are always bacterial poisons, the majority of which are aromatic compounds. The saligenin in the wounded bark of the willow has the same function as salicylic acid in the treatment of wounds in man. In the bark of the conifers the balsams (p. 208) assume the functions of the glucosides; at each incision in the bark, this liquid, composed of bacterial poisons, flows over the wounded spot. In olden times surgeons poured balsam into wounds, and they learnt this method of treating wounds antiseptically from the pine trees.

In the higher animals it is not glucosides, or aromatic compounds, which defend them against the invasion of bacteria, but probably albuminous substances from the group of the toxalbumins (cf. Lecture 17), whose poisonous intensity greatly exceeds that of all the aromatic compounds, and even of prussic acid. But there are some animals which appear to protect themselves against micro-organisms by glucosides. In certain hothouses in Holland a large number of millipedes are found, which have come in with foreign plants, and which are recognised by the distinct smell of bitter almonds diffused by them. According to certain chemical investigations,¹ these millipedes contain a substance which, under the action of a ferment present in the animals, breaks down into prussic acid and another volatile body, probably benzaldehyde.

In the seeds of the black mustard potassium myronate, a glu-

¹ C. Guldensteeden-Egeling, *Pflüger's Arch.* 1882, vol. xxviii. p. 576.

coside containing both nitrogen and sulphur, is found, together with myrosin, a ferment like emulsin, by whose action the potassium myronate is split up into glucose, mustard oil (allylsulphocyanide, pp. 98 and 144), and acid potassium sulphate :



The acid potassium sulphate in aqueous solution partially breaks down into neutral potassium sulphate and free sulphuric acid :¹



Here, together with the mustard oil, a well-known bacterial poison, another antiseptic occurs, by which the mustard seed protects itself against its enemies, namely the strongest mineral acid ; mineral acids belong to those bodies which kill all bacteria.

This curious fact that the strongest mineral acid is liberated by simple ferment action from potassium myronate, a perfectly neutral compound, is worthy of notice in relation to certain questions in animal physiology. At the commencement of the alimentary canal of many animals, and also in the stomach of man, a secretion is poured out which contains free sulphuric or hydrochloric acid. This secretion has the same function as the sulphuric acid which is liberated from the mustard seeds, namely that of killing bacteria, but as yet it has never been explained how free mineral acid is separated from the alkaline blood, and the study of the hydrolysis of potassium myronate may give us a possible clue to solving this question.²

Finally, a glucoside has been discovered in the organism of mammals, in their nervous system. An amorphous nitrogenous substance, cerebrin, can be isolated from the brain, which, when boiled with dilute acids, decomposes into galactose³ (p. 116) ; the other constituent, combined with the galactose in the glucoside, has not yet been completely investigated.

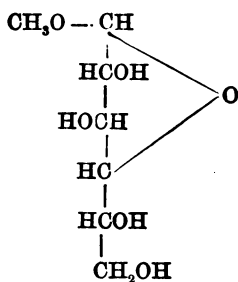
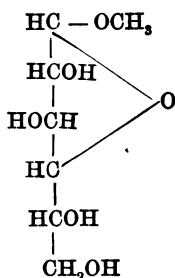
[A large number of artificial glucosides are also known ; not only are they derived from glucose, but also from galactose, mannose, maltose, etc., and they are prepared by the action of hydrochloric acid upon the sugar and alcohol. Two compounds are generally obtained, and they are termed α - and β -glucosides. The methyl-glucosides, from methyl alcohol and glucose, are of particular importance as they

¹ Thomas Graham (1805-1869), *Liebig's Ann. d. Chem.* 1851, vol. lxxvii. p. 80.

² Cf. G. v. Bunge, *Textbook of Human Physiology*, 1905, 2nd edition, vol. ii. Lect. 12 (Vogel, Leipzig).

³ H. Thierfelder, *Z. f. physiol. Chem.* 1889, vol. xiv. p. 209. Herein the earlier literature on cerebrin is cited.

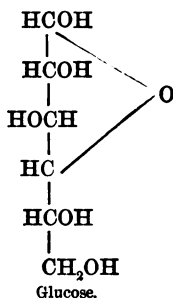
show a peculiar behaviour towards the action of the ferments maltase and emulsin. It has been found that the α - compound is only hydrolysed by maltase and not at all by emulsin, which attacks only the β - compound. Emil Fischer, who first prepared these compounds and noted these differences, concluded that their structure played a very important part as regards their behaviour to enzymes, and that the enzymes themselves must be built up in a manner correlative to that of these glucosides, like lock and key. The formulæ of these compounds show that one of the asymmetric carbon atoms is different in the α - and β - compounds—



α - and β -methyl-glucosides.

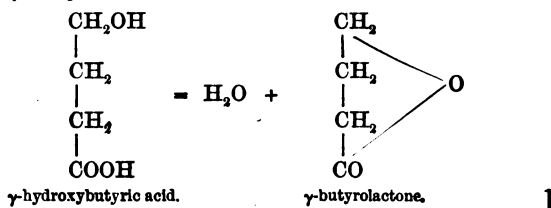
—and this difference probably accounts for the different action of these enzymes.

It will be noticed from these formulæ that the constitution of aldehyde and polyhydric alcohol, previously given to glucose, has been altered; the glucosides do not reduce, and hence do not contain an aldehyde group. The formula given is known as the γ -lactone formula, which really expresses the constitution of glucose better than the aldehyde formula :



A γ -lactone is formed when two hydroxyl groups occur in a molecule in the γ -position; it is simply an anhydride formed by the loss of a

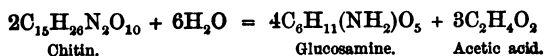
molecule of water. The simplest case is that of γ -hydroxybutyric acid which forms γ -butyrolactone:



Formerly, chitin, the chief constituent of the external skeleton of the Arthropods, was considered to be a glucoside, because glucose and ammonia could be split off from it by the action of concentrated sulphuric acid. Chitin differs from the true glucosides in that it does not split off sugar when boiled with dilute acids, or by the action of ferments. The substance which is first separated by the hydrolysis of chitin is not a sugar, but the amine of a sugar, a hexose in which a hydroxyl group is replaced by the NH_2 group. This compound, glucosamine, is partially decomposed by concentrated sulphuric acid into glucose and ammonia.

Chitin can easily be prepared in large quantities from the claws of crabs and lobsters, or the carapaces of large beetles. These are first extracted with dilute hydrochloric acid, caustic soda, alcohol, and ether, and are then decolourised with a solution of permanganate. Pure white chitin is thus obtained, which still retains the form of the external skeleton of the arthropod used; hence the name chitin, from the Greek word $\chi\iota\tau\omicron\nu\nu$, cloak. No solvent is known which can dissolve chitin without decomposing it. If it be boiled for some time with concentrated hydrochloric acid, it breaks down into glucosamine and acetic acid; the latter can be distilled off, and when the residue is evaporated down on the water bath glucosamine hydrochloride crystallises out. This decomposition of chitin is also effected by concentrated sulphuric acid; by the further action of the sulphuric acid, a portion of the nitrogen is then split off from the glucosamine as ammonia, and a compound is formed which gives all the reactions of a sugar.

George Ledderhose,¹ in Hoppe-Seyler's laboratory, estimated the quantity of glucosamine hydrochloride and acetic acid which are formed by the decomposition of chitin, and arrived at the following formula:



¹ George Ledderhose, *Z. f. physiol. Chem.* 1878, vol. ii. p. 213 and 1890, vol. iv. p. 139. Herein the earlier literature is cited.

It is, however, questionable whether the acetic acid is really formed by the hydrolytic decomposition of chitin, for Lëdderhose noticed, together with the acetic acid, small quantities of other volatile fatty acids, especially formic and butyric, and it is probable that these fatty acids are secondary products of decomposition of the carbohydrate.¹ The constitution of chitin has not yet been definitely determined.

Free glucosamine decomposes very rapidly in aqueous solution with evolution of ammonia, and in order to prepare it pure, crystals of glucosamine hydrochloride are suspended in alcohol and decomposed by the alcohol-soluble organic base, diethylamine. Free glucosamine is thereby separated in fine needles.²

By the action of nitrous acid the NH_2 radical in glucosamine was replaced by OH (p. 62) and the corresponding monosaccharide thus prepared.³ This was not fermentable by yeast, but it possessed the reducing properties of the sugars, and rotated the plane of polarisation to the right. Up to the present it has not been crystallised.

In recent years glucosamine has often been met with in the investigation of the decomposition products of the complicated compounds of the animal body. O. Schmiedeberg⁴ found it amongst the decomposition products of chondrin, the chief constituent of cartilage; and Friedr. Müller and his pupils⁵ have obtained it as a decomposition product of mucin and egg albumin. Emil Fischer has synthesised glucosamine, and he has written upon the value of this discovery as follows:

'The synthesis of glucosamine shows that it is an intermediate stage between grape sugar and the α -amino acids, and consequently it is one of the long-sought-for bridges between the carbohydrates and the proteins.'⁶

¹ E. E. Sundwik, *Z. f. physiol. Chem.* 1881, vol. v. p. 384.

² R. Breuer, *Ber. d. d. chem. Gesellsch.* 1898, vol. xxxi. 2193.

³ G. Lëdderhose, *Z. f. physiol. Chem.* 1880, vol. iv. p. 139.

⁴ O. Schmiedeberg, *Arch. f. exper. Pathol. u. Pharmacol.* 1891, vol. xxviii. p. 355.

⁵ Friedr. Müller, *Z. f. Biol.* 1901, vol. xlii. p. 468; Langstein, *Z. f. physiol. Chem.* 1901, vol. xxxi. p. 49. Cf. also E. Abderhalden, P. Bergell and T. Dörpinghaus. *Z. f. physiol. Chem.* 1904, vol. xli. p. 530.

⁶ Emil Fischer, *Syntheses in the Purine and Sugar Groups*, lecture given on December 12, 1902, before the Swedish Academy of Science, Stockholm (Vieweg & Son: Brunswick, 1903), p. 24.

LECTURE X

THE CYANOGEN COMPOUNDS

THE cyanogen radical has been previously mentioned several times, and the compounds of cyanogen might have been more properly described with the derivatives of marsh gas, and the methyl compounds. Cyanogen ($-\text{C}\equiv\text{N}$) is a methyl radical, in which the three monovalent hydrogen atoms are substituted by a trivalent nitrogen atom. In the free state cyanogen, like methyl, is unknown, but, just as two methyl radicals, when set free from their compounds, unite together to form dimethyl or ethane, so also do two cyanogen radicals unite together to form dicyanogen, a colourless gas with a pungent smell. The determination of the density of this gas shows that its molecule contains two atoms of carbon and two atoms of nitrogen :



At the ordinary temperature water absorbs four times its volume of cyanogen. In many reactions the cyanogen radical behaves like the halogens, chlorine, bromine, and iodine ; with hydrogen it combines to form an acid, prussic acid, which reacts analogously to hydrochloric acid ; with metals it forms salts which are practically isomorphous with the metallic halides ; potassium cyanide crystallises in cubes like potassium chloride, bromide and iodide.

The alkali cyanides are formed whenever carbon and nitrogen come into contact with the alkalies, or the alkali metals, at a high temperature ; thus, when potassium carbonate and carbon are heated in an atmosphere of nitrogen, or when nitrogenous organic compounds are heated with the alkali metal. Upon this latter reaction depends a method for the detection of the presence of nitrogen in organic compounds. When ammonia is passed over red-hot carbon, ammonium cyanide is formed, and this explains the occurrence of this compound in unpurified illuminating gas (cf. Lecture 12).

If cyanides be distilled with a non-volatile acid—tartaric, or dilute sulphuric—free hydrogen cyanide, or prussic acid, is obtained, as a colourless liquid with an intense smell of bitter almonds, boiling at 26.5°C . It has been shown (cf. Lecture 9) that bitter almonds contain a glucoside, from which prussic acid can be split off. Prussic acid is a very feeble acid, and is partially expelled from its salts by atmospheric carbonic acid; hence its neutral salts always smell of bitter almonds. The impression of the smell is in fact the most sensitive test for prussic acid, but it must be remembered, firstly, that other substances, e.g. nitrobenzene (cf. Lecture 14) have a similar smell, and, secondly, that the olfactory nerves very soon become blunted to the impression of prussic acid.

If mercuric oxide be dissolved in prussic acid, mercuric cyanide, $\text{Hg}(\text{CN})_2$, is obtained, which is a colourless salt crystallising in quadratic prisms. When this salt is heated it is decomposed into mercury and cyanogen, and by this method free cyanogen is prepared.

Prussic acid, the cyanides, and cyanogen are very intense poisons. Prussic acid and cyanogen produce death when they are inhaled, as well as when they are dissolved in water and taken into the stomach. Prussic acid is at once liberated from cyanides in the stomach, by the acids of the gastric juice. One milligramme of prussic acid for every kilogramme of body-weight is a fatal dose to warm-blooded animals, when injected subcutaneously, and death ensues from inhibition of the respiratory centre. Cyanogen works similarly but slower, and its lethal dose is slightly larger.¹ Both prussic acid and cyanogen paralyse the heart, as can be shown on the isolated hearts of cold-blooded animals, but probably both cyanogen and prussic acid belong to the general group of the protoplasmic poisons, i.e. poisons which destroy the life of any and every cell. All invertebrates, as well as all those unicellular animals and plants upon which experiments have been made, are killed by prussic acid and cyanogen.

A nutrient medium containing one gramme of cyanogen in 2500 cc. will kill all yeast cells in twenty-four hours, and a solution containing 1 per 1000 prussic acid will stop the development of putrefactive and lactic acid bacteria, and kill algæ in a few hours. Infusorians and smaller worms are killed in less than two minutes when the water in which they are living contains one gramme of cyanogen to two litres; prussic acid is thus less poisonous than cyanogen to lower animals, but the reverse is the case with higher animals. To the higher plants prussic acid and cyanogen are equally poisonous; the

¹ B. Bunge, *On the Action of Cyanogen*, Diss. Dorpat, 1879.

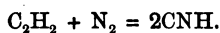
seedlings of peas and grain are killed within three days when their nutrient medium contains one gramme of the poison in five litres; young lupines, 8 cm. high, are killed in fifty-five hours if $\frac{1}{25000}$ part of cyanogen is contained in their nutrient solution.¹

It is a fact of the greatest interest that compounds with so simple and well-known a constitution as prussic acid and cyanogen can cause such intensely poisonous effects, and we may hope that the investigation of the chemical processes which give rise to these simple compounds in our tissues will enable us to gain an insight, not only into the manner by which the poison acts, but also into the normal processes of life. It is therefore important to physiologists to know exactly the relation of cyanogen to all the compounds which occur in our tissues, as only under these conditions can we hope to attain to a profitable position of enquiry into the nature of the chemical processes in our tissues, which are deranged through the poison: therefore it is necessary to study the chemistry of the cyanogen compounds in further detail.

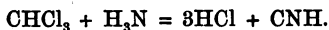
Prussic acid and cyanogen can be obtained by several other methods than those above described, and they are of considerable theoretical interest.

Cyanogen is formed by the direct combination of its elements, when electric sparks are allowed to pass between carbon poles in an atmosphere of nitrogen.² Cyanogen combines directly with hydrogen, forming prussic acid, when a mixture of the two gases is submitted to the influence of a silent electric discharge at a high temperature.

Prussic acid is also formed when electric sparks are allowed to pass through a mixture of acetylene and nitrogen: ³



A further theoretically interesting method of preparing prussic acid is from chloroform and ammonia; in this reaction three molecules of hydrogen chloride are eliminated. This reaction takes place both when the two gases are allowed to act upon one another under a high pressure and at a high temperature, and also when chloroform and ammonia are boiled with potash:



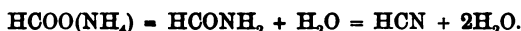
The formation of prussic acid from ammonium formate (p. 41) is

¹ O. Loew and M. Tsukamoto, *Bulletin of the Coll. of Agriculture, Tokio*, 1894, vol. ii. No. 1; *Investigations on Nutrient Media, etc.* 1894, vol. i. No. 7.

² J. Fr. Auguste Morren, *Compt. rend.* 1859, vol. lviii. p. 342.

³ Berthelot, *ibid.* 1868, vol. lxxvii. p. 1141, or *Liebig's Ann. d. Chem.* 1869, vol. cl. p. 60.

physiologically especially interesting. Ammonium formate, a deliquescent salt, on heating loses first one molecule of water giving formamide, a colourless liquid, and then by the loss of a second molecule of water, prussic acid :



The analogous conversion of ammonium acetate into acetamide and acetonitrile was described on page 59 :

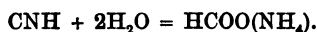


Nitriles are the compounds which are derived from acids by the substitution of cyanogen for the carboxyl radical. *Prussic acid is thus the nitrile of formic acid.*

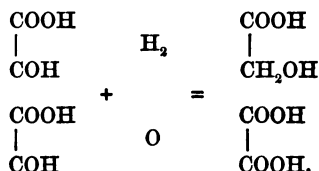
Nitriles in aqueous solution and in the presence of alkalies, or acids, have a tendency to decompose water into its elements, to unite with these elements, and be reconverted into amides and ammonium salts :



In the case of the nitrile of formic acid—prussic acid—this conversion takes place when the aqueous solution is allowed to stand at the ordinary temperature :



But when easily reducible, and at the same time oxidisable, compounds are present, the elements of water are not combined with the prussic acid, but serve for the reduction and oxidation of this compound. Such a compound is the aldehyde of oxalic acid, the so-called glyoxylic acid ; this, in the presence of prussic acid, is partly reduced to glycollic acid (p. 62), and partly oxidised to oxalic acid : ¹



O. Wallach ² has described a whole series of compounds which are oxidised and reduced, in an analogous way, in the presence of

¹ O. Böttiger, *Ber. d. d. chem. Gesellsch.* 1877, vol. x. p. 1084.

² O. Wallach, *Ber. d. d. chem. Gesellsch.* 1877, vol. x. p. 2120.

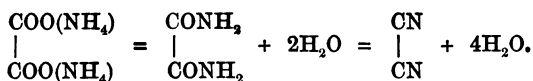
prussic acid, without the prussic acid itself undergoing any change; it acts here as a ferment or catalyser.

This is a fact of great physiological and toxicological interest. It is conceivable that the poisonous action of prussic acid depends upon its capability of decomposing water, thereby evoking oxidation and reduction processes. In every animal and plant cell oxidation processes, and possibly also reduction processes, take place, and if prussic acid likewise can bring about such processes, but in the wrong place and at the wrong time, it may be supposed that the normal chemical processes and the normal functions are thereby deranged, and so intensely poisonous effects are produced.

It is possible that by reason of its power of decomposing water prussic acid inhibits the catalysis of hydrogen peroxide by organic ferments, and by finely divided platinum. Schönbein¹ (1799–1868) showed that many constituents of plant and animal tissues exercised a so-called catalytic action upon hydrogen peroxide, producing water and oxygen, and that a small quantity of prussic acid inhibited this catalytic action. Later experiments have shown that the catalysis of hydrogen peroxide can also be brought about by ferments—digestive ferments, yeast ferments, etc.—and that this catalysis is also stopped by prussic acid.

E. Buchner² showed that small quantities of prussic acid not only hindered the catalytic action of yeast-juice upon hydrogen peroxide, but also its specific catalytic action upon sugar, i.e. alcoholic fermentation. These facts may perhaps give an impulse to fruitful investigation upon the poisonous action of cyanogen.

The so-called free cyanogen, or dicyanogen, is also a nitrile: it is the nitrile of oxalic acid. Dicyanogen results from ammonium oxalate in the same way as prussic acid from ammonium formate, and acetonitrile from ammonium acetate (p. 134); when ammonium oxalate is heated it loses water, and is converted into oxamide (p. 64), which on further heating with a dehydrating agent, such as phosphoric acid anhydride, yields dicyanogen:



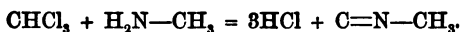
¹ C. F. Schönbein, *Journ. f. prakt. Chem.* 1868, vol. cv. p. 202; *Z. f. Biol.* 1867, vol. iii. p. 140. G. Bredig, *Inorganic Ferments* (Engelmann: Leipzig, 1901), pp. 68 ff. Herein the literature on the inhibition of catalysis by prussic acid is collected together.

² E. Buchner and R. Rapp, *Ber. d. d. chem. Gesellsch.* 1897, vol. xxx. p. 2672; Buchner, *ibid.* 1898, vol. xxxi. p. 568.

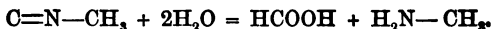
Conversely, dicyanogen, by the absorption of the elements of water, is reconverted into oxamide and ammonium oxalate, when cyanogen is passed into water in which a small quantity of acetaldehyde is dissolved.¹ Under similar conditions cyanogen produces a decomposition of water molecules in the cells of plants and animals, and its poisonous action can be hypothetically explained in a similar way to that of prussic acid. Certain reactions point to the presence of aldehyde groups in the side chains of the protein molecules of living cells,² which might behave like acetaldehyde in the conversion of cyanogen into oxamide.

Cyanogen and prussic acid are the only two nitriles which show no isomerism; all other nitriles exist in two isomeric forms, as nitriles in the strict sense, and as isonitriles or carbylamines, which have different physical properties, different methods of preparation, and different products of decomposition.

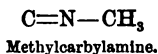
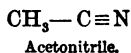
The isonitrile corresponding to acetonitrile (pp. 59 and 134) is formed when methylamine and chloroform act upon one another in alcoholic potash solution:



The hydrochloric acid which is formed naturally combines with the potash. The isonitrile, or methylcarbylamine, is split up very quickly by aqueous solutions of mineral acids, with absorption of water, into methylamine and formic acid:



The methyl radical in the isonitrile is combined with the nitrogen, and is split off in combination with it, as expressed in the formula. In the nitrile the methyl radical is bound to the carbon, and on hydrolysis, by boiling with alkali, it is split off, still bound to the carbon, as acetic acid. The formulæ are therefore written as follows:

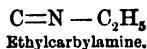


Acetonitrile boils at 82° C., the corresponding isonitrile or methylcarbylamine at 60° C.; acetonitrile has a not unpleasant aromatic smell; the isonitrile, on the other hand, has a penetrating and disgusting smell. The nitrile is not poisonous, but the isonitrile is a deadly poison.

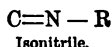
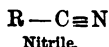
¹ Liebig, *Liebig's Ann. d. Chem.* 1860, vol. cxiii. p. 246.

² O. Loew and Th. Bokorny, *Pflüger's Arch.* 1881, vol. xxv. p. 150; 1881, vol. xxvi. p. 50; *Ber. d. d. chem. Gesellsch.* 1881, vol. xiv., p. 2508.

Propionitrile is formed from ammonium propionate in an analogous manner to acetonitrile from ammonium acetate; and ethylcarbylamine, the corresponding isonitrile, is obtained from ethylamine and chloroform:

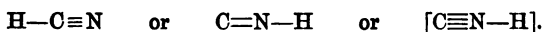


In this way, starting from the homologous series of fatty acids and the homologous primary alkylamines, we can obtain two homologous series of isomeric nitriles, whose general formulæ, if R designates the alkyl radical, are the following: ¹



As the isonitriles are characterised by their penetrating and disgusting smell, their formation is a very sensitive reaction for primary amines. The smallest trace of these heated in alcoholic solution with caustic potash and a drop of chloroform at once produces the particular nauseous odour (A. W. Hofmann's reaction), and conversely the primary amines are a very delicate reagent for chloroform. By means of this reaction it was shown that, in the chloroforming of the mother during parturition, the chloroform passed through the placenta into the blood of the child; chloroform was detected in the blood from the umbilical cord, and in this manner the time of the separation of the placenta was determined. ²

Since prussic acid shows no isomerism, it remains unsettled which structural formula should be assigned to it, the nitrile or isonitrile:



Its reactions make both assumptions possible (see methods of preparation, p. 133).

Prussic acid and potassium cyanide are prepared on the large scale from the complicated compound potassium ferrocyanide or yellow prussiate of potash, a so-called double salt of prussic acid, which crystallises in monoclinic plates. It is formed when a ferrous salt, such as ferrous sulphate, is boiled in aqueous solution with excess of potassium cyanide; ferrous cyanide $\text{Fe}(\text{CN})_2$ and potassium sulphate are first formed, and the ferrous cyanide then combines

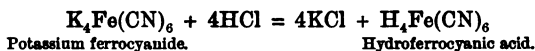
¹ [It is still an open question whether the group NC contains divalent carbon $\text{C}=\text{N}-$, or tetravalent carbon $\text{C}\equiv\text{N}-$.]

² Will. Zinsstag, *Studies in the Mechanism of the Physiological Separation of the Placenta*, Diss. Basel, 1888, p. 37.

with four molecules of potassium cyanide, forming potassium ferrocyanide :



Potassium ferrocyanide is, however, not a double salt like alum, or potassium platinochloride. The iron in it cannot be detected by the ordinary reactions ; ammonium sulphide not only gives no black precipitate with the yellow solution of potassium ferrocyanide, but also does not produce the slightest change in colour ; further proof that potassium ferrocyanide is not a double salt is the following : if a mineral acid, e.g. hydrochloric acid, be added to the solution, ferrous chloride is not formed and the cyanogen is not removed as prussic acid, but the six molecules of the cyanogen remain combined with the iron, and only the four atoms of potassium combine with the chlorine :



The tetrabasic hydroferrocyanic acid is formed, which is soluble with difficulty in water ; and if a concentrated solution of yellow potassium ferrocyanide be treated with concentrated hydrochloric acid, a white precipitate of hydroferrocyanic acid is obtained.

Potassium ferrocyanide is prepared on the large scale from charcoal rich in nitrogen, which is obtained by the incomplete carbonisation of animal refuse of all kinds, e.g. blood—hence the German name ‘ Blutlaugensalz = blood-lye salt ’—horn, hoofs, wool-dust, leather cuttings, etc. This charcoal is fused with potassium carbonate and iron filings, and the black mass is then extracted with hot water ; from the filtered extract the yellow potassium ferrocyanide crystallises out on concentration and cooling, and is purified by recrystallisation.

This process of its formation can be understood if it be remembered how potassium cyanide is made, and how potassium ferrocyanide is formed from potassium cyanide and ferrous salts.

In recent times another method has been used for the preparation of potassium ferrocyanide. In this process, the prussic acid which collects in the gas-washing apparatus in the coal-gas works is made use of. The formation of cyanogen compounds by the dry distillation of nitrogenous coal can be understood from what has been stated before.

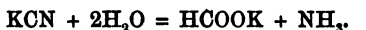
Potassium cyanide is prepared from potassium ferrocyanide by fusing it in the absence of air, whereby the following decomposition into potassium cyanide, iron carbide and nitrogen occurs :



[If potassium ferrocyanide be heated with metallic sodium, a mixture of potassium and sodium cyanides is obtained, and the whole of the cyanogen retained as cyanide :

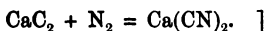


The molten potassium cyanide is cast into sticks and comes in this form into the market ; it can be kept unchanged in well-stoppered bottles. The aqueous solution soon decomposes at the ordinary temperature, but, more rapidly on boiling, into potassium formate and ammonia :



Potassium cyanide has a wide technical use in the preparation of the double salts with gold and silver cyanides, which are used for electro-plating in gold and silver ; also in photography, and as a reducing agent for metallic oxides (p. 142). Of late years large quantities have been used for extracting gold from gold ores ; on account of its extended use potassium cyanide can be obtained in the market everywhere, and the frequent use of this poison for suicidal purposes is thus explained.

In recent times many experiments have been made with a view to preparing potassium cyanide on the large scale directly from the nitrogen of the air, which have not been altogether unsuccessful ; [calcium cyanide is prepared by heating calcium carbide, obtained from powdered limestone and coke, to the fusion point in the electric furnace, when it combines with the nitrogen of the air :



Potassium ferrocyanide is also employed in the preparation of prussic acid ; at the ordinary temperature, as above described, prussic acid is not liberated from potassium ferrocyanide by the stronger acids, but hydroferrocyanic acid ; this, on heating, is decomposed with liberation of prussic acid. In the preparation of the latter, potassium ferrocyanide is therefore distilled with a non-volatile organic acid, tartaric acid, or with dilute sulphuric acid, and the distillate is collected in thoroughly well-cooled receivers. The resulting prussic acid contains water, and if distilled again over calcium chloride, anhydrous prussic acid is obtained ; this is a colourless liquid boiling at 26°C. , which solidifies in the cold, forming colourless crystals melting at -14°C.

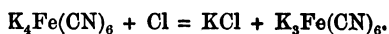
Anhydrous prussic acid can be kept without decomposition, but if it contains only a small quantity of water it very quickly decomposes,

as stated above, into ammonium formate ; at the same time it becomes brown, and other decomposition products, e.g. oxalic acid and a brown precipitate of unknown composition, are formed. All these products of decomposition are not poisonous, and this explains why the prussic acid used for suicidal purposes often fails in its effect, whereas potassium cyanide generally leads to the desired result.

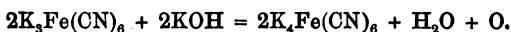
A dilute solution of prussic acid is employed in therapeutics under the name of water of bitter almonds, *Aqua amygdalarum amararum*. This solution contains 0.1 per cent. prussic acid, together with benzaldehyde and alcohol. It is obtained by distilling crushed bitter almonds with weak alcohol. The prussic acid and benzaldehyde arise by hydrolysis from amygdalin (cf. Lecture 9). Only small quantities of this bitter almond water can, of course, be prescribed, since a decigramme of prussic acid (100 cc. bitter almond water) can kill a man ; the maximal single dose is therefore fixed at 2 grammes, the maximal day's dose at 8 grammes. There is no rational indication for the exhibition of water of bitter almonds in any disease, and with our present knowledge, it should only be used as a means of masking medicines with a nasty taste and smell.

Potassium ferrocyanide has also an important technical use in the preparation of prussian blue, which is the ferric salt of hydroferrocyanic acid. It will be remembered, from analytical chemistry, that potassium ferrocyanide gives a blue precipitate with neutral and acid solutions of ferric oxide. This precipitate is used as a colouring matter.

When chlorine is passed into a solution of potassium ferrocyanide, an atom of potassium is removed, and the potassium ferrocyanide is converted into potassium ferricyanide :



Potassium ferricyanide crystallises in dark red-brown crystals, and is called red prussiate of potash in contradistinction to the yellow. It removes the alkali metal from alkaline solutions, liberating oxygen, and is reconverted into potassium ferrocyanide :



Potassium ferricyanide is therefore used as an oxidising agent, whereas potassium ferrocyanide is a reducing agent.

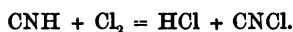
Potassium ferricyanide does not produce a precipitate with a ferric salt, only a dark olive-green colouration, but with a ferrous salt it gives a blue precipitate, very similar to that which potassium ferrocyanide gives with a ferric salt. Both precipitates are insoluble in acids. Potassium ferricyanide is therefore used in analytical

chemistry to recognise a ferrous salt in the presence of a ferric salt, in neutral and acid solutions. The blue precipitate given by potassium ferricyanide is also found in commerce as a colouring matter, under the name of Turnbull's blue.

When potassium ferrocyanide is oxidised with nitric acid, nitroprussic acid is formed; its sodium salt, $\text{Fe}(\text{CN})_5(\text{NO})\text{Na}_2 + 2\text{H}_2\text{O}$, which forms red crystals soluble in water, is a delicate reagent for sulphuretted hydrogen in alkaline solution, with which it gives a beautiful violet colouration.

Potassium ferrocyanide is not poisonous, as the dilute acids of the gastric juice do not, at the body temperature, liberate prussic acid from it. It is used as a purgative, like Glauber's salt; it has no advantages over other purgatives, and there seems no necessity for its use. Certain cases are known where suicides have taken potassium ferrocyanide and then tartaric acid, and have died with the characteristic symptoms of prussic acid poisoning, and it is conceivable that the therapeutical doses of potassium ferrocyanide, if they chanced to meet with acid foods in the stomach, might produce an injurious effect.

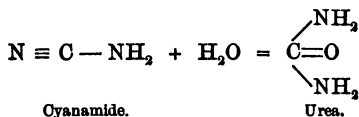
If chlorine be allowed to act upon potassium cyanide or prussic acid, the potassium, or the hydrogen, is substituted by chlorine, and we obtain cyanogen chloride, a colourless gas with a penetrating pungent smell:



This gas is interesting on account of its employment as the starting point in the preparation of more complicated compounds. If it be passed into an ethereal solution of ammonia, cyanamide is formed, which is a colourless crystalline compound:



Cyanamide is used in the synthetical preparation of the nitrogenous compound creatine, which occurs in large quantities in our body (cf. Lecture 11). Cyanamide also stands in close relationship to the most important nitrogenous end-product of our metabolism, namely urea; into which it passes by simply taking up a molecule of water; when concentrated sulphuric acid is mixed with an equal volume of water and this diluted acid is allowed to act upon cyanamide, the chief product is urea, or the diamide of carbonic acid¹ (cf. Lecture 11):

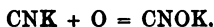


¹ E. Baumann, *Ber. d. d. chem. Gesellsch.* 1873, vol. vi. p. 1373.

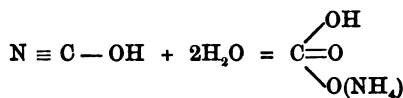
A further physiologically interesting derivative of cyanogen chloride is cyanic acid, CNOH . This, like cyanamide, has not been recognised as a constituent of our body, but it nevertheless stands in close relationship to urea. The potassium salt of cyanic acid is obtained by passing cyanogen chloride into caustic potash :



Potassium cyanate is also formed when potassium cyanide is heated to redness in the air. Potassium cyanide is completely converted into potassium cyanate when it is heated with an easily reducible metallic oxide, such as manganese dioxide, or red lead :

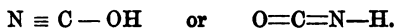


Potassium cyanate consists of colourless platelets or needles, easily soluble in water ; if we attempt to liberate the free acid from its aqueous solution by the addition of a strong acid like dilute sulphuric acid, the liberated cyanic acid at once changes into acid ammonium carbonate with absorption of water :



The acid ammonium carbonate is naturally decomposed by the excess of sulphuric acid, and an effervescence of carbonic acid is observed, whilst the solution is found to contain potassium and ammonium sulphates.

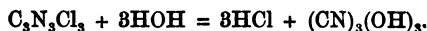
According to this reaction we can regard cyanic acid as a nitrile, as the nitrile of carbonic acid. Nitriles, as above stated, are carbonic acids in which the carboxyl group is replaced by cyanogen (p. 134) ; with the absorption of two molecules of water they are changed into ammonium salts (pp. 124 and 135). On this account many authors consider the structure of cyanic acid to be different, and it remains indeterminate like that of prussic acid, the two following structural formulæ having been assigned to it :



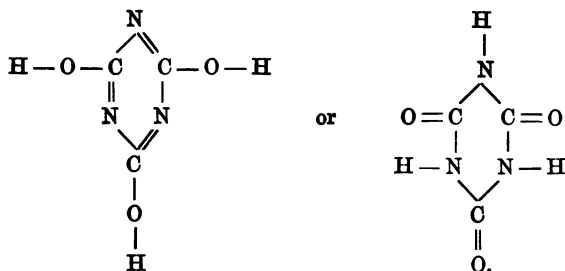
In order to prepare cyanic acid we must start from the polymeric cyanuric acid, $\text{C}_3\text{N}_3\text{O}_3\text{H}_3$, the formation of which will shortly be described. When cyanuric acid, a solid compound, is heated in a current of carbon dioxide, it is decomposed into three molecules of cyanic acid ; this distils over and is collected in well-cooled receivers.

Cyanic acid, as thus obtained, is a pungent smelling, very unstable liquid; on removal from the freezing mixture, as soon as it is warmed above 0°C ., it begins to boil violently and changes into the polymeric cyamelide $(\text{CNOH})_x$, an opaque white mass, which, on heating, is reconverted into cyanic acid.

Cyanogen chloride is an easily condensed gas, which boils at 15.5°C ., and, like all cyanogen compounds, shows a great tendency to polymerisation. The liquid, on simply keeping, partially polymerises into cyanuric chloride, which at the ordinary temperature forms crystals melting at 145°C ., and boiling at 190°C . Cyanuric chloride is converted into cyanuric acid, the polymer of cyanic acid, by boiling with water:

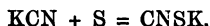


Cyanuric acid is most easily prepared from urea. (Cf. Lecture 11.) It is a tribasic acid, crystallising in prisms, which are easily soluble in hot water. Two structural formulæ have been assigned to it, corresponding to the two formulæ for cyanic acid:



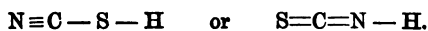
Cyanuric acid itself shows no isomerism, but two series of isomeric esters can be prepared from it.

Potassium sulphocyanide, or thiocyanate, or rhodanate, is analogous to potassium cyanate. It is potassium cyanate in which the divalent oxygen atom has been replaced by the divalent sulphur atom. Its method of formation is also analogous; just as potassium cyanide, when heated in the air, takes up oxygen and is converted into potassium cyanate, so also potassium thiocyanate is prepared by heating potassium cyanide with sulphur. It suffices, however, to simply boil an aqueous solution of potassium cyanide with sulphur, or to evaporate a solution of potassium cyanide with yellow ammonium sulphide:



The free thiocyanic acid, or hydrosulphocyanic acid, can easily be prepared from thiocyanates. By decomposing barium thiocyanate with dilute sulphuric acid, an aqueous solution of thiocyanic acid is obtained, which is much more stable than a solution of cyanic acid. The anhydrous thiocyanic acid can be prepared from the aqueous solution by distillation under diminished pressure, drying the vapours with calcium chloride, and collecting in a freezing mixture. The pure acid so obtained is a volatile, pungent smelling liquid, which decomposes and polymerises rapidly on removal from the freezing mixture, like cyanic acid.

Two structural formulæ are also assumed for thiocyanic acid, although it shows no isomerism :



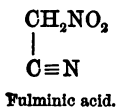
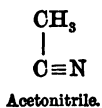
Two isomeric series of esters are known ; one of them, the allyl ester (p. 98), the active constituent of mustard, has been previously mentioned (cf. Lecture 9).

Physiologically, thiocyanic acid is of interest, because small quantities of it occur as the potassium salt in the saliva of man and many mammals ; at present we do not know the importance of the small quantities of potassium thiocyanate for any of the vital functions. Its recognition would have escaped our notice if we had not a very delicate reagent for it in the ferric salts. The smallest quantity of potassium thiocyanate gives an intense red colour with ferric chloride in neutral or acid solution. Conversely, in analytical chemistry, potassium thiocyanate is a very valuable reagent for detecting traces of ferric salts in solution, in the presence of ferrous salts. Ferrous salts give no colour reaction with thiocyanates. As we can easily convert cyanides into thiocyanates, ferric chloride is also a very delicate, in fact the most delicate, reagent for prussic acid.

In addition to these most reliable reactions for prussic acid, small quantities of it can be detected in corpses exhumed for medico-legal purposes, where poisoning by prussic acid has been suspected, by the following method. The most delicate reaction for prussic acid is its odour ; in cases of poisoning by prussic acid, the contents of the stomach, and all the organs, especially those rich in blood, smell distinctly of bitter almonds ; cases are known where the exhumation has taken place as long as ten days after the poisoning, and the smell of bitter almonds has been still clearly perceptible. But all people have not a fine sense of smell, and in the same person the sense of smell can be very different at different times ; and further, not only prussic acid but also other poisons, especially nitrobenzene,

have a similar smell, so that in legal cases the sense of smell alone is not sufficient, and consequently the following reactions should be used. The contents of the stomach, or the crushed-up organs, are distilled with tartaric acid, and the following two reactions are carried out with the distillate: (1) A portion of the distillate is treated with solutions of ferrous and ferric salts, and then with caustic soda, until a precipitate of the oxides of iron is formed; it is then heated and acidified with hydrochloric acid; if prussic acid be present, a precipitate of prussian blue results. The formation of this precipitate can be understood from the methods of preparation of potassium ferrocyanide (p. 137). (2) The following reaction is still more sensitive: a portion of the distillate is treated with yellow ammonium sulphide and a drop of dilute caustic soda; it is then evaporated on the water bath and the residue tested with ferric chloride for ammonium thiocyanate.

Fulminic acid, which was formerly regarded as a cyanogen compound, since it is a polymer of cyanic acid, is of practical importance. It has the empirical formula $C_2N_2O_2H_2$, and its mercury salt is used in filling the explosive capsules of cartridges. The mercury salt is prepared by dissolving mercury in excess of nitric acid, and carefully mixing the solution with alcohol; heat is evolved and a violent reaction takes place. During the cooling, the mercury fulminate gradually separates in white crystals; it has the composition $C_2N_2O_2Hg$, and it explodes violently when struck or heated. Very little is known of the free acid on account of its instability. The silver salt $C_2N_2O_2Ag_2$ is still more explosive than the mercury salt. The structure of fulminic acid is still undetermined; from its method of preparation fulminic acid might be expected to be a nitro-compound, and Kekulé regarded it as acetonitrile in which a hydrogen atom is replaced by the NO_2 radical of nitric acid, and he gave it the formula:



But its decomposition into formic acid and hydroxylamine by concentrated hydrochloric acid is against this view. Further references on the structure of fulminic acid can be obtained from the

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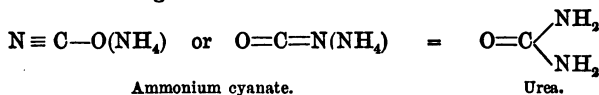
original papers; ¹ they are of interest in that they show how difficult it sometimes is to determine the structure of so simple a compound with only two carbon atoms, when nitrogen atoms are also concerned in its constitution, because the methods of combination of the nitrogen atoms can be so various.

¹ The newer work is by R. Scholl, *Ber. d. d. chem. Gesellsch.* 1890, vol. xxiii. p. 3505; 1891, vol. xxiv. p. 580; 1894, vol. xxvii. p. 2816; J. U. Nef, *Liebig's Ann. d. Chem.* 1894, vol. cclxxx. p. 263; A. F. Hollemann, *Ber. d. d. chem. Gesellsch.* 1890, vol. xxiii. p. 2742; and *Rec. trav. chim. Pays-Bas*, 1892, vol. xi. p. 258. The older literature is cited in these papers.

LECTURE XI

UREA AND ITS DERIVATIVES

UREA, the most important nitrogenous end-product of our metabolism, stands in close relationship to the cyanogen compounds. It was first prepared synthetically from a cyanogen compound by Woehler, who wished to prepare ammonium cyanate from potassium cyanate (p. 142); with this intention he added ammonium sulphate to a solution of potassium cyanate and evaporated the solution to dryness. As potassium sulphate is insoluble in absolute alcohol, he expected that on treating the residue with alcohol only ammonium cyanate would go into solution. Instead of this, however, on evaporation of the alcoholic solution, pure urea separated out in beautiful crystals. A rearrangement of the atoms had taken place, ammonium cyanate and urea being isomers :



This discovery of the preparation of urea, made by Woehler (1800-1882) in 1828, produced a great sensation, as it was the first instance of the artificial preparation of a compound which so far had only been produced by vital processes. His colleagues said : ' Woehler went out to find an ass, but found a kingdom,' alluding to the Jewish legend of King Saul (1 Samuel ix. 10). It was not the first time that an investigator had found more than he looked for—Columbus searched for a passage to the East Indies and found a world; the alchemists searched for the philosopher's stone and found certain laws of nature.

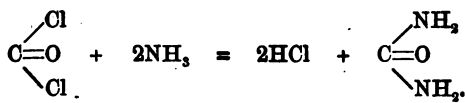
Essentially, however, the preparation of urea by Woehler was not a real synthesis of an organic compound, as he started from cyanic acid, whose synthesis was already known. At that time there was no clear conception of the nature of an organic compound; organic compounds were not then simply defined as compounds of carbon; they were only those carbon compounds which were produced by plant and animal life. After Woehler's discovery the

supporters of the mechanical theory of life triumphed over the vitalists, who taught that the constituents of animals and plants, the so-called organic substances, were the products of an inexplicable 'vital force.' But the vitalists showed that urea stands just at the margin between organic and inorganic substances; the plant always forms more complicated compounds from carbonic acid, ammonia, and water, which in the animal body are broken down into simpler ones; urea is an end-product of animal metabolism, and, outside the body, decomposes very quickly into carbonic acid and ammonia, which are the inorganic foodstuffs of plants. Artificial synthesis had reached to urea, but further it would never be possible to go. The people who said 'never' were right—for thirty years: but then the synthesis of one organic substance after another was discovered in rapid succession (cf. Lecture 1).

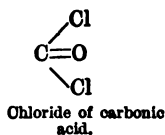
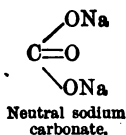
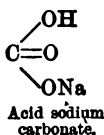
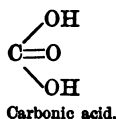
This historical fact is an instructive example to all those who believe that there is an insurmountable barrier in front of science. Science will put forward ever bolder questions and will always obtain more certain answers. Nothing can restrain it in its path to victory.

The preparation of urea from ammonium cyanate shows the close relationship of urea to the cyanogen compounds; it explains further the above-mentioned formation of urea from cyanamide, by absorption of water (p. 141). Urea, however, is not a cyanogen compound, but must be regarded as the diamide of carbonic acid, because it is formed from carbonic acid by all the typical and general methods of preparing the amides from the acids. (Cf. preparation of acetamide, pp. 59 and 60, and oxamide, p. 64.)

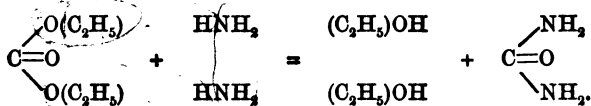
In the preliminary descriptions of the conquests of organic chemistry, the preparation of the chloride of carbonic acid, the so-called phosgene, or carbonoxychloride, was described (p. 6). If this gas be allowed to act upon ammonia, under a great pressure and at a high temperature, the following reaction occurs:



This preparation is exactly analogous to the preparation of acetamide from acetyl chloride and ammonia (p. 59); the only difference is that acetic acid is monobasic, whilst carbonic acid is dibasic; at any rate we must assume this for an aqueous solution of carbonic acid, as this gives two series of salts:

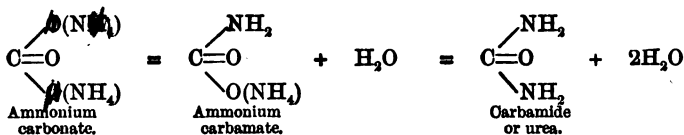


A second method of synthesising urea is from the ethyl ester of carbonic acid, which is prepared by the action of ethyl iodide upon silver carbonate,¹ and forms an ethereal smelling liquid boiling at 126° C.; when it is heated in a sealed tube to 180° C. with ammonia the following reaction occurs:



This is exactly analogous to the preparation of acetamide from acetic ester and ammonia (p. 59).

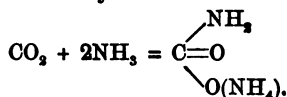
A third method of synthesising urea consists in removing two molecules of water from ammonium carbonate by a high temperature and a high pressure:



This process is exactly analogous to the formation of acetamide from ammonium acetate (p. 59), and of oxamide from ammonium oxalate (p. 64). Ammonium carbamate is formed in the technical preparation of ammonium carbonate; it is made from the ammonium chloride obtained from the wash waters in the preparation of coal gas. The ammonium chloride is sublimed with calcium carbonate (chalk). The neutral ammonium carbonate which is first formed in the reaction partially loses water and passes over into ammonium carbamate; partially it also loses ammonia and passes into acid ammonium carbonate. The product of sublimation, the so-called 'commercial ammonium carbonate,' is therefore always a mixture of these two salts. When commercial ammonium carbonate is heated to 130° C. in a sealed tube, the ammonium carbamate contained in it loses a second molecule of water, and is changed into urea. Ammonium carbamate can also be prepared directly by passing dry

¹ [This is another general mode of preparing esters: the action of an alkyl halide upon a silver salt.]

ammonia gas and dry carbonic acid gas into alcohol, when ammonium carbamate separates out in crystals :

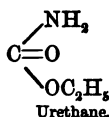


When pure ammonium carbamate is heated in a sealed tube at 130 to 140° C., the contents of the tube subsequently dissolved in water leave on evaporation a considerable quantity of urea.¹

From ammonium carbamate other carbamates can be prepared ; the free acid



is unknown ; it at once breaks down into CO₂ and NH₃. Its esters, however, can be prepared ; the ethyl ester, which is known as urethane, forms crystals easily soluble in water ; it was recommended by Schmiedeberg² as a hypnotic :



Urea crystallises in anhydrous, non-hygroscopic, long tetragonal prisms, which are easily soluble in water and alcohol, but not in ether. The aqueous solution can be heated to boiling without any considerable decomposition, but if the solution be heated in a sealed tube to 180° C., it is decomposed completely, with absorption of two molecules of water, into ammonium carbonate. If alkalis or acids be present in the solution, the decomposition takes place at a lower temperature. In the first case—in the presence of alkalis—ammonia is evolved and the carbonic acid combines with the base ; Bunsen's method³ of estimating urea depends upon this. In the second case—in the presence of acids—carbonic acid is evolved and the ammonia combines with the acid ; Kjeldahl's method of estimating urea—by correct nitrogen estimation—depends upon this reaction. The conversion of urea in aqueous solution into ammonium carbonate is brought about by the action of certain bacteria, and upon this the

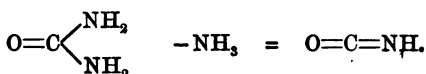
¹ A. Basaroff, *Journ. f. prakt. Chem.* 1870, N.F. vol. i. p. 285.

² O. Schmiedeberg, *Arch. f. exper. Pathol. u. Pharmacol.* 1885, vol. xx. p. 203.

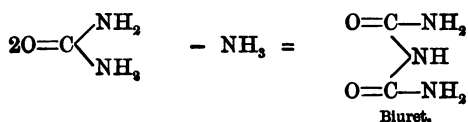
³ Bunsen, *Liebig's Ann. d. Chem.* 1848, vol. lxx. p. 375. A simplification of this method is described by G. Bunge, *Z. f. anal. Chem.* 1874, vol. xiii. p. 128.

so-called 'alkaline fermentation,' which voided urine very quickly undergoes, depends; the neutral urea is changed into the alkaline ammonium carbonate. If this fermentation occur in the bladder, as in cystitis, there is a danger of the formation of stones, because the calcium and magnesium, which are dissolved in the urine as acid salts, then separate out as calcium phosphate and ammonium magnesium phosphate.

If crystals of urea be heated above 120° C., they melt and slowly decompose, with evolution of ammonia, the end-product cyanic acid being formed :

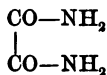


This polymerises to cyanuric acid, which, on prolonged heating of the molten urea, remains behind as an opaque white mass (p. 143). Biuret occurs as an intermediate product between urea and cyanic acid, when two molecules of urea together lose only one molecule of ammonia :

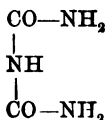


Biuret is a crystalline compound soluble in water; with dilute copper sulphate in alkaline solution it gives an intense red colour, and this reaction is the most delicate test which we possess for determining the presence of urea.

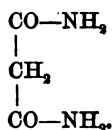
[This reaction is known as the biuret reaction; it consists in the formation of a pink colour when a few drops of dilute copper sulphate are added to an alkaline solution of biuret. It is also given by other compounds, especially the proteins. It depends upon the presence of two —CO—NH groups in a molecule, either when they are combined together directly, as in oxamide,



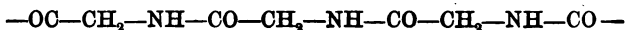
or by a nitrogen atom, as in biuret,



or by a carbon atom, as in malonamide,

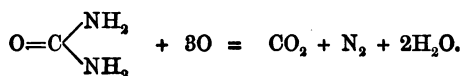


Several of these CO—NH groupings occur in the protein molecule, e.g.



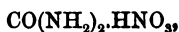
and on this account the reaction is given by proteins.]

By strong oxidising agents—nitrous acid, salts of hypobromous acid, etc.—urea is completely oxidised to carbonic acid, water and nitrogen :

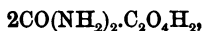


The qualitative detection, and Hüfner's method of estimating urea, depend upon this reaction.

Urea adds itself to acids like ammonia and all substituted ammonias, amines or amides, do ; it should be noticed, however, that a molecule of urea only adds itself to one molecule of a monobasic acid, the second ammonia residue, or the second amide radical, remaining uncombined. The compounds with nitric acid

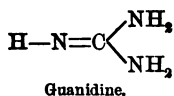
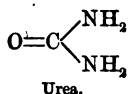


and with oxalic acid

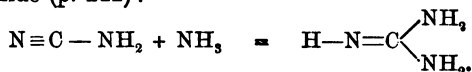


are soluble with difficulty in water, from which they separate in large crystals. The most convenient method of preparing urea from urine depends upon this.

When the divalent oxygen atom in urea is replaced by the divalent imide radical (=NH), guanidine is obtained, the organic compound which is richer in nitrogen than all others :

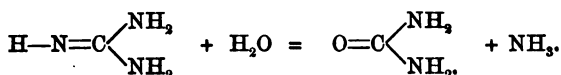


Guanidine can be prepared synthetically by the action of ammonia upon cyanamide (p. 141) :



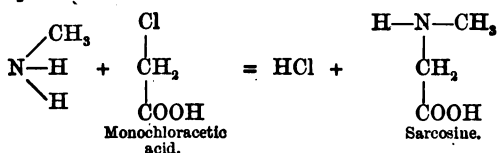
This synthesis is carried out by heating cyanamide with ammonium chloride in alcoholic solution, when the hydrochloric acid salt of guanidine is obtained, from which the free base can be prepared.

Guanidine is a colourless crystalline compound with a strongly alkaline reaction, which deliquesces and takes up carbonic acid from the air. It combines with an equivalent proportion of acid to form salts, which readily crystallise. When guanidine is boiled with baryta water it is converted into urea and ammonia with absorption of water :



Guanidine does not occur in our body, but it is of great physiological interest, because substituted guanidines occur amongst the decomposition products of the proteins, and amongst the intermediate products of metabolism : guanine, creatine, arginine, belong to the group of substituted guanidines. Guanidine was first prepared by Adolf Strecker¹ (1822–1871) from guanine, from which it obtained its name. Its preparation will be described under the chemistry of guanine (p. 162).

Creatine is that nitrogenous end-product of our metabolism which occurs in the greatest quantity in our tissues. We have in our bodies about 100 grammes, chiefly in the muscles, but also in the nervous tissues, and in the blood. Creatine is shown to be a substituted guanidine by its synthesis, and by its decomposition by baryta water, which are exactly analogous to the synthesis and decomposition of guanidine; just as guanidine is obtained by synthesis from cyanamide and ammonia, so also is creatine obtained by synthesis from cyanamide and the substituted ammonia, sarcosine. Sarcosine is glycocoll, in which one of the hydrogen atoms of the amino group is substituted by methyl. The synthetical preparation of sarcosine is exactly analogous to that of glycocoll (p. 60); it is obtained by the action of methylamine on monochloroacetic acid :



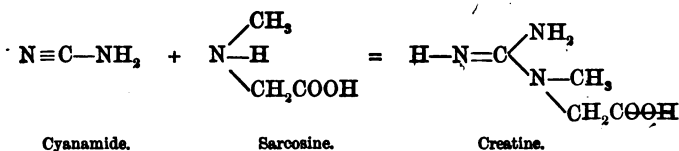
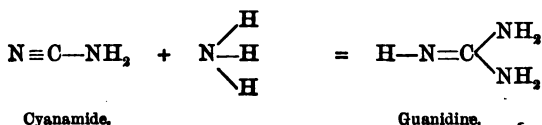
Creatine was synthesised by Volhard,² by heating an alkaline

¹ A. Strecker, *Liebig's Ann. d. Chem.* 1861, vol. cxviii. p. 159.

² J. Volhard, *Sitzungsber. d. Münchener Akad.* 1868, vol. ii. p. 472; or *Z. f. Chem.* 1869, p. 818.

solution of sarcosine and cyanamide in a sealed vessel for some hours at 100° C.; on cooling, crystals of creatine separated out. Strecker obtained it by simpler means: 'If a saturated aqueous solution of sarcosine be treated with the requisite quantity of cyanamide and a few drops of ammonia and allowed to stand in the cold, a good yield of creatine will be obtained.'¹

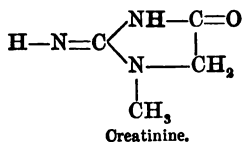
The completely analogous syntheses of creatine and guanidine can be seen from the following equations:



The decompositions of the two compounds are also exactly analogous; guanidine, on boiling with baryta water, decomposes into urea and ammonia, with absorption of water; creatine by the same treatment is converted into urea and the substituted ammonia, sarcosine.²

Sarcosine has not yet been detected in the body, but urea is probably formed there by the decomposition of creatine, since the quantity of creatine in our tissues is so great, and the amount of it which passes into the urine is, in comparison, so small.

Creatine crystallises from its solutions in rhombic prisms containing a molecule of water of crystallisation; it dissolves in seventy-four parts of cold water, much more easily in hot, scarcely at all in alcohol, and it is insoluble in ether. Its solutions react neutral to litmus. When boiled with dilute acids it loses a molecule of water, and is converted into the basic creatinine:



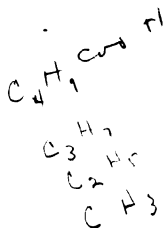
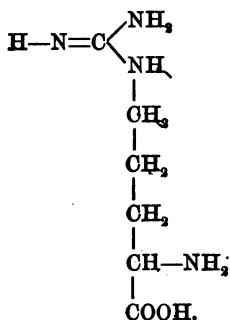
¹ A. Strecker, *Jahresber. über d. Fortschr. d. Chemie*, 1868, p. 686; also J. Horbaczewski, *Wiener Med. Jahrb.* 1885, p. 459.

² This reaction does not proceed so smoothly as expressed in the equation; bye-products consisting of methylhydantoin, ammonia, and carbonic acid are also formed. See C. Th. L. Neubauer, *Liebig's Ann. d. Chem.* 1866, vol. cxxviii. p. 294.

Creatinine is again converted into creatine in alkaline solutions, and this may account for the presence of creatinine in acid urine, and of creatine in alkaline urine.¹

Creatinine is much more soluble in water and alcohol than creatine; it forms a crystalline compound with zinc chloride which is soluble with difficulty in cold water and is insoluble in alcohol. Its presence and its amount in urine were formerly thus determined, [but Folin's recent method² is now almost exclusively used].

Arginine occurs amongst the hydrolytic decomposition products of the proteins (cf. Lecture 17), and was discovered by E. Schulze and E. Steiger³ in the cotyledons of lupine seeds. It is guanidine combined with α -aminovalerianic acid, and has the following structural formula:



This complex compound has often been obtained from proteins in the form of beautiful crystals, which are very soluble in water, and have a strongly alkaline reaction. It is not decomposed by boiling with concentrated hydrochloric acid, but it is broken down by boiling with baryta water into urea and α -, δ -, diaminovalerianic acid, which is called ornithine, as it occurs in the urine of birds, combined with benzoic acid, as ornithuric acid.⁴

Amongst the most important derivatives of urea is uric acid, a complicated compound from which two molecules of urea can easily be split off. [It is a ureide, that is a combination of urea with an acid, which is analogous in constitution to acid amides, the urea radical taking the place of the amide radical.] Its empirical formula is $\text{C}_5\text{H}_4\text{N}_4\text{O}_3$. The greater part of the nitrogen leaves the organism of reptiles and birds as uric acid, but in mammals only a small

¹ C. Voit, *Z. f. Biol.* 1868, vol. iv. p. 115.

² [O. Folin, *Z. f. physiol. Chem.* 1904, vol. xli. p. 223.]

³ E. Schulze and E. Steiger, *Z. f. physiol. Chem.* 1886, vol. ii. p. 43.

⁴ M. Jaffé, *Ber. d. d. chem. Gesellsch.* 1877, vol. x. p. 1926, and 1878, vol. xi. p. 406.

portion of the nitrogen leaves the organism in this form. In man its quantity reaches 0.5 to 1 gramme in the twenty-four hours, whereas the quantity of urea in the urine is 40 grammes or more in that time. In whatever form nitrogen be taken in by birds, it always appears in the urine as uric acid; if, e.g., urea be given, a corresponding increase in the amount of uric acid appears in the urine; if uric acid be given to dogs, it appears in the urine as urea. Up to the present time no *chemical* explanation has been found for this difference in metabolism between birds and mammals; it can be explained *teleologically* by the insolubility of uric acid; at the body temperature a gramme of uric acid requires seven litres of water for its solution, and consequently the greater part of the uric acid is excreted by birds and reptiles in a solid form, in microscopically small crystals. No danger is attached to this, since in both these classes of animals the ureters open into the cloaca, and the solid uric acid can be passed out by the pressure of the contents of the intestines. But if in mammals uric acid separates out in the urinary passages, painful symptoms must ensue, and consequently the quantity of uric acid in mammals is so small.

The small quantity of uric acid in the metabolism of man is pathologically of much importance; in man under abnormal conditions uric acid can separate out, not only in the urinary passages, but also as urates in the tissues and in the joints, when it gives rise to the painful symptoms of gout.

In order to regulate metabolism and reduce the formation of uric acid, its constitution must first be known, for then only can a satisfactory answer be obtained to the many questions involved in the ætiology and therapy of the uric acid diathesis.

Great difficulties have been encountered in the study of the structure of uric acid, just as with all nitrogen compounds (p. 146), and during the last eighty years it has been carefully investigated by Woehler,¹ Liebig,² Baeyer,³ Strecker,⁴ Kolbe,⁵ Medicus,⁶ Hill,⁷ Horbaczewski,⁸ Emil Fischer,⁹ etc.

¹ Woehler, *Poggendorff's Ann. d. Chem.* 1829, vol. xv. p. 119; Woehler and Liebig, *Ann. d. Chem. u. Pharm.* 1838, vol. xxvi. p. 241.

² Liebig, *Poggendorff's Ann. d. Chem.* 1829, vol. xv. p. 569; *Ann. d. Chem. u. Pharm.* 1833, vol. v. p. 288.

³ A. Baeyer, *Liebig's Ann. d. Chem.* 1863, vol. cxxvii. pp. 1 and 199.

⁴ Ad. Strecker, *Liebig's Ann. d. Chem.* 1868, vol. cxlvi. p. 142, and 1870, vol. clv. p. 177.

⁵ A. W. H. Kolbe, *Ber. d. d. chem. Gesellsch.* 1870, vol. iii. p. 183.

⁶ L. Medicus, *Liebig's Ann. d. Chem.* 1875, vol. clxxv. p. 230.

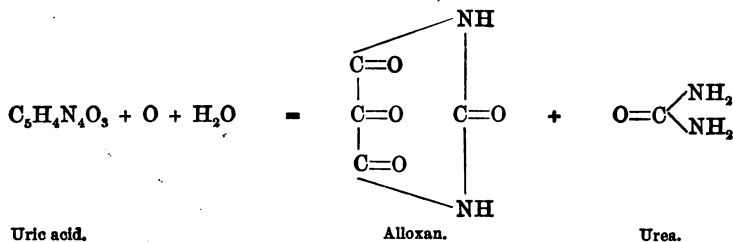
⁷ H. B. Hill, *Ber. d. d. chem. Gesellsch.* 1876, vol. ix. p. 370, and 1878, vol. xi. p. 1329.

⁸ J. Horbaczewski, *Sitzungsber. d. Wien. Akad.* 1882, vol. lxxxvi. p. 936, or *Monatshefte f. Chem.* 1882, vol. iii. p. 796, and 1885, vol. vi. p. 356.

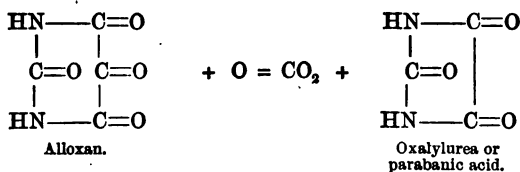
⁹ E. Fischer, *Ber. d. d. chem. Gesellsch.* 1884, vol. xvii. pp. 328 and 1776.

The study of its products of decomposition and of oxidation by nitric acid gave an especially valuable insight into its constitution.

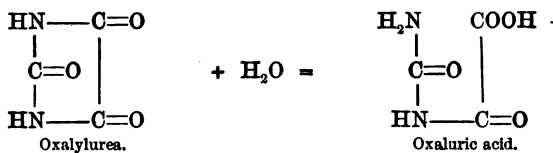
When uric acid is acted upon by nitric acid at the ordinary temperature it breaks down into alloxan and urea :



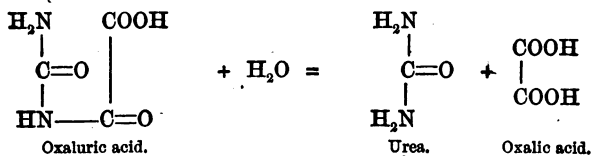
and alloxan, when heated with nitric acid, is converted into oxalylurea and carbonic acid :



Oxalylurea, when gently warmed with dilute alkalis, takes up a molecule of water, and passes into oxaluric acid :



and when oxaluric acid is heated with alkalis for a long time, it takes up a second molecule of water, and is broken down into oxalic acid and urea :

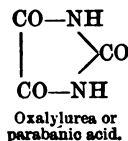
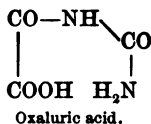
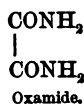
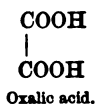


Oxaluric acid is found in small quantities in human urine.¹

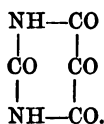
[Parabanic acid and oxaluric acid are ureides, i.e. compounds of

¹ E. Schunck, *Proc. Roy. Soc.* 1866, vol. xv. p. 259; 1866, vol. xvi. p. 140.
C. Neubauer, *Z. f. anal. Chem.* 1868, vol. vii. p. 225.

urea with acids. They are analogous to the amides, especially those of the dibasic acids, e.g.:

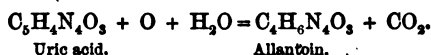


Alloxan is the ureide of mesoxalic acid:



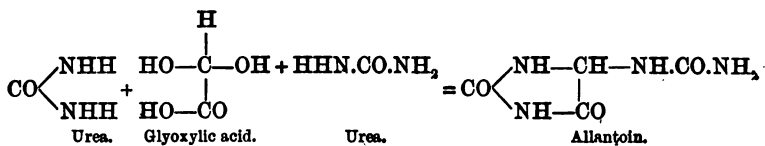
The following decompositions of uric acid should be noticed, since products are formed which play a rôle in animal metabolism.

By the action of a solution of potassium permanganate at the ordinary temperature, uric acid breaks down, with absorption of water, into allantoin and carbonic acid: ¹



Allantoin was discovered by Vauquelin² in the allantoic fluid of cows. Woehler³ found it in the urine of calves, and it was studied in more detail by him and Liebig.⁴ Later, this compound was found in the allantoic fluid, and in the urine of new-born children; it is sometimes found in dog's urine.⁵

[Allantoin is a diureide of glyoxylic acid, and is obtained by heating this substance with urea:



¹ A. Claus, *Ber. d. d. chem. Gesellsch.* 1874, vol. vii. p. 227.

² Buniva and Vauquelin, *Ann. de Chim.* 1799, vol. xxxiii. p. 269. Cf. Lassaigne, *Ann. de Chim. et de Phys.* 1821, vol. xvii. p. 301.

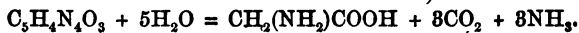
³ Woehler, *Nachrichten von d. k. Gesellsch. d. W. zu Göttingen*, 1849, p. 61.

⁴ Woehler and Liebig, *Ann. d. Chem. u. Pharm.* 1838, vol. xxvi. p. 244.

⁵ E. Salkowski, *Ber. d. d. chem. Gesellsch.* 1876, vol. ix. p. 719; 1878, vol. xi. p. 500.

Allantoin probably represents one of the stages in the oxidation of uric acid in the body; uric acid has recently been found by Wiechowski¹ to be converted into allantoin by the oxidising action of the liver.]

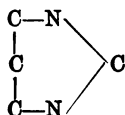
Ad. Strecker² showed that uric acid, when heated in a sealed tube to 170° C., is split up into glycocoll, carbonic acid, and ammonia, with absorption of water :



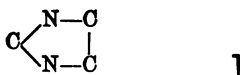
This decomposition led J. Horbaczewski,³ in Ludwig's laboratory, to attempt to synthesise uric acid by heating glycocoll with urea; on heating these two compounds at 220 to 230° C., he found in the fused mass, together with other products, 5 to 15 per cent. of the weight of the glycocoll employed as uric acid,

It follows from these products of decomposition, that the molecule of uric acid contains two molecules of urea, which are combined with an acid containing three atoms of carbon.

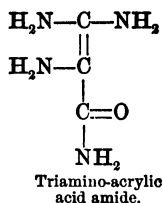
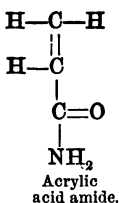
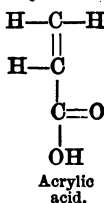
[The formation of alloxan indicates the presence of the complex



and of allantoin that of



Acrylic acid (p. 98) is an acid containing three carbon atoms, and if we imagine that the hydroxyl of the carboxyl group in this acid is substituted by the amino radical NH_2 , the amide of acrylic acid is obtained. Further, if the three hydrogen atoms of acrylic acid, which are attached to the carbon atoms, be replaced by NH_2 , we obtain triamino-acrylic acid amide :

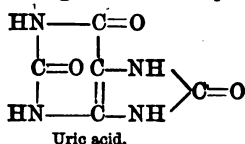


¹ [W. Wiechowski, *Beitr. chem. Physiol. Path.* 1907, vol. ix. p. 295.]

² Ad. Strecker, *Liebig's Ann. d. Chem.* 1868, vol. cxlvi. p. 142.

³ J. Horbaczewski, *Sitzungsber. d. Wien. Akad.* 1882, vol. lxxxvi. p. 963; or *Monatshefte f. Chem.* 1882, vol. iii. p. 796, and 1885, vol. vi. p. 356.

and if now the four NH_2 radicals be substituted by the four ammonia residues of two molecules of urea, we obtain the structural formula of uric acid which was first put forward by Medicus :



All the reactions of uric acid, [as well as the products of its oxidation], agree with this formula, and also its synthesis from trichlorolactic acid and urea, which was carried out by Horbaczewski.¹

Uric acid generally crystallises in microscopic, colourless, rhombic plates or prisms ; if it separates from the urine it carries down colouring matter with it, and then forms larger, incompletely formed, whetstone-like, red-brown crystals. One gramme of uric acid requires for its solution at the ordinary temperature about forty litres of water, at the body temperature seven litres, and at boiling point about two litres. Its aqueous solution is acid to litmus. Uric acid is insoluble in alcohol and ether. Two of its hydrogen atoms are replaceable by metals ; when it is dissolved in caustic soda, the neutral salt of the composition $\text{C}_5\text{H}_2\text{N}_4\text{O}_3\text{Na}_2$ is obtained. This salt does not occur in the body, nor does it exist in nature. When uric acid is dissolved in excess of sodium carbonate, it always forms the acid salt of the composition $\text{C}_5\text{H}_3\text{N}_4\text{O}_3\text{Na}$, which is soluble with difficulty in water, one gramme at the ordinary temperature requiring more than a litre for its solution. Still more insoluble is the acid ammonium salt. Both these salts are often found in urinary sediments, the ammonium salt in the form of the characteristic, incompletely crystalline masses, the so-called hedgehog spines, and the sodium salt as an amorphous precipitate, which, like free uric acid, carries down with it the brown-red colouring matter ; it is therefore known in medicine as *Sedimentum lateritium*, or brick-dust deposit.

Uric acid dissolves in nitric acid with effervescence ; if the solution be evaporated to dryness it leaves a red residue, which on the addition of a drop of ammonia becomes purple, and on the addition of a drop of caustic soda violet-blue. This is known as the 'murexide' reaction and is the most delicate test for uric acid.

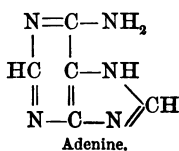
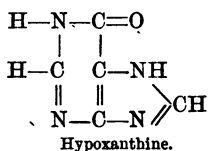
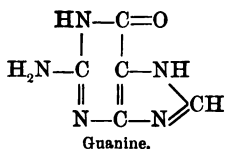
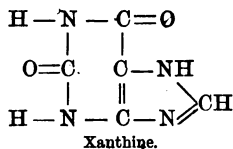
Very widely distributed in the body, especially in the nuclei of cells, are found four bases, rich in nitrogen, whose close relationship

¹ J. Horbaczewski, *Sitzungsber. d. math. natw. Cl. d. k. Akad. d. W. in Wien* 1887, vol. xev. pt. 2, p. 825, and 1888, vol. xevi. pt. 2, p. 849 ; or *Monatshefte f. Chem.* 1887, vol. viii. pp. 201, 548.

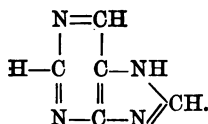
to uric acid is shown by their empirical formulæ; these are xanthine, hypoxanthine or sarkine, guanine and adenine.

Uric acid	$C_5H_4N_4O_3$
Xanthine	$C_5H_4N_4O_2$
Hypoxanthine	$C_5H_4N_4O$
Guanine	$C_5H_5N_5O$
Adenine	$C_5H_5N_5$

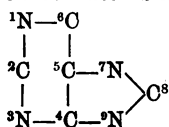
Emil Fischer has succeeded in preparing all these bases artificially from uric acid, and he assigns to them the following structural formulæ:



[He regards them as derivatives of purine, to which he assigns the formula



All these compounds thus possess the following complex of atoms, in which the nitrogen and carbon atoms are numbered in order



Uric acid	is thus 2, 6, 8, trioxypurine
Xanthine	„ „ 2, 6, dioxypurine
Hypoxanthine	„ „ 6, monoxypurine
Guanine	„ „ 2, amino- 6, oxypurine
Adenine	„ „ 6, aminopurine.

The hydrogen atoms become attached to the nitrogen atoms when the carbon atoms have oxygen attached to them; in this way, the nitrogen and carbon atoms remain trivalent, and tetravalent, respectively. The double bonds, except those between carbon atoms 4 and 5, do not here behave as in unsaturated compounds.]

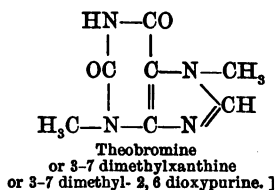
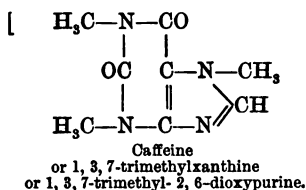
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Xanthine is constantly found in small quantities in human urine; it is almost insoluble in water, and sometimes forms calculi. When oxidised by nitric acid it gives, like uric acid, alloxan, and when acted upon by fuming hydrochloric acid, glyccoll; on evaporating the nitric acid solution it leaves a golden yellow residue—hence its name from the Greek *ξανθός*, yellow—which, on the addition of a drop of caustic soda, becomes red. By this very delicate reaction the rarely occurring xanthine stones can be distinguished from all others.

Guanine is converted into xanthine by the action of nitrous acid (p. 62), and it gives the same colour reactions as xanthine, when evaporated with nitric acid. Guanine is, as previously mentioned (p. 153), a substituted guanidine. This is expressed in Fischer's formula, and follows from the following reaction: by the action of hydrochloric acid and potassium chlorate, guanine is decomposed into carbonic acid, parabanic acid, and guanidine. Guanine occurs in large quantities in guano. Fish scales owe their peculiar glitter to its calcium compound, which is deposited in them in small crystals.

Adenine was discovered by Kossel,¹ first in the pancreas, and later in many other tissues. It is a polymer of prussic acid, and is related to hypoxanthine in the same way as guanine is to xanthine; it is converted into hypoxanthine by nitrous acid.

Closely related to xanthine is the active constituent of our favourite drinks, tea and coffee, which contain the base theine or caffeine; it is xanthine in which three hydrogen atoms have been replaced by methyl radicals. The crystalline compound, theobromine, is found in cocoa beans; this is also xanthine, in which two hydrogen atoms have been replaced by methyl radicals. Both theobromine and theine can be artificially prepared from xanthine. Xanthine contains three hydrogen atoms, which can be substituted by metals, and when its divalent lead salt is prepared and heated with methyl iodide, theobromine, or dimethylxanthine, is obtained. The silver salt of theobromine, on treatment with methyl iodide, yields caffeine, or theine (methyltheobromine or trimethylxanthine):



¹ A. Kossel, *Z. f. physiol. Chem.* 1886, vol. x. p. 250, and 1888, vol. xii. p. 241.

LECTURE XII

THE AROMATIC COMPOUNDS

BENZENE AND ITS OXIDATION PRODUCTS

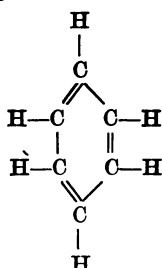
WE pass now to the second main group of carbon compounds, the Aromatic Group, so called in contradistinction to the Fatty or Aliphatic Compounds, the general name applied to all those compounds so far described. The designation 'aromatic compounds' has been unfortunately chosen, because aromatic pleasant-smelling substances, as well as those without smell, and those with a bad smell, occur amongst both groups of the carbon compounds. The aromatic compounds differ from those of the aliphatic series in possessing a common radical, *a nucleus composed of six carbon atoms* firmly linked together, which enter as a group into other compounds, are split off in the same combined manner, and are difficult to separate from each other.

Eighteen of the twenty-four valencies of the six atoms of carbon are used up in linking the carbon atoms to each other, and only six remain over for combining with other elements. The nucleus of carbon atoms is, therefore, a hexavalent radical, and if all its six valencies be saturated by hydrogen, we have the simplest aromatic hydrocarbon, benzene, C_6H_6 , which is the mother substance of the whole aromatic group of carbon compounds. All the aromatic compounds can be derived from benzene, just as all the aliphatic compounds can be derived from methane.

There are many very different conceptions as to how the six carbon atoms are linked together, and it is still undecided which is most in unison with the facts of the chemical processes, i.e. the various substitutions and reactions, and which will lead to the discovery of new chemical facts. The hypothesis of Kekulé¹ (1829–1896) enunciated in 1865, has been the most copious in results. Kekulé

¹ F. A. Kekulé, *Liebig's Ann. d. Chem.*, 1866, vol. cxxxvii. p. 129 ; *Textbook of Organic Chemistry* (Stuttgart, 1861–1882), vol. ii.

supposed that the six carbon atoms formed a *closed chain* or *ring*, the atoms themselves being bound together alternately by a double linking and a single linking :

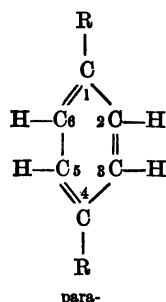
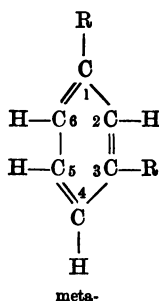
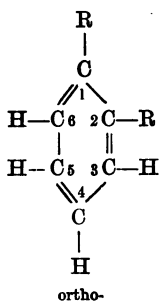


Benzene.

Kekulé's formula shows, firstly, that the benzene nucleus is hexavalent. Each carbon atom has three of its four valencies used up in linking with its neighbouring atoms, and only one remains over for combination with other elements or radicals.

The formula shows, secondly, that the six hydrogen atoms of benzene are 'equi-valent,' that is, when one of them has been substituted by another atom or radical, only *one* mono-derivative can be obtained under any conditions. According to the hypothesis, the six hydrogen atoms are equally divided amongst the six carbon atoms, which are joined together in a similar way. More than one mono-chloro-, monobromo-, mononitro-, monoamido-, monomethyl-, etc. derivative of benzene has never been prepared. *There are no isomeric mono-derivatives of benzene.*

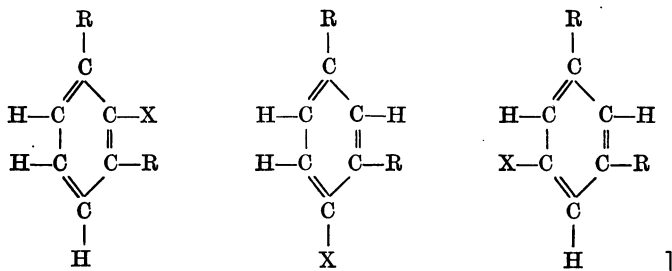
Thirdly, the hypothesis explains the fact that the di-substituted derivatives of benzene always exhibit three isomers: when two hydrogen atoms are substituted by other elements or radicals, three isomeric compounds, called the ortho-, meta-, and para- compounds, designated shortly by the letters *o*-, *m*-, *p*-, are obtained :



The hypothesis does not allow of more isomers, and as a matter of fact no others have ever been obtained, either when the two substituting radicals are the same, as in dimethylbenzene, or when the two substituting radicals are different, as in methylamido-benzene.

The six carbon atoms, and the hydrogen atoms attached to them, are numbered in the formulæ. An ortho-position is that in which any hydrogen atom, such as that numbered 1, is substituted at the same time as that numbered 2, or as that numbered 6, [i.e. when two adjacent carbon atoms are substituted, such as 2 and 3, 4 and 5, 5 and 6.] A meta-position is that in which 1 and 3, or 1 and 5 [or 3 and 5, 2 and 6, or 2 and 4] are substituted; [i.e. when alternate carbon atoms are substituted.] A para-position is that in which each hydrogen atom has only *one* other appertaining to it, 1 and 4, 2 and 5, 3 and 6; [i.e. when every third carbon atom is substituted.]

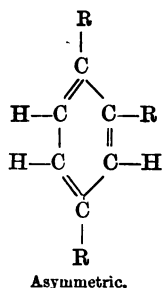
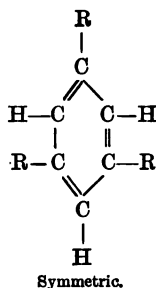
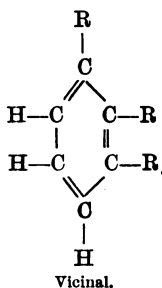
It is theoretically easy to determine, which of the three isomeric di-substituted derivatives with similar radicals is the ortho-, or the meta-, or para-compound, for it is only necessary to introduce a third radical into the molecule and to ascertain how many isomeric tri-substitution products can arise thereby. If e.g. another radical enters the para-compound (1, 4), only one arrangement is possible, since the atoms 2, 3, 5, and 6 have all the same relationship in the molecule. If another radical enters the ortho-compound (1, 2), two isomers are possible, since the atoms 3 and 6 have a different position in the molecule to the atoms 4 and 5. In the case of the meta-compound, as can easily be seen, three isomers are possible when a third radical enters the molecule, [thus :



The experimental details of these investigations are naturally very tedious, and are attended with many difficulties, but experiments have been carried out in the case of many isomeric di-substitution products, and the facts fully confirm the *a priori* theoretical assump-

tions. Here again the structural theory has achieved a great triumph.

Fourthly, Kekulé's theory entirely agrees with the observations concerning the isomeric tri-substitution derivatives. According to his theory, when three similar radicals substitute the hydrogen atoms, only three isomers, and no more, are possible. The three positions in the ring for these isomers are the adjacent or vicinal (*v*), the symmetric (*s*), and the asymmetric (*a*) :



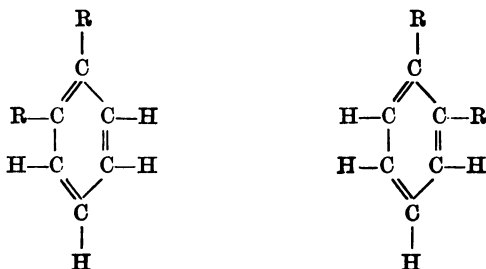
and, as a matter of fact, only three tri-substitution derivatives, with similar radicals, have ever been prepared. If the three substituting radicals be different, the number of isomers is naturally much greater.

These, and many other facts, agree entirely with Kekulé's hypothesis, but some chemists have brought forward certain facts which are in opposition to Kekulé's benzene ring theory, especially to the assumption of the three double linkings.

The unsaturated compounds of the fatty series in which a double linking between two carbon atoms is assumed, such as ethylene, allyl alcohol, and acrylic acid, possess the property of very easily *adding on* two atoms of bromine at the ordinary temperature, without the separation of hydrogen atoms, i.e. without the formation of hydrobromic acid, in contradistinction to the saturated compounds, in which the hydrogen atom is *substituted* by halogen (see pp. 34 and 98). If Kekulé's assumption of three double linkings in the benzene nucleus be correct, benzene should add on six atoms of bromine at the ordinary temperature without the aid of any active force, but this is not the case, as the addition of bromine occurs only in direct sunlight.

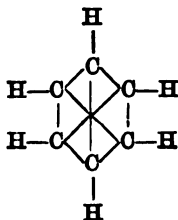
Again, according to Kekulé's theory, two ortho-compounds of all di-substituted derivatives must be possible; in one of them the two neighbouring carbon atoms to which the radicals are attached

will be linked together by a double bond, in the other by a single bond :



but, as a matter of fact, only *one* ortho-compound of the di-substituted compounds can be obtained.

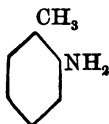
These, and similar reasons, have compelled many chemists to relinquish Kekulé's formula, and to assume, instead of the three double linkings and the three single linkings, nine single linkings, and they accordingly write the benzene formula as follows :



This formula explains the above four facts as well as that of Kekulé's. Most chemists nowadays avoid any definite hypothesis concerning the structure of the benzene ring, and they represent the nucleus only by a simple hexagon :

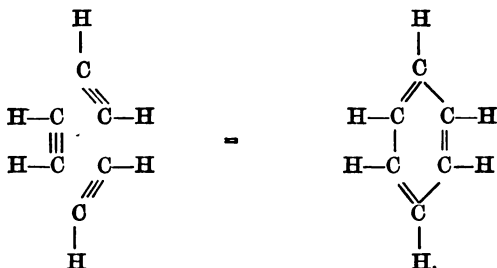


A carbon atom and a hydrogen atom are assumed to be present at each angle ; and only the radicals which substitute the hydrogen atoms are represented, e.g. ortho-methylamidobenzene is written thus :



In the description of the discoveries made in synthetic chemistry

a method of synthetically preparing benzene was given (p. 6). Acetylene can be obtained by the direct combination of its elements, and when it is passed through a red-hot tube, it polymerises to benzene:



The reverse process takes place if the vapours of pure benzene be passed through red-hot tubes, a portion of the benzene breaking down into molecules of acetylene; the reaction, however, is never complete.

Benzene at the ordinary temperature is a colourless liquid with an aromatic smell; it boils at 80.5°C ., and solidifies to a crystalline mass when cooled to 0°C . It burns with a smoky flame, is not miscible with water but floats on it, and is an excellent solvent for resins, fats, sulphur, etc.

On the large scale benzene is obtained from coal-tar. Coal is not pure carbon, but contains compounds of carbon with hydrogen, oxygen, nitrogen, etc. Even in the oldest coal—anthracite—the process of carbonisation is not complete, for it contains 10 to 20 per cent. of other elements, and the more recent coals contain from 20 to 40 per cent., and brown coal even up to 70 per cent. When coal is submitted to dry distillation for the preparation of illuminating gas, products arising in the distillation process, which are not gaseous at the ordinary temperature, condense in the receivers, where they form two layers, just as occurs in the dry distillation of wood (p. 56), an aqueous layer, the so-called 'gas water,' and a layer, which is not miscible with water, coal-tar. A portion of the coal also remains behind in the retorts as coke, which is used as a fuel and in metallurgical processes. The gas water differs from the aqueous product of condensation obtained by the distillation of wood in its alkaline reaction; it smells of ammonia, whereas the aqueous distillate from wood contains acetic acid (p. 57) as its chief constituent.

Coal-tar is a thick black mass; its black colour comes chiefly from finely divided admixed coal, which may make up 10 to 30 per cent. of

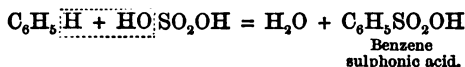
the whole quantity. The remainder consists for the most part of aromatic compounds, which were not all pre-formed in the coal, the majority having arisen by condensation of carbon compounds of the fatty series, by the high temperature of the distillation retorts. The condensation of acetylene into benzene has just been mentioned, and it has been shown by direct experiment that marsh gas, ethylene, alcohol, acetic acid, and many other simple organic compounds of the aliphatic series, are also converted into aromatic compounds at high temperatures by the splitting off of hydrogen and the separation of carbon.

Up to the present time over forty different aromatic compounds have been isolated from coal-tar; and together with these, small quantities of compounds belonging to the fatty series have also been found. The various constituents of coal-tar are first separated by fractional distillation, different methods being in use in different works. The products of distillation, which pass over at temperatures up to $170^{\circ}\text{C}.$, are generally first collected. This distillate is specifically lighter than water, and is known as 'light coal-tar' or 'light oil'; it consists chiefly of benzene and its next homologues—methylbenzene or toluene, dimethylbenzene or xylene, and trimethylbenzene. Then, when the temperature is raised to $270^{\circ}\text{C}.$, an oily liquid distils over; this sinks in water and is called 'heavy coal-tar' or 'heavy oil,' and it contains chiefly phenol, cresol, naphthalene, aniline, pyridine, and quinoline. At still higher temperatures, more complex hydrocarbons pass over, and of these anthracene is the most important. Finally, pitch remains behind in the retorts and constitutes 50 to 60 per cent. of the tar; it cannot be distilled without decomposition, and has not yet been separated into chemically well-characterised substances. It is used technically in the preparation of briquettes (carbon bricks), for asphaltting roofs, varnishes, etc.

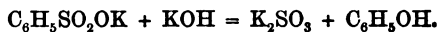
The light coal-tar is shaken with acids and alkalis, in order to separate the admixed basic and acid substances, and then again fractionally distilled. At a temperature between 80 and $85^{\circ}\text{C}.$ almost pure benzene passes over, which is further purified by cooling to -5 to $-10^{\circ}\text{C}.$ and crystallising, and the crystals are then pressed between cold filter-paper.

If we wish to prepare from benzene its hydroxyl derivative, oxybenzene or phenol, the method which is used in the synthetical preparation of alcohol from the saturated hydrocarbons—i.e. (pp. 4 and 45) by first substituting a hydrogen atom by chlorine or bromine, and then, by the action of potassium hydroxide or silver hydroxide, replacing the halogen atom by an hydroxyl group—cannot be used.

Monochlorobenzene and monobromobenzene can, however, be easily prepared; when chlorine is passed into benzene, in which a little iodine has been dissolved, chlorobenzene is formed, the iodine acting as a carrier in the process. Bromobenzene is obtained in the same way, when a little iodine is added to a mixture of benzene and bromine. In these compounds the halogen atom is firmly bound, and cannot be exchanged for hydroxyl by the action of moist silver oxide or potassium hydroxide, and hence another method for preparing oxybenzene has been devised. This consists in first preparing the sulphonic acid of benzene, and then decomposing it by the action of potassium hydroxide. Benzene sulphonic acid is formed when benzene is heated with concentrated sulphuric acid in a retort under a reflux condenser :



When the potassium salt of the sulphonic acid is fused with potassium hydrate, potassium sulphite and oxybenzene are obtained :



If benzene be administered to the animal body, it is oxidised to oxybenzene.¹ Outside the body oxygen does not attack benzene, and this led to the supposition that in the body ozone, or nascent oxygen, was the active principle, since Nencki² showed that outside the animal body ozone can oxidise benzene to oxybenzene. Atmospheric oxygen in the presence of ferrous oxide, or cuprous oxide, can also effect this oxidation ;³ in this process it may be supposed that the ferrous oxide combines with one of the two oxygen atoms of an oxygen molecule, and that the other free atom then oxidises the benzene to oxybenzene.

Palladium hydrogen can play the same rôle as the ferrous, or cuprous, oxide. The English chemist Graham (1805–1869) showed that when palladium foil is used as the negative electrode in the electrolysis of water, no hydrogen is evolved from it, and that the hydrogen combines with the palladium, which takes up 900 times its volume of the gas with a simultaneous increase of its own volume. This compound gradually liberates a portion of the hydrogen, and behaves as nascent hydrogen. When, therefore, palladium hydrogen comes into contact with atmospheric oxygen, the hydrogen is

¹ Schultzen and Naunyn, *Du Bois' Arch.* 1867, p. 349.

² Nencki and Giacosa, *Z. f. physiol. Chem.* 1880, vol. iv. p. 339.

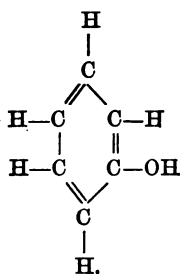
³ Nencki and Sieber, *Journ. f. prakt. Chem.* 1882, vol. xxvi. pp. 24 and 25.

oxidised and a portion of the oxygen becomes 'active'; and if benzene be present it is oxidised to phenol, just as it is by ozone.¹

On the large scale oxybenzene, or phenol, is prepared from heavy coal-tar, by extracting it with caustic soda and then fractionally distilling.

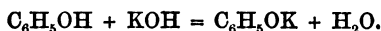
Pure phenol consists of colourless crystals, which melt at 42° C. and boil at 180° C. They take up water from the air, and are converted into a red-brown liquid; if mixed with water, this sinks to the bottom in the form of heavy drops. At the ordinary temperature phenol is soluble in fifteen parts of water, and the solution is coloured violet by ferric chloride.

Oxybenzene is a tertiary alcohol (p. 71), as the following formula clearly shows :



C₆H₅OH

Hence it also bears the name phenyl alcohol, phenyl being the monovalent radical C_6H_5 . That phenyl alcohol is a tertiary alcohol follows from the fact that it, like all tertiary alcohols, cannot be oxidised to an aldehyde, ketone, or acid, and that it is an alcohol is shown by its combination with acids to form esters. Thus, phenyl alcohol, which is formed by the oxidation of benzene in the animal body, appears as the potassium salt of its acid ester with sulphuric acid in the urine, as potassium phenyl sulphate $\text{C}_6\text{H}_5\text{O}.\text{SO}_2.\text{OK}$. Phenyl alcohol differs from the alcohols of the fatty series, in that the hydrogen atom of its hydroxyl group is easily replaceable by metals [when treated with caustic alkali] :



The alcohols of the fatty series—e.g. ethyl alcohol—do not possess this property. The hydrogen atom of the hydroxyl group in ethyl alcohol can only be replaced by potassium or sodium, when the

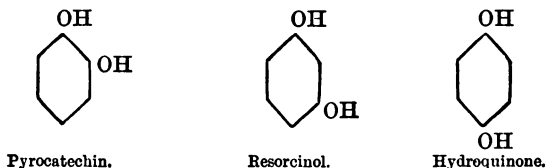
¹ Hoppe-Seyler, *Z. f. physiol. Chem.* 1878, vol. ii. p. 22; 1886, vol. x. p. 35; *Ber. d. d. chem. Gesellsch.* 1879, vol. xii. p. 1551; 1883, vol. xvi. pp. 117 and 1917.

metals themselves are allowed to act upon it. The aromatic alcohols have therefore the character of acids, and, consequently, phenyl alcohol is also called carbolic acid, by which name it is almost exclusively known in medicine: but chemists now designate the hydroxyl derivatives of the aromatic hydrocarbons neither as alcohols nor as acids, but have introduced for them the special name of Phenols.

Carbolic acid is, as is well known, an energetic disinfectant, and formerly was much employed as an antiseptic in the treatment of wounds, but nowadays its place has been taken by other antiseptics, for the following reasons: Carbolic acid, if not used in a very dilute solution, acts as a caustic, and causes necrosis of the skin and of the surfaces of wounds; its unpleasant, penetrating, and persistent smell is tiresome to the patient and his surroundings, and there is also the danger that it may be absorbed from the wound surface. It is a deadly poison; when taken internally large doses produce gastro-enteritis, and, after absorption, severe brain symptoms. Phenol when introduced into the body appears in the urine partly as the alkali salt of phenylsulphuric acid, which is not poisonous, and, for this reason, Baumann suggested sodium sulphate as an antidote to phenol in cases of poisoning.

Sodium phenylsulphate occurs in the urine of mammals, not only after the administration of phenol, or benzene, but also as a constant constituent; it occurs in large quantities in the urine of the herbivora, and in small quantities in the urine of man; the greater part arises from the decomposition of the aromatic constituents of the proteins (cf. Lecture 17).

When two hydrogen atoms in benzene are substituted by two hydroxyl groups, three isomers are obtained, the ortho-, meta-, and para-dioxybenzenes, which are generally known as pyrocatechin, resorcinol, and hydroquinone:



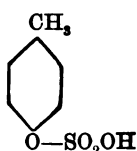
Of these three isomers, pyrocatechin is always found in horses' urine, and often in human urine; like phenol, it occurs as the alkali salt of the conjugated sulphuric acid. Hydroquinone-sulphuric acid has been observed in the urine after the administration of phenol.

Together with oxybenzene and dioxybenzene, methoxybenzene,

or cresol, combined with sulphuric acid is found in the urine, and of the three isomers chiefly para-cresol:



Para-cresol.

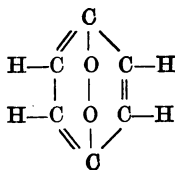


Para-cresol-sulphuric acid.

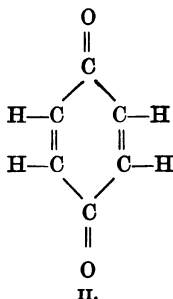
although ortho-cresol is found in small quantities; it is not yet certain whether meta-cresol-sulphuric acid occurs in the animal body.

If hydroquinone be treated with oxidising agents—chromic acid, ferric chloride—it loses two atoms of hydrogen and is converted into quinone, a compound which crystallises in yellow prisms having a characteristic pungent odour. Conversely, quinone can easily be transformed into hydroquinone by reduction. The other two dioxy-benzenes do not yield quinones on oxidation.

Theoretically, quinone is a very interesting compound. Its empirical formula is $C_6H_4O_2$, but chemists are not unanimous with regard to its constitution; of the many suggested constitutional formulæ, the following two may be put forward:

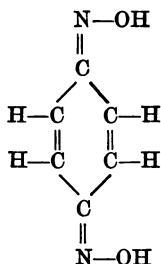


I.

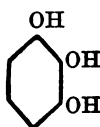


II.

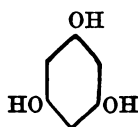
The second formula agrees with the fact that quinone easily adds on four atoms of bromine, and behaves like a diketone, e.g. it combines with two molecules of hydroxylamine (NH_2OH), with the loss of two molecules of water, forming quinone dioxime:



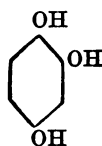
When three hydrogen atoms in benzene are replaced by three hydroxyl groups, we again obtain three isomers, the three hydroxyl groups being placed either vicinally, symmetrically or asymmetrically (p. 166). The three isomers are known as pyrogallol, phloroglucinol, and oxyhydroquinone :



Pyrogallol.



Phloroglucinol.



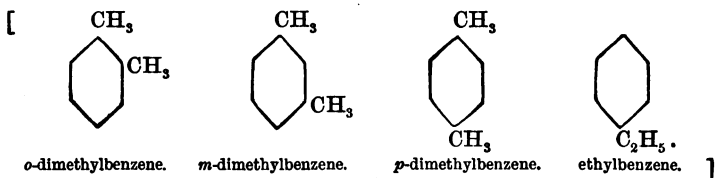
Oxyhydroquinone.

Of these three isomers, pyrogallol is of practical importance; on account of its antiseptic properties it is used as an external remedy; internally it is very poisonous. Pyrogallol is also called pyrogallie acid, as, like all phenols, it has acid properties, i.e. contains hydrogen atoms capable of substitution by metals (p. 171). It is prepared from gallic acid (p. 184), and crystallises in colourless platelets which melt at 132°C. , and sublime without decomposition; it is soluble in water and is an energetic reducing agent; upon which property depends its use as a developer in photography. In alkaline solution it eagerly absorbs oxygen from the air and becomes brown, and hence is used in gas analysis [for the estimation of oxygen].

LECTURE XIII

THE HOMOLOGUES OF BENZENE AND THEIR OXIDATION PRODUCTS

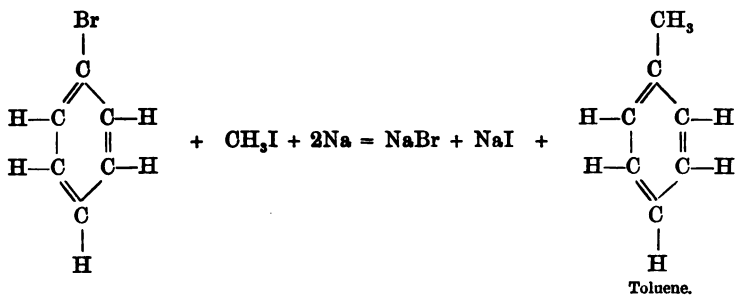
WHEN the hydrogen atoms in benzene are substituted by saturated hydrocarbon radicals, we obtain an endless series of hydrocarbons of the general formula C_nH_{2n-6} , which can be regarded as an homologous series in which many isomers are possible. If e.g. the hydrogen atoms be replaced by two methyl radicals, we obtain the three so-called 'position isomers' or the ortho-, meta-, and para-dimethylbenzenes; a fourth isomer is the mono-substituted derivative, ethylbenzene:



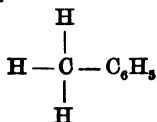
If three methyl radicals replace three hydrogen atoms, we obtain eight isomers: the vicinal, the symmetric, and the asymmetric trimethylbenzenes, the ortho-, meta-, and para-methyl-ethyl-benzenes, normal propylbenzene, and isopropylbenzene. On the further substitution of a still larger number of hydrogen atoms by different hydrocarbon radicals, the number of possible isomers increases very rapidly.

The first homologue of benzene, methylbenzene or toluene, is a constituent of light coal-tar (p. 169), from which it is obtained by fractional distillation. It can be obtained synthetically by the general method for linking saturated hydrocarbon chains to a benzene nucleus, by the method frequently used in the fatty series, whereby we can ascend from simple hydrocarbons to more complicated ones [p. 44].

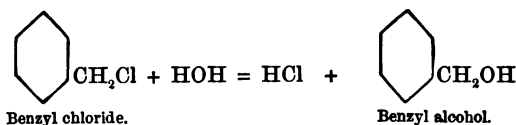
A mixture of bromobenzene and alkyl bromide or iodide is treated in ethereal solution with sodium :



Toluene can be equally well regarded as a substituted methane, or as a substituted benzene, as phenylmethane or methylbenzene, and the formula can be written :



Toluene is a colourless liquid which boils at 110°C . If chlorine be passed into boiling toluene, one of the hydrogen atoms of the side chain is substituted by chlorine,¹ and we can now carry out all the reactions which have been described in the aliphatic series of hydrocarbons; thus, by boiling with water the chlorine can be replaced by hydroxyl, when benzylalcohol is obtained. The monovalent radical $\text{C}_6\text{H}_5\cdot\text{CH}_2$ is known as benzyl, and it behaves in most reactions like the alkyl radicals of the fatty series :

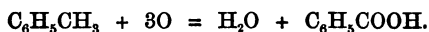


Benzylalcohol is a primary alcohol; on oxidation it yields firstly an aldehyde, and then an acid :



¹ [By side chain is understood the hydrocarbon radical, which replaces a hydrogen atom in the benzene ring. These compounds therefore consist of a benzene nucleus, which behaves like benzene in its reactions, and a hydrocarbon radical, which behaves like the saturated hydrocarbons.]

Benzaldehyde when treated with nascent hydrogen is again converted into benzylalcohol; it absorbs oxygen easily from the air, and becomes changed into benzoic acid. Benzoic acid can also be obtained directly from toluene by oxidation with chromic acid, the methyl group of the side chain being converted into the carboxyl radical:



[All side chains, however long, are ultimately oxidised to the carboxyl radical, the benzene nucleus alone remaining unattacked.]

Another synthetical method for preparing benzoic acid has been already described (p. 7).

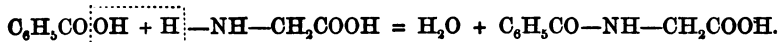
Benzaldehyde has been met with under the glucosides, i.e. the compounds, which are decomposed into sugar and certain other constituents, with absorption of water (cf. Lecture 9). The glucoside amygdalin is found in bitter almonds, which breaks down into glucose, prussic acid, and benzaldehyde, and on this account benzaldehyde bears the name 'oil of bitter almonds.' It is a colourless liquid with a very pleasant aromatic smell, which boils at 179° C. On standing in the air, or when contained in vessels which it does not completely fill, it slowly deposits crystals consisting of benzoic acid.

Benzoic acid consists of white shining platelets, or flat needles, which melt at 121° C., and sublime without decomposition at 250° C.; it is soluble with difficulty in cold water, but more easily in hot, and is volatile with steam. When heated with excess of alkali, or lime, benzoic acid is decomposed into carbonic acid and benzene, and upon this a method depends for preparing the purest benzene; this decomposition of benzoic acid is completely analogous to that of acetic acid into carbonic acid and methane (p. 53).

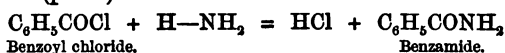
Benzoic acid was first obtained by sublimation from gum benzoin, an obsolete remedy, from which it obtained its name. The pure acid up to quite recent times was employed as a remedy, but nowadays its use has been completely replaced by other and better means. Benzoic acid is of great physiological interest. If introduced into the animal body it combines with amino-acetic acid, or glycocoll, with the loss of a molecule of water, and appears in the urine as hippuric acid (p. 8). This process was already observed in 1830 by Friedr. Woehler¹ (1800–1882), and his discovery aroused great interest; it was the first instance of a synthesis occurring in the animal body, but it was not

¹ From J. Liebig's and Fr. Woehler's Letters, vol. i. p. 35 (Vieweg and Son: Brunswick, 1888).

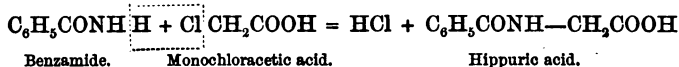
a synthesis in the more exact sense—that is, not a combination of carbon atoms to one another as e.g. in the formation of stearic acid from sugar; for in the synthesis of hippuric acid a carbon atom only combines with a nitrogen atom. Hippuric acid is an amide of benzoic acid, but not a simple amide; the hydroxyl group of the benzoic acid is not replaced by a simple amido group, but by a substituted amido group:



The structure of hippuric acid will appear indubitable from the following synthesis: Benzoyl chloride—benzoyl is the monovalent radical of benzoic acid, $\text{C}_6\text{H}_5\text{CO}$, just as acetyl, CH_3CO , is the monovalent radical of acetic acid—is first prepared by the action of phosphorus pentachloride upon benzoic acid, in the same way as acetyl chloride from acetic acid (p. 55); then, by the action of ammonia on benzoyl chloride, benzamide is obtained, just as acetamide from acetyl chloride (p. 59):



and benzamide easily combines with monochloroacetic acid with the elimination of hydrochloric acid, forming hippuric acid:



In order to directly combine together benzoic acid and glycocholic acid, as occurs in the animal body, the two acids in a dry state must be finely powdered, mixed together and heated in a sealed tube for twelve hours at 160°C ., as was shown by Victor Dessaignes¹ (1800–1885) in 1857. This synthesis, however, gives us no idea as to the factors which produce the synthesis in the animal body. The conditions are absolutely different; in the artificial synthesis a high temperature, a high pressure, and the absence of water are necessary; in the animal body synthesis occurs in the presence of water, at the ordinary temperature and ordinary pressure; cold-blooded animals even form hippuric acid. It is therefore of great interest to enquire into the conditions of the synthetical processes in the animal body, not only to physiologists, but also to chemists, since thereby new means may be given to the latter for attaining to more and more complicated compounds by artificial synthesis.²

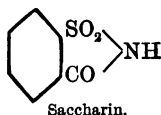
¹ V. Dessaignes, *Journ. Pharm.* 1857 (iii.), vol. xxxii. p. 44.

² A summary of the experiments upon the conditions of synthesis in the animal body is contained in Bunge's *Textbook of Human Physiology*, 1905, vol. ii. (Vogel: Leipzig).

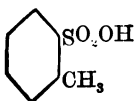
Hippuric acid occurs in the animal body not only after the administration of benzoic acid, but it is also constantly found in human urine in small quantities. It was first discovered by Liebig in 1829 in horses' urine; hence its name. In herbivora, benzoic acid arises from the various aromatic compounds contained in their food, by the oxidation of their side chains, to carboxyl; it also arises partly from the aromatic constituents of the proteins, especially from phenylalanine (cf. p. 186). The small quantities of hippuric acid which occur in human urine on a purely flesh diet, and in starvation, apparently arise from the latter source. The glycocoll necessary for the synthesis of the hippuric acid, at all events, arises from the decomposition of proteins.

Hippuric acid forms rhombic prisms, which are soluble with difficulty in cold, but easily in hot water. In the urine of herbivora it is present as alkali salt, and separates in a crystalline form from the cold concentrated urine on the addition of acids. When boiled with acids it is decomposed, with absorption of water, into benzoic acid and glycocoll. This decomposition is also brought about by the action of ferments, and this explains the occurrence of benzoic acid in the decomposing urine of herbivora, which was already observed by Liebig when he discovered hippuric acid.

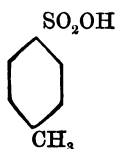
A physiologically interesting derivative of benzoic acid is saccharin, a compound which is characterised by its intensely sweet taste; a gramme of saccharin imparts to seventy litres of water a taste as sweet as that imparted by 280 grammes of cane sugar. Saccharin is the imide of ortho-sulphobenzoic acid:



In its preparation we start from toluene (p. 175); by the action of sulphuric acid at a temperature not above 100° C., toluenesulphonic acids (p. 170) are obtained, of which three are theoretically possible, but under the given conditions only the ortho- and the para-toluenesulphonic acids are formed:

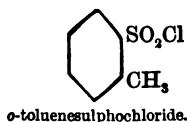


o-toluenesulphonic acid.

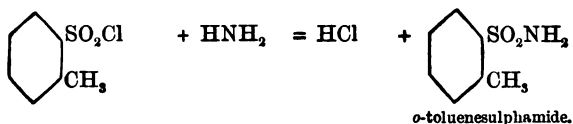


p-toluenesulphonic acid.

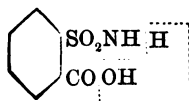
The sodium salts of these two acids are then converted into the toluenesulphochlorides by the action of phosphorus pentachloride (p. 55); of these, the para-compound at the ordinary temperature is a crystalline solid, and the liquid ortho-toluenesulphochloride, from which it is separated, serves as the material for the further operations :



By passing dry ammonia gas into it, the ortho-toluenesulphochloride is converted into ortho-toluenesulphamide, which is soluble with difficulty in water, and can therefore be freed by washing from the ammonium chloride which is also formed :



The methyl group is next oxidised to the carboxyl group by adding the toluenesulphamide to a solution of potassium permanganate; ortho-sulphamino-benzoic acid is first formed, which, by losing water, is changed into the imide, or saccharin, which is soluble with difficulty in cold water, and on the addition of acids crystallises from the solution :

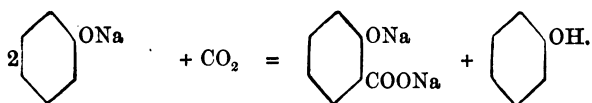


A large number of aromatic acids are found widely distributed in the vegetable kingdom; in these one or more hydroxyl groups are attached to the benzene ring besides the carboxyl group, and they are therefore to be regarded as oxybenzoic acids. Of these, mono-ortho-oxybenzoic acid or salicylic acid, and trioxybenzoic acid or gallic acid are interesting and important from a pharmacological point of view.

All the three isomeric monooxybenzoic acids have been synthetically prepared, but the ortho-compound, salicylic acid, is also found in nature. It has been found in the blossoms of *Spiraea ulmaria* and it can be easily prepared by hydrolysis and oxidation from salicin, a glucoside (cf. Lecture 9) which is found in the bark of the willow,

Salix; hence its name. The methyl ester of salicylic acid is found in *Gaultheria procumbens*, one of the Ericaceæ indigenous in North America. This ester, which is volatile, forms the chief constituent of the ethereal oil obtained by the distillation of the leaves and flowers of the gaultheria with water; it is known as 'oil of winter green' and is used in perfumery. Salicylic acid was formerly prepared from gaultheria oil by decomposition with alkalis, but nowadays it is prepared on the large scale from phenol.

Phenol behaves as a feeble acid; it combines with sodium hydroxide forming sodium phenylate C_6H_5ONa (p. 171), which consists of colourless crystals. By passing carbon dioxide into the molten sodium phenylate at 180 to 220° C., the following reaction occurs:

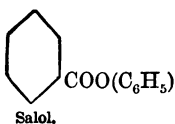


Half of the phenol distils over as phenol, and in the residue is found 'basic sodium salicylate.' Salicylic acid is a monobasic acid, but it can take up a second atom of sodium, because its hydroxyl group behaves just as it does in the phenols. The free acid is precipitated from the aqueous solution of the basic sodium salicylate by hydrochloric acid; it is soluble with difficulty in water and is purified by recrystallisation.

Salicylic acid forms colourless monoclinic prisms, which dissolve in 600 parts of cold water, but easily in hot water, alcohol and ether.

Salicylic acid finds many uses as a remedy; above all, it is a specific against acute rheumatism; not only does it diminish the fever, but also it causes the pain and swellings to disappear quickly, and hinders the complication of endocarditis. It is also used in other fevers, and was the first antipyretic brought forward after quinine; besides this, it is also employed as an external remedy on account of its antiseptic properties.

Sometimes the phenyl ester of salicylic acid, or salol, is given instead of salicylic acid:



This ester is prepared from salicylic acid and phenol by the action of dehydrating agents, and it forms a white crystalline powder, soluble with difficulty in water but fairly easily in alcohol. Its slight solubility in water explains the reason why salol tastes more pleasantly than salicylic acid, and less easily causes gastric disturbances. Against these advantages it must be remembered that the salol is decomposed by the ferments of our body into salicylic acid and phenol, and that the latter can manifest its poisonous action (p. 172).

Physiologically the relation of salicylic acid to glycocoll in the animal body is interesting; it combines with it forming salicyluric acid, which is analogous in constitution to hippuric acid; it passes into the urine partly unchanged, where it is easily detected by the intense violet colour which it gives on the addition of ferric chloride.

Gallic acid is found very widely distributed in the vegetable kingdom, not as such, but in compounds which bear the common name tannin. The tannins are either compounds of gallic acid with a sugar, i.e. a glucoside, or they are anhydrides of gallic acid, i.e. compounds of two molecules of gallic acid, with the loss of a molecule of water. Such a digallic acid is tannic acid, which occurs in many parts of plants, especially in oak galls, pathological swellings produced by the irritation of an insect on the branches of certain oak trees. The tannic acid is extracted from the oak galls by water, or by a mixture of ether, water and alcohol. The extract is evaporated down until it solidifies to a hard cake, which is rubbed up into a fine powder. This powder, when absolutely pure, is colourless, generally, however, it is coloured faintly yellow and is easily soluble in water; it has not yet been crystallised.

Tannic acid gives an insoluble compound with albumin and gelatin; the use of tannic acid in the tanning industry depends upon this, and also upon its antiseptic properties. The corium of animal skin, which consists for the most part of albuminous and gelatinous substances, loses its property of swelling up, and of putrefying in the presence of moisture, after it has been treated with tanning materials; it becomes resistant to all physical and chemical changes. When animal skins are placed in tannin solutions, the tannin is withdrawn from the solution, and the skins are converted into leather.

Tannic acid finds a second technical use in the preparation of ink. Its aqueous solution gives a blue-black, finely-divided precipitate with ferric chloride, which, when suspended in gum-water, forms ink.

The manifold uses of tannic acid in medicine depend, firstly, on its antiseptic, and secondly on its astringent properties.

Astringents are those medicaments which diminish the hyperæmia of catarrhal mucous surfaces, moderating the swelling, and the growth of cells, and lessening their secretion. This action is probably connected with the precipitation of the proteins; as a matter of fact, all remedies which are useful as astringents have the common property of forming compounds with proteins, which are insoluble in water. The salts of lead, iron, zinc, silver, copper and aluminium, as well as the tannins, belong to this group.

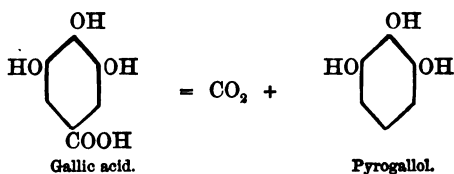
Tannic acid also precipitates nearly all the alkaloids, and on this account it is administered as an antidote in cases of poisoning by alkaloids.

Tannins are found in some of our favourite beverages, particularly abundantly in tea, and in red wine; for this reason red wine is recommended as a 'stomachic' in catarrhal conditions of the stomach. If the favourable action of tannin be required without the harmful action of the alcohol, bilberry lemonade is recommended in place of the red wine. Bilberries are rich in tannins, and are a common domestic remedy against digestive disturbances of all kinds. If the tannin is to act not only on the stomach, but also on the mucous membrane of the intestines, instead of a clear bilberry lemonade the whole boiled fruit must be taken, since the tannic acid in the clear extract will be taken up by the mucous membrane of the stomach, whereas the tannin-rich skins of the fruit and also their colloidal contents, which are rich in tannin, will reach the lowest portions of the intestines.

The tannic acid in tea is an undesirable adjunct, and on this account the leaves should be extracted with water which is not too hot; the ethereal oils and the theine then pass into solution, with very little of the tannin, which gives a bitter taste to the tea. If tea be drunk with milk or cream, the tannin is converted into an insoluble, and therefore tasteless, compound by the proteins of the milk. The danger of drinking too strong tea depends upon this fact, as the poisonous theine (p. 162) remains in solution, and the most concentrated tea tastes weak. If, on the other hand, tea be taken without milk, the harsh astringent-tasting tannin warns us from drinking too strong tea. The real tea-drinker drinks his tea without milk, and always very weak.

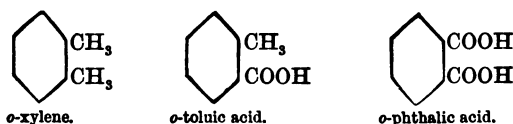
Gallic acid is obtained from tannic acid by hydrolysis, which is brought about both by ferments, and by acids, and alkalies. Gallic

acid crystallises in fine silky needles which are soluble in water, alcohol and ether. On heating it is decomposed into carbonic acid and pyrogallol (p. 174) :



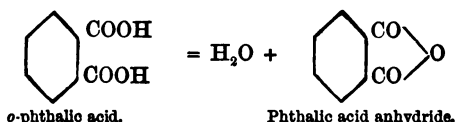
With ferric chloride gallic acid gives a blue-black precipitate, and, like tannic acid, is used in the manufacture of inks.

The three dimethylbenzenes, generally called xylenes, are all found together in light coal-tar; on oxidation they yield firstly the three isomeric monobasic toluic acids, and then the three dibasic phthalic acids, e.g. :



The oxidation of the xylenes in the animal body only goes so far as the formation of the monobasic toluic acids. Outside the body, the toluic acids are obtained on oxidation by dilute nitric acid. Concentrated nitric acid and potassium permanganate convert the xylenes into the phthalic acids, and if chromic acid be used as the oxidising agent, the whole molecule is completely oxidised to carbonic acid and water.

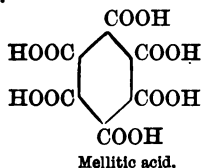
If ortho-phthalic acid be heated above its melting point, it is converted into its anhydride, which distils over unchanged, and crystallises in long rhombic prisms :



If the phthalic acids, or benzenedicarboxylic acids, be heated with excess of alkali, they are decomposed into two molecules of carbonic acid and one molecule of benzene.

Benzenetricarboxylic acids and benzenetetracarboxylic acids have been prepared. No isomers are possible in the case of benzenepenta-

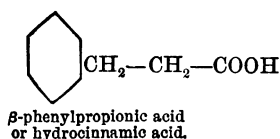
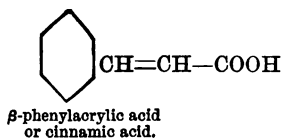
carboxylic acid. Benzenhexacarboxylic acid, or mellitic acid, is of great theoretical interest:



This complex acid is formed directly by the oxidation of chemically pure carbon, which is one of the most astounding facts in the whole of organic chemistry, for we thus obtain an insight into the structure of the carbon molecule, in which the benzene nucleus appears to be pre-formed! Franz Ferdinand Schulze¹ (1815–1873) prepared pure carbon by heating wood-charcoal in a current of chlorine, or by reducing carbonic acid with phosphorus. This carbon, and also pure graphite, yielded on oxidation with permanganate in alkaline solution a considerable quantity of mellitic acid, together with oxalic and other acids.

In nature mellitic acid is found in beautiful crystals, combined with alumina, as the rare mineral, which is sometimes found in manganese dioxide deposits, known as honey-stone, or mellite; hence the name mellitic acid. By boiling the powdered honey-stone with a solution of ammonium carbonate, the ammonium salt of mellitic acid is obtained, and from this the free acid, which forms silky needles, easily soluble in water and alcohol. When heated with excess of lime it is decomposed into one molecule of benzene and six molecules of carbonic acid, and its constitution was thus proven²: further the synthesis of hexamethylbenzene has actually been accomplished, and from it mellitic acid has been obtained by oxidation.³

Numerous aromatic acids are known in which the carboxyl group is not attached directly to the benzene nucleus, but to a side chain. Of these, phenylacrylic and phenylpropionic acids are physiologically and medicinally interesting examples:

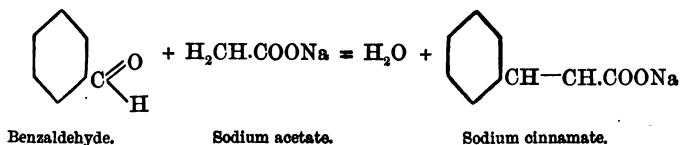


¹ F. F. Schulze, *Ber. d. d. chem. Gesellsch.* 1871, vol. iv. pp. 801, 802 and 806.

² A. Baeyer, *Liebig's Ann. d. Chem. u. Pharm.* 1870, supplementary vol. vii. p. 1.

³ C. Friedel and J. M. Crafts, *Ann. de Chim. et de Phys.* 1884 (vi.), vol. i. p. 470.

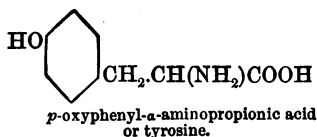
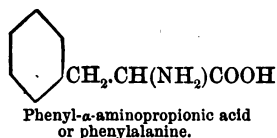
Cinnamic acid is found in certain balsams which are used as medicaments, in storax, in balsam of Peru, and balsam of Tolu (cf. Lecture 15). It has been prepared synthetically by several methods, e.g. by heating benzaldehyde with sodium acetate in the presence of a dehydrating agent, acetic anhydride :



Cinnamic acid is an acrylic acid (p. 98) in which the phenyl radical has taken the place of a hydrogen atom in the β -position. It crystallises from its aqueous solution in long needles, which melt at 49°C ., and boil at 280°C . It has recently been used as a therapeutic agent in tuberculosis.

By the action of nascent hydrogen cinnamic acid is converted into hydrocinnamic acid, or phenylpropionic acid. The α -amino derivative of this acid is found amongst the hydrolytic decomposition products of the proteins, and is known as phenylalanine. It is an alanine (p. 80) in which a hydrogen atom in the β -position has been replaced by the phenyl radical.

Amongst the hydrolytic decomposition products of proteins, together with phenylalanine, that oxy-derivative of this amino-acid is found in which the hydroxyl group occupies the para-position in the benzene ring. This compound is called tyrosine, as it was first found amongst the decomposition products of cheese (*τυρός*) :

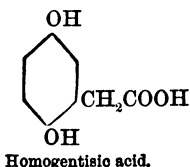


The constitution of tyrosine is known from its synthesis by Erlenmeyer and Lipp,¹ whose work lays the exact foundation for the above formula.

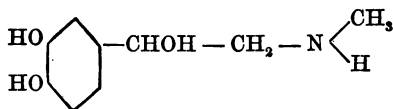
[Another important compound physiologically is homogentisic acid. It occurs in the urine in certain cases of abnormal metabolism, and patients having this peculiar anomaly are known as alkaptonuric patients. It is hydroquinone-acetic acid. Owing to the presence of

¹ E. Erlenmeyer and A. Lipp, *Ber. d. d. chem. Gesellsch.* 1882, vol. xv. p. 1545.

hydroquinone, the urine turns brown on standing, which is due to the alkaline reaction produced by its ammoniacal fermentation.



An organic base which arises in the animal body, in which it plays a very important rôle, may be described here; it has recently found an extensive therapeutic use. This is adrenaline, also known as epinephrine, or suprarenine. In common with the alkaloids [cf. Lecture 16] it has an intense physiological action, but differs from most alkaloids in not having a ring containing nitrogen; it is a constant constituent of the adrenal or suprarenal bodies from which it was isolated and obtained in a crystalline state by J. Takamine¹ and T. B. Aldrich.² It has the following constitution:



The reasons for this structural formula are given in the original papers.³ The formula shows that it contains an asymmetric carbon atom, corresponding to the fact that adrenaline is optically active, rotating the plane of polarised light to the left, [and that it is derivative of pyrocatechin, a secondary alcohol and also a secondary amine.] Adrenaline, in the smallest quantities, produces contraction of the muscular coat of the blood vessels, and is therefore used as a means of arresting hæmorrhage.

¹ J. Takamine, *Amer. Journ. Pharmacy*, 1901, vol. lxxiii. No. 11.

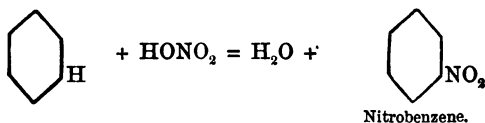
² T. B. Aldrich, *Amer. Journ. Physiology*, 1901, vol. v. p. 457.

³ H. Pauly, *Ber. d. d. chem. Gesellsch.* 1903, vol. xxxvi. p. 2944, and 1904, vol. xxxvii. p. 1388. F. Stolz, *ibid.* 1904, vol. xxxvii. p. 4149. T. B. Aldrich, *Journ. Amer. Chem. Soc.* 1905, vol. xxvii. p. 1074.

LECTURE XIV

AROMATIC NITROGEN COMPOUNDS

WE have seen that nitrogen can be most easily introduced into the molecule of the saturated hydrocarbons by allowing ammonia to act upon the halogen substitution products: alkylamines are thus prepared. The NH_2 radical, however, cannot be introduced into the benzene ring in this manner. We have already seen that the halogen atom is very firmly attached to the benzene ring, and that it cannot be substituted by the hydroxyl group, as in the aliphatic compounds; neither can the halogen atom in the benzene ring be replaced by NH_2 by the action of ammonia. On the other hand, the nitro-radical NO_2 can be introduced more easily into the aromatic compounds than into those of the fatty series. It has been shown that sulphuric acid reacts with benzene to form benzenesulphonic acid, with the elimination of a molecule of water (p. 170), and in an analogous way benzene reacts at the ordinary temperature with concentrated nitric acid: water is eliminated and the nitro-radical NO_2 substitutes a hydrogen atom in the benzene ring, and nitrobenzene is formed:

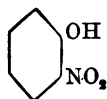
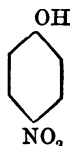


Nitrobenzene is a pale yellow liquid, which boils at 208°C , without decomposition; it has a pleasant smell resembling bitter almonds, and is therefore used in perfumery, especially in the manufacture of soap; it is, however, poisonous, the simple inhalation of its vapours producing violent headache.

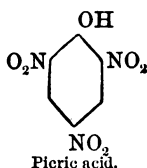
If methylbenzene, or toluene, be treated with concentrated nitric acid, the substitution of a hydrogen atom by a NO_2 group always occurs in the benzene ring, but never in the methyl group, and the three isomeric nitrotoluenes (p. 164) are formed; the ortho- and para-compounds are the chief products, the meta-compound being obtained

only in traces; the para-compound at the ordinary temperature is solid, and on cooling crystallises in large prisms from the liquid mixture of the three isomers.

Nitric acid acts in the same way upon phenol as it does upon benzene; when phenol is mixed with dilute cold nitric acid, *o*- and *p*-nitrophenol result:

*o*-nitrophenol.*p*-nitrophenol.

By the further action of nitric acid, by heating the nitrophenols with excess of nitric acid, dinitrophenols and trinitrophenols are formed. One of the latter, the symmetrical trinitrophenol, or picric acid, has many technical uses:

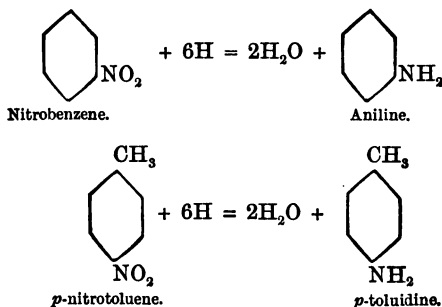


Picric acid crystallises from alcohol, or water, in pale yellow glistening platelets or prisms; it is a strong monobasic acid [the phenolic OH group becoming more acid in character, due to the presence of the NO₂ groups]. It dyes silk and wool a beautiful yellow colour, and is therefore used in the dyeing industry. Picric acid is poisonous, and its use in the dyeing of woollen fabrics has the advantage of protecting the materials from moths. Picric acid is an explosive, and therefore a very dangerous substance, its salts being exploded by a knock or a blow. Picric acid is used in histology for fixing and staining microscopical specimens. Calcium picrate is soluble in water, and fixation with picric acid is especially advantageous in the treatment of embryological specimens containing calcified cartilage and bone, which are freed from calcium salts and can then be sectioned without difficulty. In recent times picric acid has been recommended as an external remedy, especially as an antiseptic in the treatment of burns, and for allaying their pain.¹ Picric acid is so called from its intensely bitter taste, and on this

¹ W. Maclellan, *Brit. Med. Journ.* 1896, p. 1826; and Beauxis-Legrave, *Gaz. Hebdom.* 1896, No. 91.

account was sometimes used formerly as a substitute for hops in the preparation of beer; it is used in analytical chemistry as a precipitant for organic bases.

If nascent hydrogen be allowed to act upon nitrobenzene or nitrotoluene, the nitro-group NO_2 is converted into the amido-group NH_2 . Phenylamine, or aniline, and the three isomeric toluidines are thus obtained :



This is the method generally employed for preparing the aromatic amines or organic bases; it was discovered by the Russian chemist Nikolai Zinin¹ (1812–1880) in 1842, and has since proved to be of extensive use. Zinin used sulphuretted hydrogen as the reducing agent, but, in the commercial preparation of aniline and toluidine, the hydrogen is evolved from iron and hydrochloric acid.

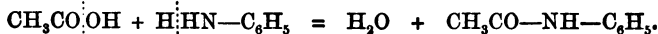
Aniline was known before it was synthetically prepared by Zinin; it was obtained by Otto Unverdorben in 1826 by the distillation of indigo, and hence its name from the Spanish term for indigo—anil. Fr. Runge (1795–1867) discovered aniline in coal-tar in 1834.

Aniline is a colourless oily liquid with a feeble characteristic smell; it is somewhat heavier than water, of which it requires thirty-one parts for its solution. It boils at 183°C ., and in the air soon becomes yellow, and then brown. With acids it combines like ammonia, forming crystalline salts. Aniline is poisonous, and has often caused severe poisoning in man; the symptoms are giddiness, coma, cramps, and collapse.

Acetanilide, or antifebrine, is a derivative of aniline which is of medical interest. This compound is an acetamide (p. 59) in which one of the hydrogen atoms of the amide group is replaced by the

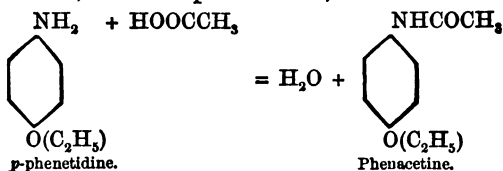
¹ N. Zinin, *Journ. f. prakt. Chem.* 1842, vol. xxvii. p. 149.

phenyl radical, and it is obtained by simply boiling aniline with glacial acetic acid :

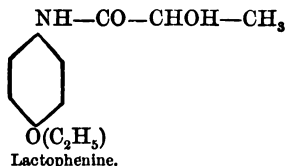


Acetanilide forms beautiful white prisms, which are soluble in hot water, alcohol and ether ; it is often used as a drug for lowering the temperature in cases of fever.

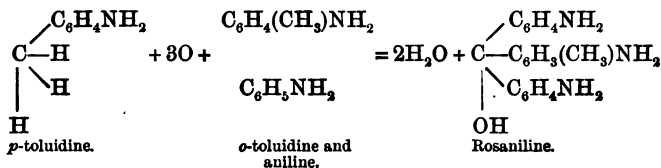
Another antipyretic which is often used, namely phenacetine, is quite analogous to, but somewhat more complicated than acetanilide. Instead of aniline, the more complicated amine, the ethyl ether of para-amidophenol, or para-phenetidine, is combined with acetic acid, and the acid amide, which is phenacetine, is formed :



Lactophenine is obtained when lactic acid, instead of acetic acid, is made to combine with *p*-phenetidine to form the acid amide ; it is also used as an antipyretic.



Both aniline and toluidine are used in the technical preparation of the very complicated aniline dyes. If certain oxidising agents, e.g. arsenic acid, mercuric nitrate, etc., be allowed to act upon a mixture of aniline, ortho- and para-toluidines, these compounds combine together, with the loss of hydrogen atoms, to form a large molecule, rosaniline, which can be regarded as a substituted methane (p. 176) ; it stands in close relationship to many commercially important aniline dyes. The reaction in the formation of rosaniline is the following :



Rosaniline crystallises from hot water, or alcohol, in colourless needles; it is a triacid base, and its hydrochloride, with one equivalent of acid, is the well-known dye fuchsine. In the solid state this consists of beautiful green crystals with a metallic lustre, soluble in water and alcohol, giving an intensely red colour.

If a hydrogen atom in each of the amido groups of rosaniline be replaced by phenyl, the beautiful blue dye, triphenylrosaniline, or aniline blue, is obtained. Other dyes are obtained by substituting different radicals for hydrogen atoms in the amido groups—e.g. the iodide of pentamethylrosaniline is a green dye; the hydrochloric, or acetic acid salt of trimethylrosaniline is violet.

The chemistry of the aniline dyes forms a very large chapter in organic and technical chemistry, but, except in the case of histological staining technique, is of no particular physiological or medicinal interest.¹ One aromatic dye must be now mentioned, as it is of great physiological importance, standing, as it does, in close relationship to a constant constituent of our body, and to a constant constituent of most proteins—namely, indigo.

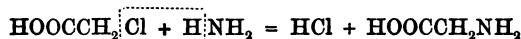
The beautiful blue dye known as indigotin has the empirical formula $C_{16}H_{10}N_2O_2$; it forms either an amorphous blue powder, or glittering copper-coloured crystals. At 300° C. it is converted into a purple-red vapour, the density of which has been determined, and crystals are formed when the vapour is cooled. Indigo is insoluble in water, alcohol, ether, dilute acids and alkalis, and upon this its value as a 'fast' dye depends—[i.e. one which cannot be washed out]; it is soluble in chloroform, aniline, and petroleum ether, and it dissolves in concentrated sulphuric acid with a deep blue colour, forming the two sulphonic acids, indigomonosulphonic acid, or phoenicin sulphuric acid, and indigodisulphonic acid. The sodium salt of the latter is soluble in water, and comes into the market as indigo-carmin. The colour given by these compounds—Saxon blue—is less fast. If a fast dye be required, the indigo is first converted into indigo white, a colourless crystalline compound, the alkali salts of which are soluble in water. Indigo white is a reduction product of indigo; it contains two atoms of hydrogen more, and has the composition $C_{16}H_{12}N_2O_2$. The reduction of indigo to indigo white

¹ The histological staining technique is at present only empirical; it is not based upon the chemical action of certain dyes on the constituents of the tissues. Martin Heidenhain has attempted to explain the process in the dyeing of certain tissue elements, from the behaviour of dyes of definite constitution upon various proteins and nucleins, in *Pflüger's Arch.* 1902, vol. xc. p. 115, and 1903, vol. xcvi. p. 440. [The process is also physical and due to adsorption (see Bayliss, *Biochem. Journ.* 1906, vol. i. p. 175).]

in various dye-works is carried out by different reducing agents, ferrous sulphate, or grape-sugar, or calcium hyposulphite being allowed to act upon the indigo in alkaline solution. The pale yellow alkaline solution which thus results is called 'indigo vat,' and the fabrics which are to be dyed are dipped in this solution in order to impregnate them with the indigo white; on subsequently exposing them to the air, the indigo white is again oxidised to indigo by the atmospheric oxygen, and the insoluble dye is deposited in the threads of the material.

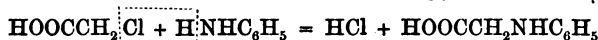
The constitution of indigo has been determined chiefly by the work of Baeyer, and its synthesis has been accomplished by several methods.¹ In all these syntheses, the facts that indigo on distillation with potassium hydrate yields aniline, and on boiling with manganese dioxide and potash yields *o*-amidobenzoic acid, are made use of. They show that the indigo molecule contains a nitrogen and a carbon atom, in the ortho-position to one another, in the benzene ring. The following, selected from the great number of syntheses, shows most clearly the structure of the indigo molecule.

The synthetical preparation of amino-acetic acid, or glycocoll, from monochloroacetic acid and ammonia has been described (p. 60); if, in the place of ammonia, we allow a substituted ammonia, phenylamine or aniline, to act upon monochloroacetic acid, we obtain anilido-acetic acid, a compound which is completely analogous in constitution to amino-acetic acid:



Monochloroacetic acid.

Amino-acetic acid
or glycocoll.

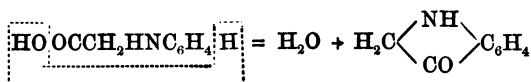


Monochloroacetic acid.

Aniline.

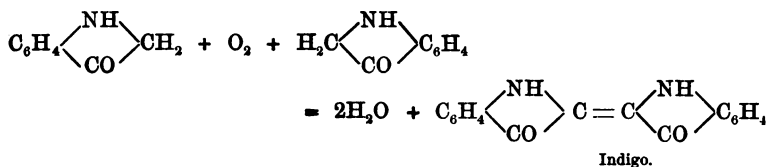
Anilido-acetic acid
or phenylglycocoll.

Anilido-acetic acid consists of small colourless crystals, which, when heated with caustic potash in the absence of air, lose a molecule of water, and probably first form the following compound:

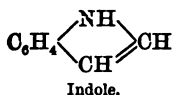


¹ The monograph by A. Reissert contains a summary of this work and the many synthetical methods, *History and Methods of the Indigo Synthesis* (Friedländer and Son: Berlin, 1898). A. Salmony's pamphlet on *A New Indigo Synthesis and a Review of the Indigo Syntheses* (Friedländer and Son: Berlin, 1905) also gives an account, and in it Engler and Emmerling's work (*Ber. d. d. chem. Gesellsch.* 1870, vol. iii. p. 885), wherein the first synthesis of indigo is recorded, is abstracted.

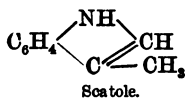
in which the four divalent radicals, CH_2 , CO , C_6H_4 , and NH , form a closed ring; if the molten mass be dissolved in water, and atmospheric oxygen be allowed to act upon it, it becomes blue and indigo separates out.¹ We must regard the process as if the oxygen oxidised away the two hydrogen atoms of the methylene radical, and that two of the molecules formed by the oxidation then combine together, since the vapour density of indigo shows that the formula $\text{C}_8\text{H}_5\text{NO}$ must be doubled:



If energetic reducing agents—nascent hydrogen followed by distillation with zinc dust—be allowed to act upon indigo, two atoms of oxygen are removed and four atoms of hydrogen enter the molecule, and we obtain the colourless volatile compound of the composition $\text{C}_{16}\text{H}_{14}\text{N}_2$, namely indole. The determination of its vapour density shows, however, that in the reduction process a splitting of the molecule has occurred, and that the molecule of indole has the composition $\text{C}_8\text{H}_7\text{N}$. Its structural formula can be regarded as the following:



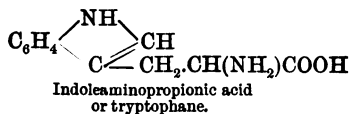
Physiologically, indole is a very interesting compound, since it is formed by the bacterial decomposition or putrefaction of proteins, and is constantly found in the contents of the intestine; at the same time the methylated indole, or scatole, occurs:



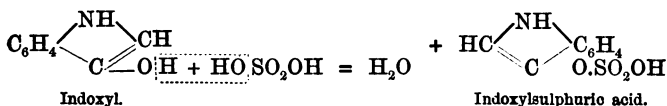
Scatole and indole are crystalline volatile compounds with

¹ This synthetical method was discovered almost simultaneously in 1890 by Heumann, Lederer, and Biedermann and Lepetit. Heumann, *Ber. d. d. chem. Gesellsch.* 1890, vol. xxiii. pp. 3043 and 3431; *Journ. f. prakt. Chem.* 1901, vol. xliii. p. 111; Biedermann and Lepetit, *Ber. d. d. chem. Gesellsch.* 1890, vol. xxiii. p. 3289; Lederer, *Journ. f. prakt. Chem.* 1890, vol. xlii. pp. 383 and 565, and 1901, vol. xliii. p. 303.

nauseous smells, and they impart to fæces their characteristic odour; they are formed during the putrefaction of proteins from the still more complicated compound, indoleaminopropionic acid or tryptophane,¹ which can be prepared by hydrolysis from proteins by the action of ferments or acids (cf. Lecture 17).



In the urine of man a small quantity of indoxyl, an oxidation product of indole, constantly occurs, as the alkali salt of its ester with sulphuric acid; [it is generally known as indican]:



Indoxyl forms pale yellow crystals, soluble in water. If the urine be treated with a large amount of concentrated hydrochloric acid indoxyl is separated from its combination with sulphuric acid, with absorption of water, and if an oxidising agent—bromine, bleaching powder, ferric chloride—be added, the indoxyl is oxidised to indigo, and the urine becomes green-blue in colour, and when shaken with chloroform a beautiful deep-blue solution of indigo is obtained.

If indole be injected subcutaneously into an animal, the quantity of potassium indoxyl sulphate in the urine is largely increased; the oxidation of indole to indoxyl in the tissues of animals is an exactly analogous process to the oxidation of benzene to phenol (pp. 170 and 171).

Nothing definite is known about the fate of indoleaminopropionic acid, which arises by the decomposition of proteins in the tissues; it is probably oxidised completely to the end-products, carbonic acid, water, and urea. The indoxyl, which occurs in the urine, probably arises entirely from the indole which is formed by putrefactive processes in the intestine. Consequently, the quantity of indoxylsulphuric acid in the urine is a measure of the intensity of the putrefactive processes occurring in the intestine, and the determi-

¹ [Hopkins and Cole, *Journ. Physiol.* 1901, vol. xxvii. p. 418 and 1903, vol. xxix. p. 451; A. Ellinger, *Ber. d. d. chem. Gesellschaft.* 1907, vol. xl. p. 3029.]

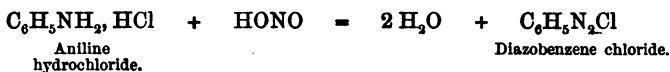
nation of its quantity might be of great use in the diagnosis of many diseases.

Indigo, until recent times, was entirely prepared from certain plants, from species of the indigofera, etc. In these plants, chiefly in the leaves, a glucoside (cf. Lecture 9) indican, a combination of indigo with sugar, is found. Indigo is prepared on the large scale in India from the leaves and branches of the indigofera, which are broken up and allowed to stand covered over with water, when the indican passes into solution, together with a ferment, which decomposes it into indoxyl and sugar. After a few hours the solution is poured off from the portions of the plant and exposed to the action of atmospheric oxygen, by stirring with a paddlewheel. The indoxyl is thereby oxidised to indigo, which separates out as an insoluble amorphous powder; this is purified by decantation, dried, and cast into the form of cubes, in which form it comes into the market. In the last few years the manufacture of synthetical indigo (p. 13) has competed successfully with this process.

[When describing the compounds of the fatty or aliphatic series, it was mentioned that nitrous acid was a very important reagent for distinguishing primary, secondary, and tertiary amines (p. 36).

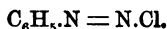
Aniline or phenylamine is a primary amine, and by the action of nitrous acid should be converted into the corresponding alcohol, i.e. phenol. In the aliphatic series this reaction takes place in one stage, but in the aromatic series an intermediate compound, known as the diazo-compound, is first formed.]

If nitrous acid be allowed to act upon aniline hydrochloride, diazobenzene chloride, or benzenediazonium chloride, is formed, with the loss of two molecules of water :

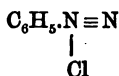


Diazobenzene chloride forms colourless needles, which in the dry state are very explosive; the aqueous solution, however, is free from danger. It has not yet been definitely decided how the two nitrogen atoms are combined in diazobenzene.

[Two formulae have been proposed for the diazo-compounds; in that proposed by Kekulé, the two nitrogen atoms are doubly linked together :



In the formula proposed by Blomstrand

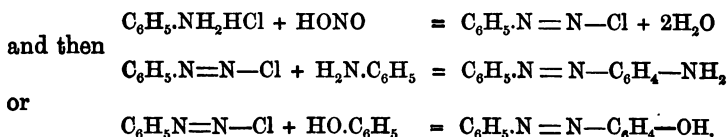


one of the nitrogen atoms is pentavalent, and the two nitrogen atoms are linked together by a triple bond; it expresses the basic character of these compounds better, and they are often called diazonium salts.

If the aqueous solution of diazobenzene chloride be boiled, nitrogen is evolved and phenol is formed, and the complete conversion of the primary amine into the corresponding alcohol takes place.

The diazo-compounds are of the very greatest importance in synthetical organic chemistry, as they can take part in numerous reactions: e.g. if diazobenzene chloride be boiled with alcohol, nitrogen is evolved, as with water, but the product is benzene, not phenol; reduction of the phenol group occurs, the alcohol being oxidised to aldehyde. If diazobenzene chloride be added to a solution of a cuprous salt, bromide or chloride, dissolved in the corresponding acid, or of cuprous cyanide dissolved in potassium cyanide, an evolution of nitrogen again occurs, and the halogen atom, or the CN radical, enters the benzene ring in the place of the diazo group. This is known as Sandmeyer's reaction.

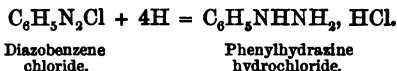
A very large number of aniline dyes are prepared from diazo-compounds; aniline, or any homologue of aniline can be employed in the diazotisation process, and when this is completed, either a phenol or an amine is added. This combines with the diazotised substance and forms a dye. This series of dyes is known as the azo-dyes. If aniline be added to a solution of diazobenzene chloride a yellow crystalline substance is formed. This is aniline yellow. Similarly, if phenol or α -naphthol be added to a solution of diazobenzene chloride a yellow or orange colour is produced. The various tropaeolins (methyl orange, etc.) are prepared from the sulphonic acid of aniline and a phenol, or a secondary amine. In each case the reaction is as follows:



The various amines and phenols which can be used in the process have naturally given rise to the enormous number of azo-dyes which can be obtained.]

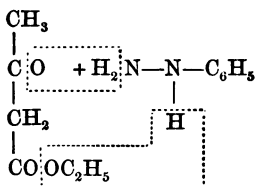
Another important derivative of aniline has yet to be described, as it plays an important part as a reagent in the chemistry of the sugars, namely phenylhydrazine.

When diazobenzene chloride in hydrochloric acid solution is reduced with stannous chloride, four atoms of hydrogen are taken up, and phenylhydrazine hydrochloride is obtained :

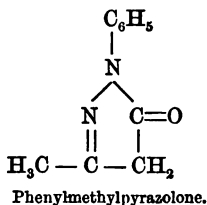


Phenylhydrazine hydrochloride consists of colourless, glistening, crystalline platelets; the free base at the ordinary temperature is a colourless liquid, which soon turns brown in the air. If cooled, it solidifies to a colourless crystalline mass which melts at 17.5°C . and boils at 242°C ., almost without decomposition.

Antipyrine, which is used, and misused, in medicine very widely as an antipyretic, is an important derivative of phenylhydrazine. It is prepared from the ethyl ester of acetoacetic acid, which contains a ketone group (p. 83); this combines with phenylhydrazine in the above-mentioned way, the following reaction taking place :

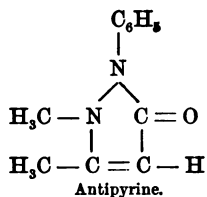


The resulting compound is very unstable; it loses a molecule of ethyl alcohol, and a stable ring, containing three carbon and two nitrogen atoms, the so-called pyrazolone ring, is formed :



By the action of methyl iodide another methyl group is then introduced into the molecule, and phenyldimethylpyrazolone or

antipyrine, which was first prepared by Ludwig Knorr,¹ is obtained :



Antipyrine consists of colourless crystals, almost without smell, easily soluble in water. Its solution is coloured red by ferric chloride, and blue-green by nitrous acid.

¹ L. Knorr, *Liebig's Ann. d. Chem.* 1886, vol. ccxxxviii. p. 137. The exact reasons for the structural formula are given in this paper.

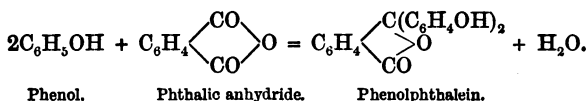
LECTURE XV

NAPHTHALENE, ANTHRACENE, TERPENES, RESINS, CAMPHOR

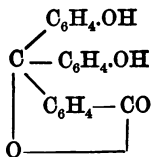
THE aromatic hydrocarbons so far described have been benzene and its derivatives, which contain only one benzene nucleus, with side chains composed of hydrocarbons of the fatty series.

[Rosaniline and the azo-dyes, which compounds contain more than one benzene ring, are, however, exceptions. The simplest example of the linking together of two benzene rings is diphenyl $C_6H_5 - C_6H_5$, in which the two benzene rings are linked directly together. If the two benzene rings be joined by a carbon atom, we obtain diphenylmethane, $C_6H_5 - CH_2 - C_6H_5$. Triphenylmethane is the mother-substance of rosaniline, in which the three phenyl groups are substituted by amino groups. The two other important compounds, phenolphthalein, and eosin, still require mention, as they are also derivatives of triphenylmethane.

Phenolphthalein is prepared by heating together two molecules of phenol with one molecule of phthalic anhydride at $115^\circ C$. in the presence of concentrated sulphuric acid :

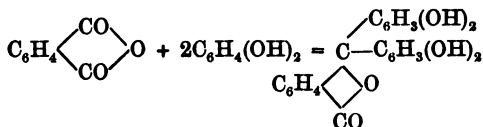


If we rewrite the formula of phenolphthalein as follows :

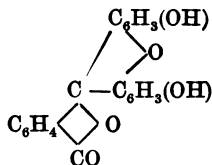


its relation to triphenylmethane can be readily seen.

By heating phthalic anhydride with resorcinol, fluorescein is obtained in a similar way to phenolphthalein :



This compound, containing four hydroxyl groups, loses water, forming fluorescein :



Fluorescein is a yellowish-red powder which is insoluble in water ; it dissolves in alcohol and dilute alkalis, giving solutions with a fine green fluorescence.

By acting upon fluorescein with the halogens, the eosins are obtained which also possess the fluorescence, but their solution is red.

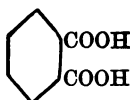
Eosin is tetrabromofluorescein ; erythrosin is tetraiodofluorescein.]

More complicated aromatic hydrocarbons, however, exist, which can be regarded as 'condensation' products of two or more benzene rings ; they contain carbon atoms which function as members of two rings at the same time. The practically important naphthalene and anthracene are examples of hydrocarbons with such condensed ring systems.

Naphthalene is obtained when the vapours of simpler compounds of the aromatic or aliphatic series—alcohol, ether, volatile fatty acids, ethylene, acetylene, benzene, toluene, etc.—are passed through a red-hot tube ; for this reason naphthalene is formed in the distillation retorts in the manufacture of coal-gas, and occurs as the chief constituent in heavy coal-tar (p. 169). On cooling, naphthalene separates in the form of rhombic platelets, which are purified by a complicated process. The crystals melt at 80° C., and boil at 218° C. ; they are insoluble in water, but easily soluble in ether and hot alcohol ; they possess a characteristic smell, and in spite of their high boiling point are very volatile ; this explains their occurrence in coal-gas, to which they impart a considerable luminosity.

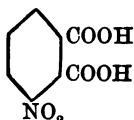
Elementary analysis, and the determination of the vapour density

of naphthalene, show that this hydrocarbon has the empirical formula $C_{10}H_8$; it contains therefore less hydrogen than benzene. In benzene to every carbon atom there is one hydrogen atom, but naphthalene has two atoms of hydrogen less. When oxidised with potassium permanganate, or with dilute nitric acid at $130^\circ C.$, naphthalene is converted into ortho-phthalic acid :

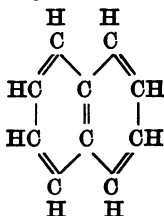


the same compound which is formed by the oxidation of ortho-xylene (p. 184). It can therefore be supposed that naphthalene is also a benzene, with two side chains in the ortho-position.

If nitronaphthalene be prepared from naphthalene by the action of concentrated nitric acid in the cold, and if this be oxidised, ortho-nitrophthalic acid is obtained :



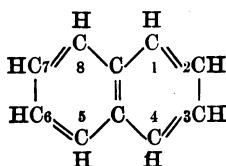
The benzene ring to which the nitro-group is attached has therefore not been attacked. When, however, nitronaphthalene is reduced to amidonaphthalene, in an analogous way to the reduction of nitrobenzene to aniline, and when this compound is oxidised, we do not obtain amidophthalic acid—i.e. we do not obtain its oxidation product—but we obtain the simple ortho-phthalic acid. The benzene ring, to which the NH_2 group was attached, has been oxidised away to two carboxyl groups, leaving one benzene ring over. It necessarily follows that naphthalene contains two benzene rings, and that these rings have two carbon atoms in common with one another, and the structure of naphthalene can therefore only be thus expressed :



Naphthalene is extensively used in the dyeing industry, and in medicine it has been used as a disinfectant in the treatment of wounds, It has the advantage over other disinfectants that, on account of its

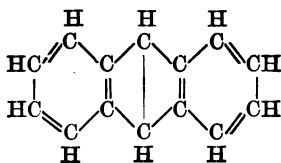
insolubility in water, it is not absorbed, and does not act as a caustic, and, on account of its volatility, it disinfects the whole neighbourhood of the wound.

If we prepare monosubstitution products of naphthalene, only two isomers, as the structural formula *a priori* shows, are possible, which are differentiated by the letters α - and β -; the substitution can either take place at one of the carbon atoms which is attached to one of the two carbon atoms common to both rings (1, 4, 5, 8, = α -compound), or to one of the other carbon atoms which are equivalent to one another (2, 3, 6, 7, = β -compound). As a matter of fact, only two isomers of all the monosubstitution products of naphthalene can be prepared :

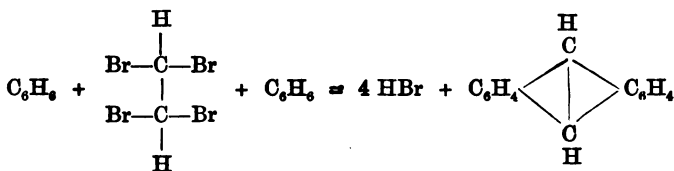


When naphthalene is heated with concentrated sulphuric acid two isomeric monosulphonic acids are obtained, and these, when they are fused with caustic potash, yield the two hydroxyl compounds—in an analogous way to the preparation of phenol from benzene (p. 170)— α -naphthol and β -naphthol. The former melts at 95°C . and boils at 282°C ., the latter melts at 122°C . and boils at 288°C . β -Naphthol is used as a disinfectant in the treatment of skin diseases, as an addition to ointments.

Anthracene is formed from simpler carbon compounds at a high temperature, under the same conditions as naphthalene (p. 201), and consequently is found with it in coal-tar, from which it is obtained on the large scale. Its empirical formula is $\text{C}_{14}\text{H}_{10}$. Just as we can regard naphthalene as having arisen by the condensation of two benzene rings, with the loss of two carbon atoms, so also we can regard anthracene as having arisen from three benzene rings, with the loss of four carbon atoms. The structural formula of anthracene is therefore written as follows :

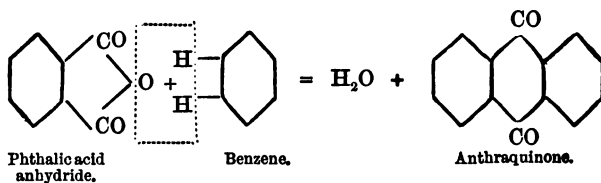


The correctness of this assumption is shown by the following synthesis from benzene and tetrabromomethane, in the presence of aluminium chloride : ¹



Anthracene consists of colourless monoclinic platelets, which melt at 213° C. and boil at 360° C. Its technically important derivatives are anthraquinone, and the beautiful dye obtained from this, alizarin. It was mentioned (p. 12) that in 1868 alizarin could only be obtained from ruberythric acid, a glucoside found in madder root (cf. Lecture 9), and how the discovery of its artificial synthesis by Graebe and Liebermann had brought about a complete change in an important branch of husbandry and industry; consequently the synthesis of alizarin will be of interest, and will give a clear insight into the structure of this complex dye.

Alizarin has the empirical formula $\text{C}_{14}\text{H}_8\text{O}_4$; by distillation with zinc dust it is reduced to anthracene $\text{C}_{14}\text{H}_{10}$. This fact led Graebe and Liebermann to suppose that, conversely, alizarin could be obtained by the oxidation of anthracene. Anthraquinone, which has the formula $\text{C}_{14}\text{H}_8\text{O}_2$, is an intermediate product in the oxidation of anthracene to alizarin, and it can be prepared by several methods of oxidation from anthracene, e.g. by the action of nitric or chromic acids; by reduction with hydriodic acid, or with zinc dust, anthraquinone is reconverted into anthracene. The structure of anthraquinone is given by its synthesis from phthalic acid anhydride (p. 184) and benzene, in the presence of a dehydrating agent, aluminium chloride :



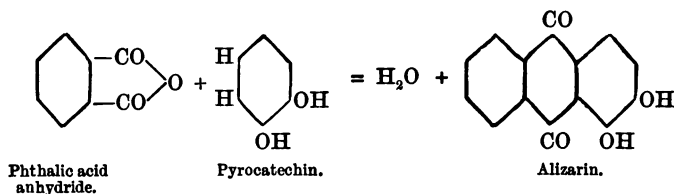
Anthraquinone is a very stable compound; it consists of yellow needles which melt at 285° C. It has more of the properties of a

¹ R. Anschütz and F. Eltzbacher, *Ber. d. d. chem. Gesellsch.* 1883, vol. xvi. p. 623.

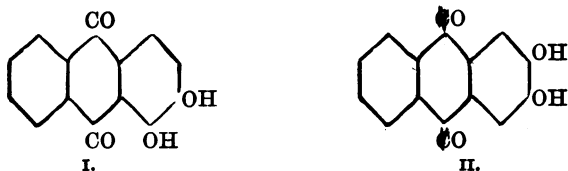
diketone than those of a true quinone; it is easily reduced, and forms an oxime with hydroxylamine (p. 173).

When two hydroxyl groups replace two hydrogen atoms in anthraquinone we obtain alizarin, which is prepared by the general method for converting aromatic hydrocarbons into phenols, i.e. by making the sulphonic acid and fusing this with alkali (pp. 170 and 203). The peculiarity in the preparation of dioxyanthraquinone consists in its not being prepared from the disulphonic acid of anthraquinone, but from the monosulphonic acid. The second hydroxyl group enters the molecule during the fusion with alkali, by absorption of oxygen from the air; this oxidation process is accelerated in the works by adding potassium chlorate, with the caustic soda, to the fusion mixture.

With regard to the position of the two hydroxyl groups, it can be shown that they are both attached to one and the same benzene ring; the synthesis of alizarin from phthalic acid anhydride and pyrocatechin (p. 172), by removal of water with sulphuric acid, at 140° C. shows this¹:



As both hydroxyl groups in pyrocatechin are in the ortho-position to one another, this arrangement must also occur in alizarin; a second position for the two ortho-hydroxyl groups in the molecule of alizarin is, however, conceivable:



The two positions of the hydroxyl groups in the alizarin molecule can be decided after a nitro-group NO₂ has been substituted for one of the hydrogen atoms; two isomeric mononitro-substitution products of alizarin can be prepared, both containing the nitro-group in the

¹ A. Baeyer and H. Caro, *Ber. d. d. chem. Gesellsch.* 1874, vol. vii. p. 972. Cf. C. Liebermann, *ibid.* 1888, vol. xxi. p. 2501.

same benzene ring in which the two hydroxyl groups are situated. Both nitro-compounds yield on oxidation phthalic acid. Formula II. does not allow of two isomeric mononitro-products, when the nitro group NO_2 is attached to the same benzene ring as the two hydroxyl groups, but this is allowed by Formula I., and it therefore follows that Formula I. expresses the correct structure for alizarin.

Alizarin crystallises in beautiful red prisms which can be sublimed without decomposition. Like all phenols it has the properties of an acid, and with alkalis it gives purple-red solutions, and with other bases insoluble salts, the so-called lakes. When tissues are mordanted with oxides they can be dyed fast with alizarin, insoluble salts being formed in the threads of the material. The lime compound is blue, the ferric oxide compound dark violet, and the alumina compound red. This latter compound is the so-called 'Turkey-red' dye.

In addition to the aromatic hydrocarbons there is another group which is found very widely distributed in the vegetable kingdom; its members do not really belong to the aromatic compounds, although they are closely related to them, and can be converted into the aromatic hydrocarbons by reactions which are not very violent. These are the terpenes.

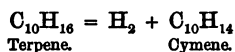
In many plants, especially in the flowers and fruits, volatile oils are found, which impart to them their characteristic odour. By distilling these parts of the plant with water the volatile oils, the so-called ethereal or essential oils, distil over with the water, and can be isolated. The essential oils are not chemical individuals.¹ Many of them contain the above-mentioned hydrocarbons, i.e. the terpenes, together with compounds containing oxygen. The terpenes obtained from the various plants are not identical, but they are isomers of the general empirical composition $\text{C}_{10}\text{H}_{16}$; their boiling point varies between 160° and 190°C. , and, in spite of this, they are volatile at the ordinary temperature, and distil over with steam. They are optically active, and their constitution is not as yet entirely worked out, though many valuable investigations² have been carried out upon them. These investigations promise us an insight into the

¹ The essential oils are made use of in perfumery, and the numerous constituents form a large chapter in organic and technical chemistry which cannot be entered into here.

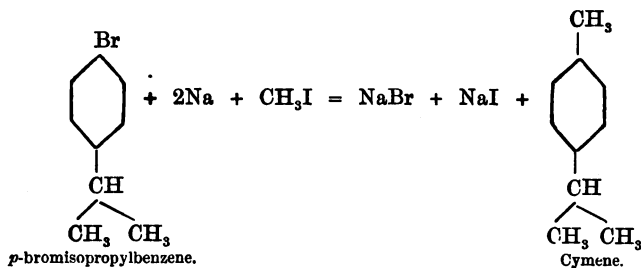
² An idea of these investigations can be obtained from the following papers: A. Baeyer, *Ber. d. d. chem. Gesellsch.* 1898, vol. xxxi. pp. 1401 and 2067; O. Wallach, *Liebig's Ann. d. Chem.* 1898, vol. ccxii. p. 371. The earlier extensive literature is cited in these papers.

chemical processes occurring in plant life. The terpenes are the end members of the reduction processes of vegetable metabolism, and the exact knowledge of their structure should be a fruitful field of inquiry for the physiological botanist; at the present time, however, the results of investigations upon the structure of the terpenes are only of interest to the specialists in this branch.

The near relationship of the terpenes to the aromatic compounds follows from the fact that they are converted by the action of mild oxidising agents into true aromatic compounds, derivatives of benzene. Thus, the practically important representative of the terpenes, oil of turpentine, when heated with iodine, changes into cymene with the loss of two atoms of hydrogen:



Cymene is an aromatic compound whose constitution has been definitely determined, as it can be prepared synthetically by the action of sodium upon *p*-bromisopropylbenzene and methyl iodide:



Thymol, an important antiseptic in medicine, which is contained in oil of thyme (from *Thymus Serpyllum*), is closely related to cymene. It differs from cymene by a hydroxyl group, which is contained in the benzene ring with the methyl and isopropyl radicals; it is an oxycymene. At the ordinary temperature it forms crystals which are soluble in 1,100 parts of water; and on account of this difficulty of solution in water, thymol is not caustic like many other phenols, and can therefore be used internally as an antiseptic; it is used for killing the dangerous intestinal parasite *Anchylostoma duodenale*.

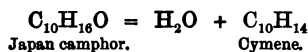
Turpentine oil is prepared on the large scale from turpentine, the resinous mass which oozes from the bark of the Coniferae. The whole gelatinous mass which oozes out from the bark is known generally as resin, but the chemist applies the term resin to the residue remaining after the distillation of the gummy mass with

water; the portion which distils over with the steam is a terpene, turpentine oil. Turpentine is a solution of resins in terpenes, and these thick solutions in the terpenes, or other ethereal oils, which ooze out from many plants have chemically the general name of balsams. Certain balsams contain, together with the resins and terpenes, specific constituents to which a healing power is attributed, such as balsam of Peru, balsam of Tolu, storax, balsam of Copaiva, etc., which are used as external and internal remedies.

Turpentine oil is a colourless liquid almost insoluble in water, but soluble in alcohol, and ether; it dissolves resins, caoutchouc, sulphur, phosphorus, etc., and technically is largely used in the preparation of oil paints, lacquers, etc.; medicinally, it is used as a skin irritant, as an antiseptic, and as an astringent.

The resins which remain behind after the distillation of the terpenes, and essential oils, from the balsams are also not chemical entities, but mixtures of still insufficiently known compounds, free from nitrogen, but containing oxygen. These mixtures form amorphous, transparent, glass-like, brittle masses with conchoidal fractures, insoluble in water and acids, but soluble in alcohol, ether, and turpentine oil. The resins dissolve in alkalis, forming soapy frothing solutions, from which they are precipitated by acids; they therefore appear to be a mixture of acids, the separation of which has not yet been accomplished, as they do not distil without decomposition. Technically the various resins are used in the preparation of varnishes, lacquers, resin soaps, etc.

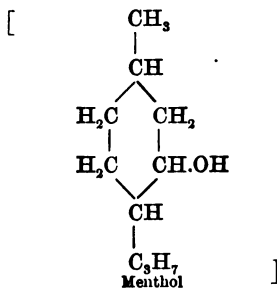
The camphors stand in close relationship to the terpenes; they contain oxygen, and are solid at the ordinary temperature. In their reactions they behave partly as ketones, and partly as alcohols. Ordinary camphor, the medicinally important Japan camphor which is obtained by distillation with water from the finely cut wood of *Laurus camphora*, differs from the terpenes in its empirical molecular formula by containing an atom of oxygen more, and, like certain terpenes, is closely related to cymene; by the action of a dehydrating agent, phosphoric acid anhydride, it is converted into cymene:



By the action of nascent hydrogen Japan camphor is converted into Borneo camphor, which has the formula $\text{C}_{10}\text{H}_{18}\text{O}$. This, as well as other reactions, shows that Japan camphor is a ketone, and Borneo camphor a secondary alcohol. In nature, Borneo camphor is found

in the wood of *Dryobalanops camphora*, a tree which grows in Borneo and Sumatra. Both camphors are used in medicine, chiefly for the stimulation of the respiratory and circulatory nerve centres, as well as of the heart muscle, in threatening collapse.

Chemically, the European camphor menthol, which is obtained by distilling with water the leaves of the peppermint-plant, *Mentha piperita*, is closely related to the above two foreign camphors; it is used as an antiseptic, and has the composition $C_{10}H_{20}O$, and behaves as an alcohol :



LECTURE XVI

THE ALKALOIDS

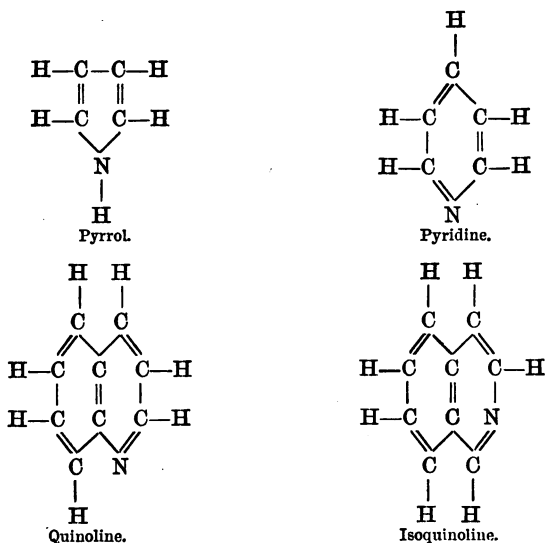
ALKALOIDS are organic bases containing nitrogen which occur in the vegetable kingdom, and are characterised by their intense action upon the animal body. Most of them are deadly poisons, and at the same time many are valuable drugs, such as quinine, morphine, atropine, and cocaine. The term alkaloid is therefore not a *chemical* one; in chemistry substances are not classified according to their origin, nor according to their action on the animal body. They are divided up according to their chemical constitution. Have the alkaloids, then, any common properties in their constitution? All organic bases are not regarded as alkaloids; a whole series of organic bases have already been mentioned, which are substituted ammonias—namely, methylamine, dimethylamine, ethylamine, oxamine, urea, guanidine, aniline, toluidine, glucosamine—and these are not classed amongst the alkaloids. The question therefore arises, do we know anything concerning the constitution of the alkaloids? This is a question of the greatest practical interest, and its solution would be of the utmost importance, as stated in the preliminary considerations upon the advances of synthetical chemistry. It was stated that the production of the practically important alkaloids, morphine, quinine, etc., required large tracts of land for their cultivation, and that after their constitution had been investigated, their synthesis might be accomplished; and still more that their production by synthesis would be associated with a smaller expenditure of time and energy than when they were produced by cultivation, so that by their synthesis, large tracts of land would again be set free for the production of food-stuffs (p. 12).

For several decades the aims of organic chemistry have therefore been directed to the study of the constitution of the alkaloids, and until recent times we were tied by the belief that the alkaloids were substituted ammonias, or ammonium bases, and in this supposition

we were confirmed, because those alkaloids whose synthesis was first determined, amanatine and muscarine, were, as a matter of fact, substituted ammonium bases (p. 11).

The investigations of the last decades first showed that the nitrogen in the practically important alkaloids, in quinine, atropine, etc., was not contained as a substituted ammonia, but was present in closer combination. It is present in a closed chain of carbon atoms, and such compounds, which contain a ring made up not only of carbon atoms, but also of other elements, are called *heterocyclic*, in contradistinction to the *homocyclic* compounds, which so far have been described, such as benzene, naphthalene, and anthracene.

The principal nitrogen-containing rings present in the alkaloids are the pyrrol, pyridine, quinoline, and isoquinoline rings :



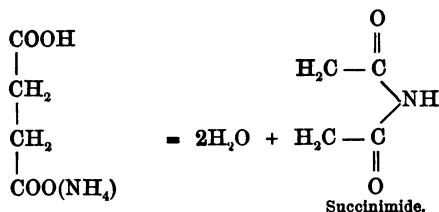
These heterocyclic ring compounds and their derivatives have been found amongst the decomposition products of many alkaloids, and this has led to the discovery of their constitution.

Before, however, passing to their chemistry, some knowledge of the above nitrogen-containing ring compounds must be obtained.

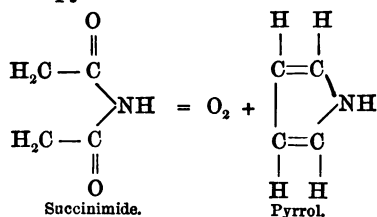
Pyrrol was discovered in 1834 by F. F. Runge (1795–1867) in coal-tar; it is also found amongst the products of distillation of animal substances, bones, etc., which are obtained as by-products in the preparation of animal charcoal, and are known as Dippel's bone-oil. Pyrrol can be isolated from these tars and oils by fractional

distillation, and is a colourless liquid with a smell resembling that of chloroform, boiling at 131°C .

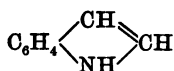
Pyrrol is prepared synthetically from succinic acid (p. 84). If the acid ammonium salt of this acid be submitted to distillation, it loses two molecules of water, and succinimide, a crystalline compound, is obtained :



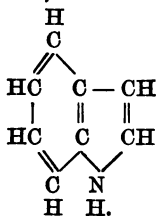
By distilling succinimide with zinc dust, two atoms of oxygen are removed from it and pyrrol results :



A derivative of pyrrol has previously been met with—namely, indole, (p. 194) whose formula was written,

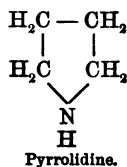
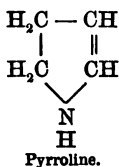
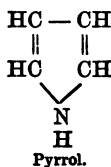


but if we introduce into this formula the structure of the benzene ring, we see that indole can be regarded as formed by the fusion of a benzene ring with a pyrrol ring, in the same way as naphthalene arises from the fusion of two benzene rings, so that they have two carbon atoms in common (p. 202) :

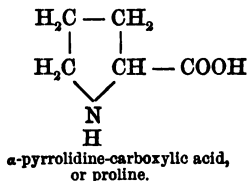


If nascent hydrogen be allowed to act upon pyrrol, it is converted

into the two compounds pyrroline and pyrrolidine, which are richer in hydrogen :



Of the derivatives of pyrrolidine, α -pyrrolidine-carboxylic acid, [or proline,] is of physiological interest :



It was discovered by Emil Fischer¹ amongst the products of the hydrolytic decomposition of proteins (cf. Lecture 17), and it has been prepared synthetically by Willstätter² and by E. Fischer.³

Pyrrol is of still further physiological interest in that the colouring matter of blood, haematin, and the chlorophyll of plants—the two substances which play such an important part in the production of energy, and in the metabolism of animal and vegetable life—are derivatives of it, as shown by the investigations of Nencki and his pupils.⁴ The structure of these colouring matters is, however, not yet definitely determined.

Pyridine was discovered in 1851 by the Scotch chemist, Thomas Anderson (1819–1874), a pupil of Liebig's, in Dippel's bone-oil, and later also in coal-tar. It is a colourless liquid boiling at 115° C., miscible with water in all proportions. Its aqueous solution reacts strongly alkaline, and pyridine adds itself to acids, just as ammonia does, forming salts, the majority of which are soluble in water.

The following methods of preparing it synthetically give us an insight into its constitution : If acetylene and the vapours of prussic acid be passed through a red-hot tube, a combination of two molecules of acetylene with one molecule of prussic acid occurs, in the

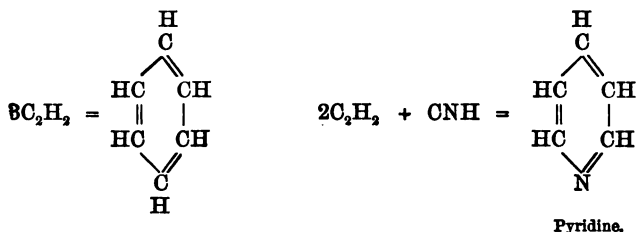
¹ E. Fischer, *Z. f. physiol. Chem.* 1901, vol. xxxiii. pp. 151 and 412; 1902, vol. xxxv. p. 70.

² R. Willstätter, *Ber. d. d. chem. Gesellsch.* 1900, vol. xxxiii. p. 1160.

³ E. Fischer, *ibid.* 1901, vol. xxxiv. p. 454.

⁴ M. Nencki and J. Zaleski, *ibid.* 1901, vol. xxxiv. p. 997. M. Nencki and L. Marchlewski, *ibid.* 1901, p. 1687. Here the earlier literature of the constitution of haematin and chlorophyll is cited, especially the work of W. Küster and of E. A. Schunck.

same way that three molecules of acetylene combine to form a molecule of benzene :



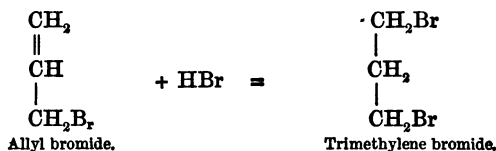
Pyridine.

This synthesis allows of the supposition that pyridine is constituted in a similar way to benzene, to which in many of its reactions it is analogous. Pyridine is a very stable compound, and is not oxidised by concentrated nitric or chromic acids ; only at a high temperature is it converted into a sulphonic acid by concentrated sulphuric acid, and by halogens it is only attacked with difficulty.

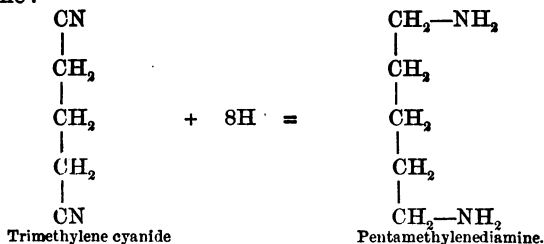
A second synthesis which gives an insight into the constitution of pyridine is that from pentamethylene diamine :



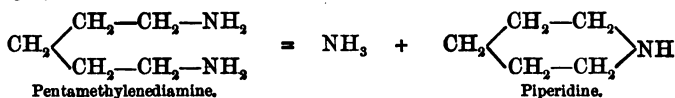
This compound is formed by the bacterial decomposition or putrefaction of animal tissues, rich in protein, and has therefore been termed cadaverine. It can be built up from its elements ; the synthesis of allyl alcohol has been already described (p. 98) and from allyl alcohol we can easily prepare allyl bromide. If this be saturated with hydrobromic acid and allowed to stand in the dark at $+35-40^\circ \text{C}$., combination occurs, and trimethylene bromide results :



Trimethylene bromide is converted into trimethylene cyanide (p. 84) by the action of potassium cyanide, and this compound is reduced by nascent hydrogen—by the action of sodium and boiling alcohol—to the diamine :

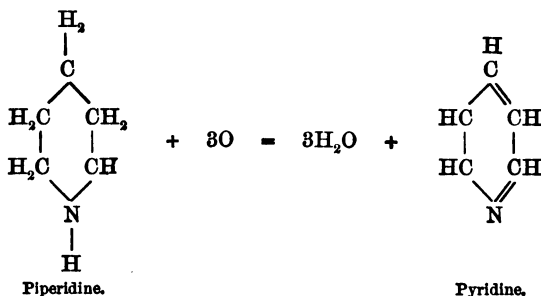


Pentamethylenediamine is a colourless, syrupy compound, which crystallises in the cold, and has the penetrating smell of semen. It is soluble in water, and forms salts by adding itself to acids. If its hydrochloride be heated, the pentamethylenediamine loses a molecule of ammonia, and piperidine, a compound with a closed ring, is formed :



Piperidine is a colourless liquid with an unpleasant smell, and of strongly basic properties. Combined with piperic acid ($\text{C}_{12}\text{H}_{10}\text{O}_4$) it is found in pepper, from which it can be obtained by distillation with caustic potash.

Six hydrogen atoms can be removed from piperidine by heating it to 300°C. with concentrated sulphuric acid ; the sulphuric acid is thereby reduced to sulphurous acid, and the piperidine is converted into pyridine :



Conversely, pyridine can be reduced to piperidine by nascent hydrogen—sodium and alcohol—and by still stronger reducing agents—hydriodic acid at 300°C. —it is reduced to normal pentane and ammonia.

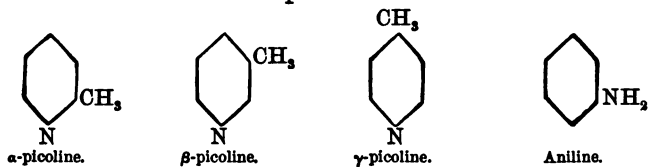
Most chemists use a simplified formula for pyridine, just as for benzene (p. 167).



In certain reactions pyridine behaves as a tertiary amine, i.e. as a substituted ammonia in which all the three hydrogen atoms are replaced by alkyl radicals ; in pyridine, the three valencies of the

nitrogen are joined to carbon. Just as a tertiary amine adds on methyl iodide, and changes into a quaternary ammonium base, so also, pyridine can add on methyl iodide to its nitrogen atom. This property is possessed by many alkaloids, as we shall see later, and in this sense we can regard these alkaloids as tertiary amines.

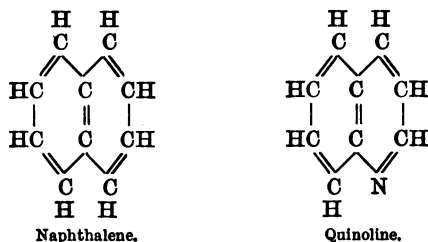
The hydrogen atoms in pyridine can be substituted by alkyl radicals just as in benzene. When one methyl group takes the place of a hydrogen atom, three isomers are possible corresponding to the three disubstitution products of benzene. They are designated as the α -, β -, and γ -compounds, according to the position of the methyl group in relation to the nitrogen atom. They are all found in coal-tar and in Dippel's bone-oil, and are known as the picolines. Aniline is a fourth isomer of the three picolines :



By the oxidation of the three picolines, three isomeric pyridine carboxylic acids are obtained; when distilled with lime these are decomposed into pyridine and carbonic acid. This process is exactly analogous to the decomposition of benzoic acid into benzene and carbonic acid, and of acetic acid into marsh gas and carbonic acid (pp. 177 and 53).

The pyridine carboxylic acids are also formed in the oxidation of certain alkaloids, and this fact has led to the discovery of the constitution of these alkaloids.

Quinoline bears the same relation to naphthalene as pyridine does to benzene :

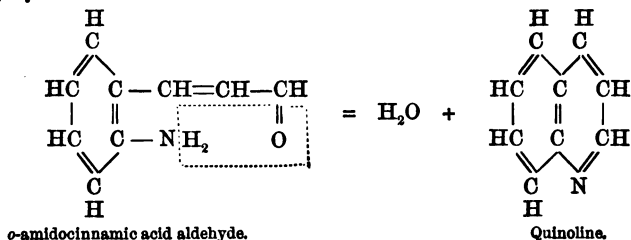


or written more simply,

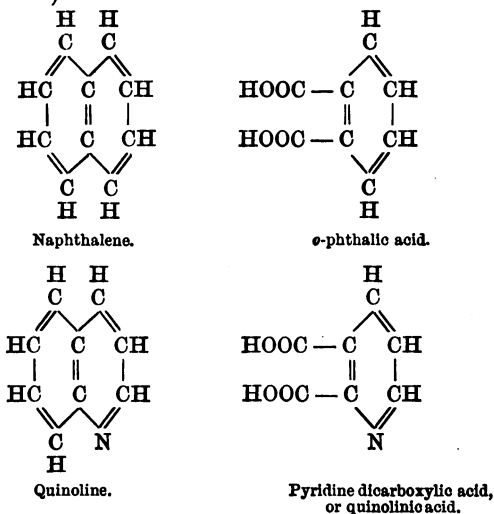


Quinoline is found in coal-tar and in bone-oil ; it is a colourless liquid with a strong characteristic smell, heavier than water and only slightly soluble in it, boiling at 236° C. Its structure can be seen from the following synthesis.

The aldehyde of ortho-amidocinnamic acid (p. 186) in alkaline solution loses a molecule of water, and is converted into quinoline¹:



This synthesis shows that quinoline is an ortho-derivative of benzene, and that the nitrogen atom is directly combined to one of the carbon atoms of the benzene ring. The structure of the nitrogen containing ring can be deduced from the following reactions. On oxidation, quinoline yields the dibasic quinolinic acid, in an analogous way to naphthalene, which, on oxidation, gives the dibasic ortho-phthalic acid (p. 202) :

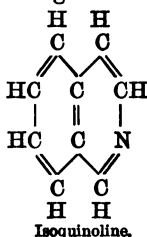


If phthalic acid be distilled with lime it is decomposed into benzene and two molecules of carbonic acid; likewise, quinolinic

¹ For details of the preparation of o-amidocinnamic aldehyde and quinoline, see Paul Friedländer, *Ber. d. d. chem. Gesellsch.* 1882, vol. xv. p. 2572.

acid, under the same conditions, breaks down into pyridine and two molecules of carbonic acid. It follows, therefore, from the synthesis and the above reactions that quinoline contains a benzene ring and a pyridine ring, and that the two rings have two carbon atoms in common, and it also follows from the synthesis that the nitrogen atom substitutes a CH group of naphthalene, in the α -position (p. 203).

In coal-tar, together with quinoline, the isomeric compound, isoquinoline, is found; its synthesis has been carried out by several methods. Isoquinoline is a naphthalene in which a CH group in the β -position is replaced by a nitrogen atom:



This follows from the simple fact that isoquinoline on oxidation yields a pyridine dicarboxylic acid as well as ortho-phthalic acid, whereas quinoline only yields a pyridine dicarboxylic acid, and never phthalic acid.

Both the bases, quinoline and isoquinoline, occur amongst the decomposition products of certain alkaloids, but before passing on to the chemistry of the alkaloids, a fact, physiologically very interesting and remarkable, must be mentioned—namely, the occurrence of a quinoline derivative amongst the end products of animal metabolism.

In 1853 Liebig¹ discovered in dog's urine an acid of the empirical formula $C_{10}H_7NO_3$. It is insoluble in water, and is precipitated on acidifying the urine with hydrochloric acid. It has so far only been found in dog's urine, and is therefore called kynurenic acid [$\kappa\upsilon\upsilon\epsilon\iota\omicron\varsigma$, canine], but it does not always occur in dog's urine, and its quantity is very small. It increases with the amount of the breakdown of protein, but which of the decomposition products of protein is the mother-substance of kynurenic acid in the organism of the dog has not yet been decided, in spite of numerous tedious and careful experiments.²

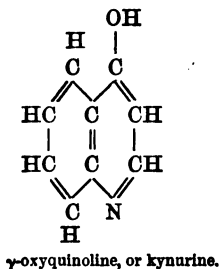
Schmiedeberg and Schultzen³ showed that kynurenic acid, when

¹ Liebig, *Liebig's Ann. d. Chem.* 1853, vol. lxxvi. p. 125.

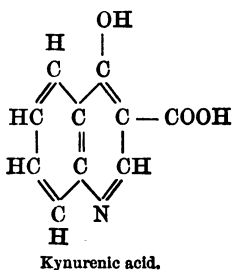
² On these experiments see K. Glaessner and L. Langstein, *Beitr. z. chem. Physiol. Path.* 1901, vol. i. p. 34. W. J. Gies, *Amer. Journ. Physiol.* 1901, vol. v. p. 191. L. B. Mendel and E. C. Schneider, *ibid.* p. 427.

³ O. Schmiedeberg and O. Schultzen, *Liebig's Ann. d. Chem.* 1872, vol. clxiv. p. 155.

heated in the dry state, melted and decomposed into carbonic acid and a crystalline base, kynurine, which has the composition C_9H_7NO . M. Kretschy¹ found that on heating kynurenic acid with zinc dust to a dull red heat, quinoline C_9H_7N distilled over, and Kretschy therefore rightly recognised kynurine as oxyquinoline, and kynurenic acid as oxyquinoline-carboxylic acid. Fr. Wenzel² synthesised kynurine, and showed that it was identical with γ -oxyquinoline :



Finally, R. Camps³ completely synthesised kynurenic acid, and showed that it was γ -oxy- β -quinoline-carboxylic acid :



The alkaloids are generally divided into those containing, and those not containing oxygen. The latter are liquids, volatile without decomposition; the former are crystalline solids, and with few exceptions are not volatile without decomposition. In the plant tissues the alkaloids are combined with organic acids, and in order to obtain the volatile alkaloids free from oxygen, it suffices to distil the broken-up portions of the plant with caustic soda, when the liberated alkaloids pass over with the steam. The non-volatile alkaloids containing oxygen are generally isolated by first extracting the portions of the plant with dilute acids, and from this acid solution many bases, which are insoluble or soluble with difficulty in water, are precipitated by alkalis; in other cases a more detailed method must be carried

¹ M. Kretschy, *Monatshefte f. Chem.* 1881, vol. ii. p. 57.

² Fr. Wenzel, *ibid.* 1894, vol. xv. p. 453.

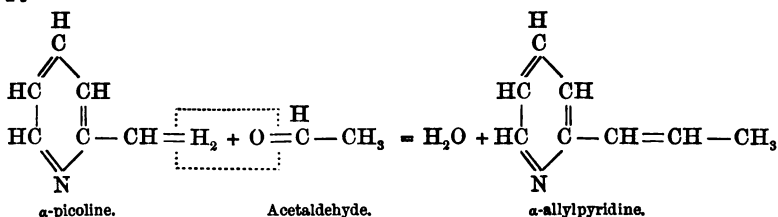
³ R. Camps, *Z. f. physiol. Chem.* 1901, vol. xxxiii. p. 390.

out. All alkaloids are precipitated from acid solution by the so-called 'alkaloid reagents': tannic acid, phosphotungstic acid, phosphomolybdic acid, potassium cadmium iodide, potassium mercuric iodide, picric acid, etc. On decomposing these precipitates with alkali, the alkaloids are liberated and can be extracted with alcohol, ether, chloroform, etc. The alkaloids add themselves to acids like ammonia, and form crystalline salts.

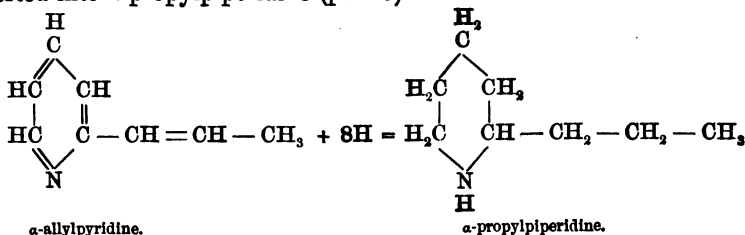
Conine and nicotine are examples of oxygen-free alkaloids.

Conine is found in all parts, but especially in the fruit, of the hemlock, *Conium maculatum*. It is a colourless liquid with a penetrating unpleasant smell, boiling at 168°C ., and rotating the plane of polarisation to the right; it is soluble in water and soon becomes brown in the air, and is an intense narcotic poison. Elementary analysis shows that it has the formula $\text{C}_8\text{H}_{17}\text{N}$, and A. Ladenburg¹ in 1886 succeeded in synthesising conine and determining its constitution.

Ladenburg started from α -picoline, which can be prepared synthetically by several methods, e.g. by heating pyridine with methyl iodide. Paraldehyde, which at a high temperature breaks down into three molecules of acetaldehyde, was allowed to act upon the α -picoline by heating them together in a sealed tube for ten hours at $250\text{--}260^{\circ}\text{C}$. Combination, with loss of water, occurred, and α -allylpyridine was formed:



When α -allylpyridine is heated to boiling in alcoholic solution with sodium, eight atoms of hydrogen are taken up, and it is converted into α -propylpiperidine (p. 215)



¹ A. Ladenburg, *Ber. d. d. chem. Gesellsch.* 1886, vol. xix. pp. 439 and 2578 and 1894, vol. xxvii. p. 3062.

The α -propylpiperidine thus prepared differed only from the naturally occurring conine of the hemlock by being optically inactive, as are all synthetically prepared compounds (p. 79). By crystallising its tartrate Ladenburg succeeded in separating his synthetically prepared conine into a dextro-rotatory and a lævo-rotatory modification.

The optical activity of conine shows that the propyl group is attached to the carbon atom in the α -position, and that the picoline from which the synthesis was started is α -picoline, for, if the propyl group were attached to the carbon atom in the β - or γ -position there would be no asymmetric carbon atom. Further proof that the propyl group occupies the α -position is given by the fact that conine, on reduction with hydriodic acid, breaks down into *normal octane* and ammonia, whereas β - or γ -propylpiperidine must yield an octane with a branched chain of carbon atoms.

The synthetically prepared dextro-rotatory conine of Ladenburg had exactly the same rotatory power as that obtained from the hemlock; its boiling point, and the melting points of its salts, also corresponded; and, finally, its toxic action was compared with that of the naturally occurring conine by A. Falck, who found that the symptoms of poisoning, and the lethal dose, were the same. Thus, the first synthesis of a true alkaloid—i.e. a poisonous plant base belonging to the heterocyclic compounds—was accomplished.

Several other bases are found with the conine in the hemlock, some of which are more poisonous than conine. One of them, coniine, which differs from conine by containing two atoms of hydrogen less, was artificially prepared from conine in 1885 by Aug. Wil. Hofmann¹ (1818–1892), who made the greatest advances in our knowledge of the constitution of the conine group of alkaloids.

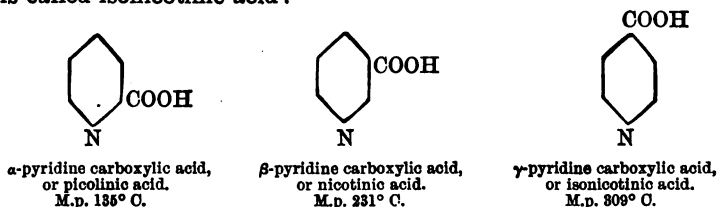
Nicotine, the poisonous constituent of the tobacco plant, is an alkaloid very similar to conine in many of its properties. It is also a colourless liquid, with the characteristic smell of tobacco, boiling at 247° C. It is partially decomposed when boiled in the air, but in a current of hydrogen it can be distilled without decomposition. It quickly turns brown in the air, like conine, is miscible with water, and forms crystalline salts with acids.

Nicotine has a more complicated composition than conine; its empirical formula is $C_{10}H_{14}N_2$; it contains two atoms of nitrogen, and is therefore a diacid base. By potassium permanganate it is

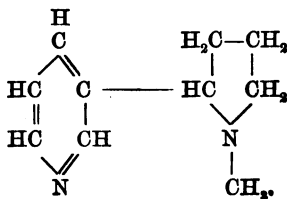
A. W. Hofmann, *Ber. d. d. chem. Gesellsch.* 1885, vol. xviii. pp. 5 and 109.

oxidised to a pyridine carboxylic acid—namely, β -pyridine carboxylic acid. The following is a proof for the β -position of the carboxyl group.

As we have seen, there are three isomeric pyridine carboxylic acids (p. 216), which differ from one another in their physical properties, especially in their melting points; by the oxidation of conine a pyridine carboxylic acid is obtained which melts at 135°C .; this must be α -pyridine carboxylic acid, since conine contains only one side chain in the α -position (p. 221), and it is called picolinic acid. By the oxidation of quinoline, a pyridine dicarboxylic acid, quinolinic acid (p. 217), is obtained; and in this acid the two carboxyl groups are in the α - and β -positions. On heating quinolinic acid, it loses a molecule of carbonic acid, yielding a monocarboxylic acid which is not identical with the α -acid, or picolinic acid; it melts at 231°C ., and must be the β -acid, and it is identical with the pyridine carboxylic acid obtained by the oxidation of nicotine. It follows that the pyridine carboxylic acid obtained by the oxidation of nicotine must be the β -acid, and it is called nicotinic acid. The third pyridine carboxylic acid, which sublimes without melting, but melts in a sealed capillary tube at 309°C ., must be the γ -pyridine carboxylic acid, and it is called isonicotinic acid:



The preparation of β -pyridine carboxylic acid from nicotine shows that nicotine contains a pyridine ring, and that attached to this ring in the β -position there is a side chain containing five carbon atoms and one nitrogen atom. Further investigations have shown that this side chain consists of a pyrrolidine ring (p. 213), in which the hydrogen atom attached to the nitrogen atom is replaced by a methyl group. The constitutional formula of nicotine is therefore:



The correctness of this formula, put forward by A. Pinner,¹ on the basis of the decomposition products, was confirmed by synthesis by Amé Pictet.²

The nicotine from tobacco leaves is lævo-rotatory. Pictet separated his synthetical nicotine, by the crystallisation of the tartrate into its two optical antipodes, and showed that his synthetical lævo-rotatory nicotine had exactly the same rotatory power, the same boiling point, and the same specific gravity as the natural nicotine, and that the two were identical in every way.

Until quite recently it was believed that the tobacco plant, amongst all the plants known to us which contain poisonous alkaloids, was the only one which contained one single poison, but Pictet and Rotschy³ showed that besides nicotine at least three other alkaloids were present in tobacco, which were poisonous, and could be distilled without decomposition. This is a fact which must be taken into consideration in any judgment upon the harmful action of smoking.

Nicotine is extremely poisonous; 4 milligrammes—i.e. about one-tenth of a drop—introduced into the stomach of a man produced severe symptoms of poisoning, giddiness, deafness, clonic spasms of the whole body, disturbances of breathing, sleeplessness, etc. The symptoms of poisoning lasted three days.⁴

Dry tobacco leaves contain 1-8 per cent. of nicotine. Smoking does not produce the more severe symptoms of poisoning, the explanation of which is that the greater part of the nicotine is destroyed by burning. The greater part of the free alkaloid would volatilise before it was burnt. In the tobacco leaves it is present in combination with tartaric and malic acids.

From a physiological point of view it is remarkable that the dextro-rotatory and lævo-rotatory nicotine behave differently in the body. The lethal dose of *l*-nicotine to guinea-pigs is half as great as that of *d*-nicotine, and the toxic symptoms are different.⁵ This reminds us of the different behaviour of diabetic patients to dextro-rotatory and lævo-rotatory sugar (p. 119), and of certain bacteria and moulds to *d*- and *l*-lactic acid, etc. (pp. 79 and 89).

The family of the *Solanaceæ*, to which the tobacco plant belongs,

¹ A. Pinner, *Ber. d. d. chem. Gesellsch.* 1893, vol. xxvi. p. 292; and 1894, vol. xxvii. p. 1053.

² A. Pictet and P. Crépieux, *ibid.* 1895, vol. xxviii. p. 1904. A. Pictet, *ibid.* 1900, vol. xxxiii. p. 2355. A. Pictet and A. Rotschy, *ibid.* 1904, vol. xxxvii. p. 1225.

³ A. Pictet and A. Rotschy, *ibid.* 1901, vol. xxxiv. p. 696.

⁴ C. D. Schroff, *Text Book of Pharmacology*, 2nd ed. (Braumüller: Vienna, 1862), p. 560.

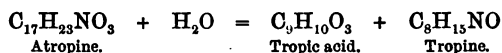
⁵ A. Mayor, *Ber. d. d. chem. Gesellsch.* 1904, vol. xxxvii. p. 1234.

is a very poisonous one. To it belongs the belladonna plant (*Atropa belladonna*), with its intensely poisonous alkaloids, atropine, hyoscyamine, and belladonine; the mandragora, with its stupefying poisons already known by the ancients and used by them as a hypnotic and as a charm, was the mandrake of the old German people, to which many superstitions were attached; further, the poisonous henbane (*Hyoscyamus niger*), and the poisonous thorn-apple (*Datura stramonium*), both of which contain the same poisons as belladonna. Even the potato (*Solanum tuberosum*), and the tomato (*Solanum lycopersicum*), which serve as foodstuffs, contain the poisonous glucoside solanine, which decomposes into sugar, and the poisonous alkaloid solanidine. The quantity of these in the potato tubers is generally very small, but occasionally rises, chiefly in young and in diseased tubers, to such a degree that severe, though non-fatal, wholesale poisoning in man has been recorded.

Of the large number of poisonous alkaloids of this plant family atropine is the most important, as it not only has an interesting physiological action upon the nervous system, and is the most important drug used in the treatment of eye-diseases, but also because its synthesis has been accomplished, and its complicated structure made clear.

Atropine, like all alkaloids which contain oxygen, is a solid at the ordinary temperature, crystallising in colourless prisms. It dissolves in 300 parts of cold water, easily in alcohol, but less so in ether. It melts at 115° C., and is optically inactive. Together with atropine, in belladonna, henbane, and the thorn-apple, the isomeric alkaloid hyoscyamine is found, which is optically active and lævo-rotatory. When heated to its melting point, 108.5° C., or by merely allowing it to stand in alcoholic solution containing a little caustic soda, it changes into atropine, the two bases being only stereoisomeric. [Atropine is in fact *dl*-hyoscyamine.]

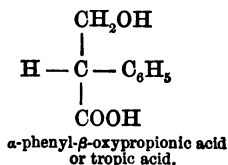
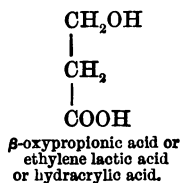
Atropine, when boiled with baryta water, is decomposed, with absorption of water, into tropic acid and the base, tropine:



If a solution of tropine and tropic acid in dilute hydrochloric acid be evaporated down, combination again occurs, with the loss of a molecule of water;¹ it therefore appears that they are combined in the form of an ester. Atropine is the tropic acid ester of tropine. Since both tropic acid and tropine can be prepared synthetically, so atropine can also be prepared by synthesis.

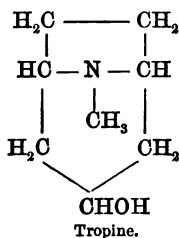
¹ A. Ladenburg, *Liebigs Ann. d. Chem.* 1883, vol. ccxvii. p. 82.

Tropic acid, a compound soluble in water and crystallising in fine white needles, is a β -oxypropionic acid (p. 75), in which a hydrogen atom in the α -position is replaced by a phenyl group:



Tropic acid contains an asymmetric carbon atom, and is therefore capable of existence in three modifications as *d*-, *l*-, and *i*- tropic acid. Ladenburg and Rügheimer¹ have synthesised tropic acid and determined its constitution.

Tropine crystallises in plates, which are easily soluble in water and alcohol, melting at 62° C. and boiling without decomposition at 229° C. The investigation of the constitution of tropine has recently been carried out by Richard Willstätter,² who finally succeeded in synthesising it. According to these investigations the constitution of tropine is the following: Tropine is a tertiary base (pp. 37 and 215), and at the same time a secondary alcohol, the hydroxyl group being attached to a closed heptamethylene ring, and the nitrogen-containing group forming a 'bridge' in this ring:

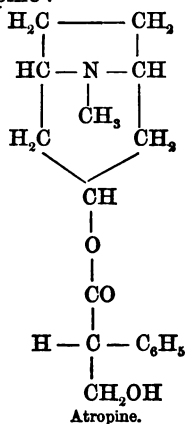


The assumption of a 'nitrogen bridge' explains the facts that from tropine, although it contains only one nitrogen atom, under different conditions, sometimes a pyrrolidine ring (p. 213), sometimes a piperidine ring (p. 215), is split off. On account of its hydroxyl group, tropine can combine with acids, with the elimination of water,

¹ A. Ladenburg and L. Rügheimer, *Ber. d. d. chem. Gesellsch.* 1880, vol. xiii. pp. 373 and 2041.

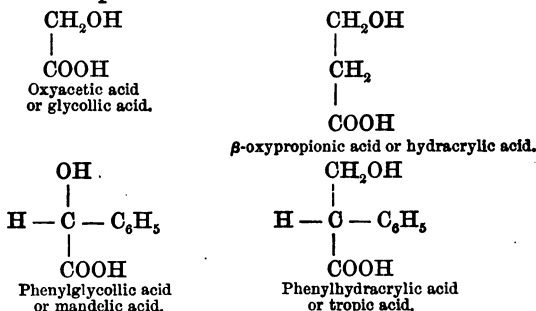
² R. Willstätter, *ibid.* 1901, vol. xxxiv. p. 3163; *Liebig's Ann. d. Chem.* 1901, vol. cccxvii. p. 204, and 1903, vol. cccxxvi. p. 1.

to form esters, and the following formula of atropine shows that it is the tropic acid ester of tropine :



Atropine has beautiful colour reactions, by which it can be distinguished from other alkaloids. If a crystal of an atropine salt be dissolved in fuming nitric acid, and the solution be evaporated to dryness and allowed to cool, and then a drop of alcoholic potash added, a beautiful violet colour appears (Vitali's reaction).

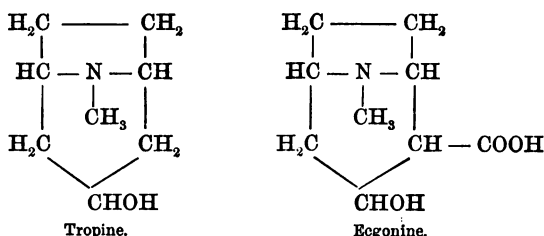
Atropine is a so-called mydriatic—i.e. it paralyses the nerve-endings in the sphincter pupillæ and in the ciliary muscle. Tropine has not this action, but its esters with aromatic acids, other than tropic acid, have, as was first shown by Rudolf Buchheim,¹ who found that the benzoic acid ester of tropine was a mydriatic. Later, many experiments were made to prepare artificial esters of tropine, the so-called tropeines, in the hope that one of them would offer advantages over atropine. The homologues of tropic acid were first thought of, and homatropine, the tropine ester of the homologue of tropic acid—namely, mandelic acid—has actually been adopted in ophthalmic practice :



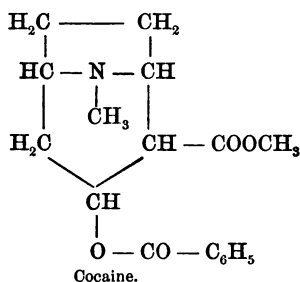
¹ R. Buchheim, *Arch. f. exper. Pathol. u. Pharmacol.* 1876, vol. v. p. 463.

From the above formula it is seen that mandelic acid is a homologue of tropic acid, and, therefore, the tropine ester of mandelic acid has been called homatropine. The mydriatic action of homatropine takes place sooner, and disappears more quickly, than that of atropine, and, consequently, homatropine is preferred to atropine as a mydriatic for diagnostic purposes.

Cocaine, one of the poisonous alkaloids of the leaves of *Erythroxylon coca*, is similarly constituted to atropine, and it has in recent years found extended use as a local anæsthetic. It is also a derivative of tropine. If cocaine be heated with hydrochloric acid, it is decomposed, with the absorption of two molecules of water, into benzoic acid, methyl alcohol, and ecgonine, a carboxylic acid of tropine :



Cocaine can be again built up from ecgonine by benzylation and methylation :



Both ecgonine and cocaine have been synthetically prepared from tropine,¹ but so far the synthetic cocaine has not been separated into its optical antipodes. Natural cocaine is lævo-rotatory.

The chemical constitution of the remaining practically important

¹ More exact reasons for the foundation of the above formulæ, and on the synthesis of cocaine, are found in the papers by R. Willstätter and W. Müller, *Ber. d. d. chem. Gesellsch.* 1898, vol. xxxi. p. 2655; and R. Willstätter and A. Bode, *ibid.* 1900, vol. xxxiii. p. 411, and 1901, vol. xxxiv. p. 1457; and *Liebig's Ann. d. Chem.* 1903, vol. cccxxvi. p. 42.

alkaloids has not yet been exactly determined. From quinine bark twenty-four different alkaloids have already been isolated. Of these, quinine is extensively used on account of its specific action in malaria. Quinine has a more complicated structure than any of the above-described alkaloids; its empirical formula is $C_{20}H_{24}N_2O_2$; it possesses two nitrogen-containing rings, and is a diacid base; its constitution, in spite of many investigations, has not yet been definitely ascertained.¹ It is soluble with difficulty in water, and the dilute solutions of its acid salts show a beautiful blue fluorescence. This, and the following colour reaction, serve to differentiate quinine from other alkaloids; if chlorine water be added to a solution of a quinine salt and then ammonia, the solution becomes grass-green in colour.

The poppy is very rich in alkaloids; the dried milky juice of half-ripe poppy capsules is the so-called opium, from which twenty different alkaloids have been isolated, of which morphine is practically the most important. This has the empirical composition $C_{17}H_{19}NO_3$, and is a monacid tertiary base. Its constitution is not as yet definitely determined, but investigations have now come very near to its solution.²

Morphine is characterised by the following colour reactions: If a solution of morphine in concentrated sulphuric acid be heated to $100^\circ C.$, and when cooled a drop of nitric acid be added, an intense blood-red colour will be observed; if a crystal of a morphine salt be covered with a dilute solution of ferric chloride, a transitory blue colour appears.

If morphine be heated with concentrated hydrochloric acid to $140^\circ C.$, or with dilute sulphuric acid to the same temperature, it loses a molecule of water and passes into an amorphous alkaloid, which has quite other physiological properties than morphine; in particular, it is no longer a narcotic. This alkaloid is called apomorphine; its most striking action is the unfailing production of vomiting when small quantities are subcutaneously injected; this has led to its practical use. The changes which occur in the constitution of morphine in its conversion into apomorphine were little investigated

¹ The most recent work on the constitution of quinine is by W. Königs, *Journ. f. prakt. Chem.* 1900, vol. lxi. p. 146; Zd. H. Skraup, *Monatshefte f. Chem.* 1900, vol. xxi. pp. 512, 535, 879, and 1903, vol. xxiv. pp. 291, 311, and 669.

² The most recent papers, in which the older literature is cited, are by E. Vongerichten, *Ber. d. d. chem. Gesellsch.* 1900, vol. xxxiii. p. 352; R. Pschorr and C. Samuleanu, *ibid.* 1900, vol. xxxiii. p. 1810; L. Knorr, *ibid.* 1903, vol. xxxvi. p. 3074, and 1904, vol. xxxvii. p. 3494.

until recent times, and only a few years ago R. Pschorr¹ and his pupils successfully took up this toxicologically interesting question.

A series of very poisonous alkaloids are found in the varieties of *Strychnos*. The most important are strychnine, brucine, and the alkaloids of the American arrow poison, curare. Certain alkaloids in curare paralyse the nerve-endings in the skeletal muscle, and it is therefore much used in physiological experiments. R. Boehm² has succeeded in isolating these alkaloids from the varieties of curare which come into the market, and in carrying out their elementary analysis; but at present it has not been possible to crystallise these alkaloids, or their salts.

Brucine and strychnine, as also their salts, have been obtained in a crystalline state and studied in detail, but their constitution as yet has not been made quite clear; of recent times the most thorough investigations have been carried out by J. Tafel.³ Strychnine has the composition $C_{21}H_{22}N_2O_2$, brucine $C_{23}H_{26}N_2O_4$; they are both tertiary bases, but, in spite of their two nitrogen atoms, they are only monacid bases. It is supposed that brucine is the dimethoxy-derivative of strychnine. On fusion with potash, quinoline and indole are obtained from strychnine, and on heating with lime, β -picoline; brucine yields, when fused with potash, homologues of pyridine.

The close relationship of the two bases is also shown by their action on the animal body; strychnine is an intense poison, raising the reflex irritability, and causing thereby tetanic spasms; brucine acts in a similar way, but is less poisonous.

Strychnine can be recognised without fail by the following colour reaction: A few crystals of strychnine are placed in a porcelain basin, a few crystals of potassium chromate are added, and then a few drops of concentrated sulphuric acid; when these substances are mixed together with a glass rod dark violet streaks appear wherever they come in contact, which, however, soon disappear. Brucine does not give this reaction, but it is coloured red by concentrated nitric acid, and on the addition of zinc chloride the colour changes to violet.

¹ R. Pschorr, *Ber. d. d. chem. Gesellschaft*. 1902, vol. xxxv. p. 4377.

² R. Boehm, *Beitr. z. Physiol. for Ludwig's seventieth birthday*, 1886, p. 173. *Abhandl. d. math. phys. Cl. d. k. Sächs. Gesellschaft. d. W. zu Leipzig*, 1895, vol. xxii. p. 199, and 1897, vol. xxiv. p. 1.

³ J. Tafel, *Liebig's Ann. d. Chem.* 1891, vol. cclxiv. p. 33; 1892, vol. cclxviii. p. 229; 1891, vol. ccci. p. 285; 1898, vol. ccxiv. p. 26; *Ber. d. d. chem. Gesellschaft*. 1893, vol. xxvi. p. 333.

LECTURE XVII

THE PROTEINS

THE most difficult and most complicated, but at the same time the most important branch physiologically of the whole of organic chemistry, is the chemistry of the proteins.

Protein makes up the chief constituent of every animal and vegetable cell, and forms the most indispensable constituent of our food. The proteins which occur in the various tissues possess, amongst themselves, very great physical and chemical differences, and the questions may be asked: What have the proteins in common with one another? Why do they differ from all the substances which we do not designate as proteins? What is the meaning of the term protein?

All proteins are organic compounds containing nitrogen, and generally sulphur, with the similar percentage composition of

C	51-55 per cent.
H	7 "
N	15-17 "
S	0.4-2.5 "
O	20-30 "

[The term protein, as recommended by the Chemical and Physiological Societies of Great Britain,¹ comprises the following sub-classes:

1. Protamines, e.g. substances such as salmine, sturine, which have been obtained from fish-sperm.
2. Histones, e.g. more complex substances, such as the histone from blood corpuscles: they are distinguished by being precipitated by ammonia. This and the previous class probably pass gradually into one another.
3. Albumins, e.g. egg albumin in egg white, serum albumin in blood.

¹ *Proc. Chem. Soc.* 1907, vol. xxiii. p. 56. *Journ. Physiol. Soc.* 1907, vol. xxxv. Proc. p. 17.

4. Globulins, e.g. serum-globulin and fibrinogen in blood. Its derivative fibrin, and the myosin of muscle, are also included in this sub-class.
5. Scleroproteins (formerly albuminoids), e.g. gelatin, keratin (horn, nails, etc.).
6. Phosphoproteins (formerly nuclealbumins), e.g. caseinogen, and its derivative casein, in milk; vitellin in the yolk of eggs.
7. Conjugated proteins :
 - a. Nucleoproteins, combinations of protein with nucleic acids.
 - b. Glucoproteins, e.g. mucin, combinations of protein with carbohydrates.
 - c. Chromoproteins, e.g. hæmoglobin, combinations of protein with chromogenic compounds.
8. Derivatives of proteins. The products of protein hydrolysis :
 - a. Metaproteins, the most complex.
 - b. Proteoses, less complex than a.
 - c. Peptones, less complex than b.
 - d. Polypeptides : the majority are synthetical substances : a few have been obtained from the proteins. They consist of combinations of two or more amino-acids the elements of the protein molecule.]

The soluble proteins again have the common property that they never occur in the state of actual solution. They are colloids,¹ i.e. their apparent solutions do not diffuse through colloidal membranes. These colloidal solutions are optically active, rotating the plane of polarisation to the left.

Some of the soluble proteins have another common property; they occur in two different modifications, in an apparently dissolved, and in a coagulated state. The conditions under which they pass from one modification to another are different for the different examples, and serve, so long as we do not know the constitution of individual proteins, as a preliminary method of differentiating between them. Some proteins are kept in solution by water alone; these are called albumins; some require for their solution the presence of a small quantity of a neutral alkali salt, e.g. sodium chloride: these are called globulins. Both these kinds of protein

¹ A summary of the latest investigations upon the nature of the colloidal state, especially by means of the ultramicroscope, is given by R. Zsigmondy, *On Colloids* (Fischer: Jena, 1905).

occur together in blood serum and in the white of hens' eggs. If such a solution of protein be put into a dialyser, the sodium chloride diffuses out and the globulins separate as a flocculent coagulum, whereas the albumins remain in solution.

There are other proteins which are not kept in solution by neutral salts; they require bases for their solution. To this class belongs caseinogen, which forms the greater part of the proteins of milk; if the alkaline milk be treated with acetic acid until it is of a distinctly acid reaction, the caseinogen is precipitated in flakes, whereas the albumin and globulin of the milk remain in solution. When the neutral sugar of the milk is decomposed by bacterial fermentation into lactic acid, the caseinogen, or cheese, is precipitated as a coherent gelatinous mass. [Caseinogen contains 1 per cent. phosphorus, and hence is placed in the class of phosphoproteins.]

Many proteins of the living tissues have such a great tendency to pass into the coagulated condition that they coagulate as soon as the life of the tissue is extinguished; upon this depends the coagulation of blood and the rigor mortis of muscle.

All the albumins and globulins are coagulated (i.e. converted into a flocculent coagulum) at the boiling point, in neutral or slightly acid solution, in the presence of alkali salts; they are also coagulated by alcohol; these coagula are again soluble in dilute caustic alkali.

Certain proteins are known in a third modification, i.e. in the crystalline state; but it is never the pure protein which crystallises, but a compound of it with inorganic salts. Pure protein never occurs in nature; when converted into ash, a residue containing calcium, magnesium, or potassium is always left behind; ash-free protein has only been obtained artificially. Proteins have both acid and basic properties, corresponding to the amino-acids (p. 60) which constitute the greater portion of their hydrolytic decomposition products; it is therefore not extraordinary that protein, which meets with inorganic bases everywhere in the tissues, is always combined with them. This circumstance enables us to estimate the minimal size of a protein molecule from the quantity of metal of known atomic weight combined with it; there is as yet no other certain method. Proteins are not only not volatile without decomposition, but they cannot even be melted without decomposition, for they begin to char on heating before the evolution of gas. In animal and plant tissues only masses of incompletely formed crystals of protein have been found, the so-called crystalloids, or aleurone grains; they occur in the seeds and tubers of certain plants, and in the egg-yolks of many animals; by the recrystallisation of these crystalloids, the potassium and mag-

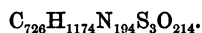
nesium compounds of the proteins have been obtained in completely formed crystals. The globulin and albumin of blood serum and of egg-white have also been successfully crystallised, and the compound of a protein with an iron compound, hæmatin, which forms hæmoglobin the red colouring matter of the blood, can be easily crystallised. This colouring matter constitutes about 15 per cent. of the weight of the total blood, and the greater portion—about 80 per cent.—of the dry substance of the red blood corpuscles; blood therefore furnishes a convenient and easily accessible material for the preparation of a crystalline protein. The empirical formula of hæmatin is $C_{32}H_{32}N_4O_4Fe$, and from the content in iron of hæmoglobin the empirical formula of the hæmoglobin molecule can be calculated; the minimal size of this molecule is obtained if we assume that the molecule contains only one atom of iron. Elementary analysis of the hæmoglobin of dog's blood gave

C	53.91	per cent.
H	6.62	"
N	15.98	"
S	0.542	"
Fe	0.333	"
O	22.62	"

from which the molecular formula can be calculated :



If we deduct from this formula the molecule of hæmatin, the molecular formula of protein is :



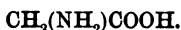
The calculation is not quite exact, as the decomposition of hæmoglobin into hæmatin and protein takes place with absorption of water. If the molecule of hæmoglobin contains more than one atom of iron, the formula must be multiplied. Hæmoglobin, therefore, at any rate, contains 758 atoms of carbon. With regard to the protein, it is conceivable that one molecule of hæmatin combines with three molecules of protein, each of which contains one atom of sulphur, and the molecular weight might be three times smaller than that calculated; but this is not probable, since the molecular weight of protein calculated from the above formula corresponds exactly with the molecular weight of protein which is calculated from the lowering of the freezing point. According to the above formula, the molecular weight is 16,122. From the lowering of the freezing point which water undergoes when egg albumin is dissolved in it,

figures are obtained which give it a molecular weight varying between 13,000 and 14,000.

These data are sufficient to give an idea of the size of the protein molecule; but regarding the figures only, it might seem doubtful whether we shall ever obtain an insight into its constitution. What induces us not to give up hope of discovering the constitution of protein is the fact that the protein molecule, without the use of energetic chemical and physical agents, and without radical change, but by simple hydrolysis alone, breaks down into a number of simple molecules, none of which, so far as we know at present, contain more than twelve atoms of carbon, and almost all of which have been already synthetically prepared. This hydrolysis can be effected both by ferments, as well as by boiling with dilute acids, and with bases, the products of decomposition being practically the same by the three methods. This is in favour of the presence of pre-formed radicals, or groups, in the protein molecule, and not of groups which have arisen by more violent decomposition.

The following compounds, almost all of which have been already referred to, have been obtained by the hydrolysis of proteins :

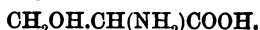
1. Glycine, glycocoll, or amino-acetic acid :



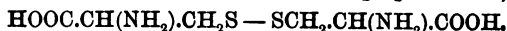
2. Alanine or α -aminopropionic acid :



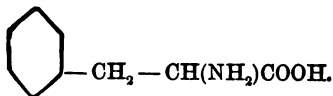
3. Serine or α -amino- β -oxypropionic acid :



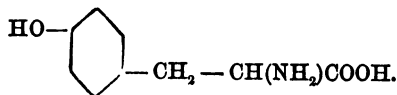
4. Cystine, or dicysteine, or di—(α -amino- β -thio-propionic acid) :



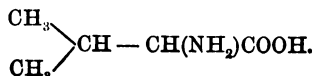
5. Phenylalanine or β -phenyl- α -aminopropionic acid :



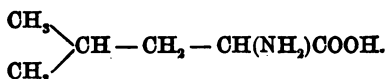
6. Tyrosine or p -oxy-phenyl- α -aminopropionic acid :



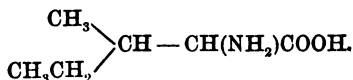
7. [Valine or] α -amino-isovalerianic acid :



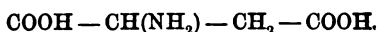
8. Leucine or α -amino-isobutylic acid:



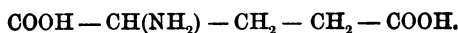
9. Isoleucine [or α -aminomethylethylpropionic acid]:



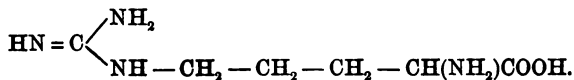
10. Aspartic acid or aminosuccinic acid:



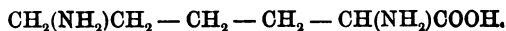
11. Glutamic acid or α -aminoglutaric acid:



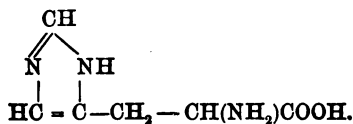
12. Arginine or δ -guanidine- α -aminovalerianic acid:



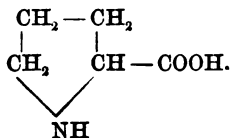
13. Lysine or α - ϵ -diaminocaproic acid:



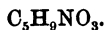
14. Histidine [or imidazole- α -aminopropionic acid]:

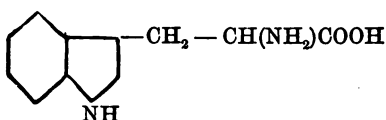


15. Proline or α -pyrrolidine carboxylic acid:



16. Oxyproline or oxy- α -pyrrolidine carboxylic acid:



17. Tryptophane or indole- α -aminopropionic acid :

The majority of these decomposition products are contained in all proteins so far as they have hitherto been examined, but in very varying proportions. In order to carry out comparative investigations it is necessary to start from material as pure as possible, such as crystalline protein, and to determine quantitatively and without loss, the decomposition products in a crystalline state. The first of such experiments was carried out in Bunge's laboratory by Fr. Pröscher,¹ who started from such compounds which could be most easily obtained in large quantities—*e.g.* hæmoglobin. Half of the carbon of the hæmoglobin was obtained in the form of crystalline and weighed products. The complete separation of the decomposition products by precipitation and fractional crystallisation is extremely difficult, and consequently Emil Fischer and his pupils² determined to use another method. They prepared the ethyl esters of the amino-acids, and separated them by fractional distillation *in vacuo*. This method also is not exactly quantitative, but it gives comparative values; some of the results are given in the following table :

100 Grammes Protein yielded

—	Globin from Oxyhæmo- globin	Serum Albumin	Serum Globulin	Caselnogen	Protein from Hempseed = edestin
Glycocoll . . .	—	—	3.52	—	3.8
Alanine . . .	4.19	2.68	2.22	0.9	3.6
Leucine . . .	29.04	20.00	18.70	10.5	20.9
α -proline . . .	2.34	1.04	2.76	3.1	1.7
Phenylalanine . . .	4.24	3.08	3.84	3.2	2.4
Glutamic acid . . .	1.73	1.52	2.20	10.7	6.3
Aspartic acid . . .	4.43	3.12	2.54	1.2	4.5
Cystine . . .	0.31	2.3	0.67	0.065	0.25
Serine . . .	0.56	0.6	—	0.23	0.33
Oxy- α -proline . . .	1.04	—	—	0.25	2.0
Tyrosine . . .	1.33	—	—	4.5	2.13
Lysine . . .	4.28	—	—	5.80	2.0
Histidine . . .	10.96	—	—	2.59	1.0
Arginine . . .	5.42	—	—	4.84	11.7
Tryptophane . . .	Present	Present	Present	1.5	Present

¹ Fr. Pröscher, *Z. f. physiol. Chem.* 1899, vol. xxvii. p. 114.² E. Fischer, *ibid.* 1901, vol. xxxiii. p. 151; 1903, vol. xxxix. p. 155; E. Abderhalden, *ibid.* 1903, vol. xxxvii. pp. 484, 495, 499; E. Fischer and E. Abderhalden, 1903, vol. xxxix. p. 81; 1903, vol. xl. p. 215.

This table shows that the greater number of the decomposition products of the various proteins are common to all, but that their proportional quantity is very different. Further, in these experiments of Fischer's the whole weight of protein has not yet been recovered in the form of its decomposition products. In the case of hæmoglobin, in the decomposition of which least loss occurred, the sum of the decomposition products only reaches 69·87 per cent. of the weight of the protein, and even then the weight of the water taken up in the process must be deducted. The loss is partially explained by the fact that the methods of isolation are not yet perfect, and that in the purification of each decomposition product great loss is unavoidable; the loss can be partially explained by our not yet knowing all the hydrolytic decomposition products of the proteins. We should not, therefore, rest until we know all the products, and until we have again found in them all the carbon, all the nitrogen, and all the sulphur of the original protein molecule. Such a result would be the foundation of a larger physiological chemistry.

The scleroproteins, or albuminoids, comprise (1) the chief constituents of connective tissue, bone and cartilage, gluten or collagen, which yield gelatin; (2) the chief constituent of elastic tissue, elastin; and (3) the chief constituent of horny tissue, keratin, epidermis, hair, nails, hoofs, feathers, etc. Hence the name scleroprotein. In common with the other proteins, they contain nitrogen and sulphur. The gelatin-yielding substances are colloids, and consequently also exist in two modifications—the apparently dissolved but not diffusible, and the insoluble or coagulated. The conditions, however, under which they are changed from one modification into the other are different. The gelatin-yielding substance of connective tissue and bone—the latter after previous extraction of the lime salts with hydrochloric acid—dissolves in water at the boiling point and more quickly at a higher temperature, and under a higher pressure. The solutions are called gelatin; on cooling, the gelatin solution sets to a solid.

The percentage composition of gelatin differs slightly from that of the other proteins; it is somewhat poorer in carbon and richer in oxygen. Gelatin is a product of the commencing decomposition, and oxidation, of proteins in the animal body. The food of the herbivora and the suckling mammal contains no gelatin, and in the organism, therefore, all the gelatin-giving substances are formed from their proteins, in which process a separation of certain radicals richer in carbon takes place, especially of tyrosine and the indole derivatives, which are not found amongst the hydrolytic decomposition products of gelatin.

Elastin and keratin differ from the gelatin-yielding substances of connective tissue and bone, i.e. from gluten or collagen, by containing a small quantity of tyrosine. Keratin is further distinguished by its strikingly great content in sulphur, up to 5 per cent.

The following table contains the quantities of the hydrolytic decomposition products obtained from gelatin,¹ horn,² elastin,³ together with those obtained from caseinogen, from which these three substances are formed in the suckling mammal :

100 Grammes Substance yielded

—	Caseinogen	Gelatin	Horn	Elastin
Glycocoll	0	16.5	0.34	25.75
Alanine	0.9	0.8	1.20	6.58
Leucine	10.5	2.1	18.30	21.38
Proline	3.1	5.2	3.60	1.74
Phenylalanine	3.2	0.4	3.00	3.89
Glutamic acid	10.7	0.88	3.00	0.76
Aspartic acid	1.2	0.56	2.50	—
Cystine	0.065	—	—	—
Valine	1.0	—	—	1.0
Serine	0.23	—	5.70	—
Tyrosine	4.5	—	0.68	0.34
Oxyproline	0.25	3.0	—	—
Lysine	5.80	2.75	—	—
Arginine	4.84	7.62	2.25	0.3
Histidine	2.59	0.40	—	—
Tryptophane	1.5	—	—	—
Diaminotrioxo- dodecanic acid }	0.75	—	—	—

From this table of compositions, it is seen what great changes and alterations, in the quantities of the radicals inside the protein molecule, have occurred in the tissues.

[Not only has Emil Fischer discovered a new method for separating and determining the quantities of the various amino-acids, as they are obtained by the hydrolysis of proteins, but also he has made enormous strides in their synthesis. The most probable manner in which the amino-acids, the ultimate constituents of the proteins, are combined together, is in the form of acid-amides, such as hippuric acid (p. 178) :



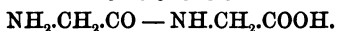
If in the place of the benzoyl radical another glycine radical, called

¹ E. Fischer, P. A. Levene, and R. H. Aders, *Z. f. physiol. Chem.* 1902, vol. xxxv. p. 70.

² E. Fischer and Th. Dörpinghaus, *ibid.* 1902, vol. xxxvi. p. 462.

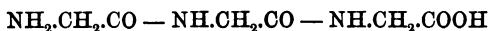
³ E. Abderhalden and A. Schittenhelm, *ibid.* 1904, vol. xli. p. 293.

glycyl, $\text{NH}_2\text{CH}_2\text{CO}$, be substituted, we obtain a compound containing two amino-acids—namely, glycylglycine :

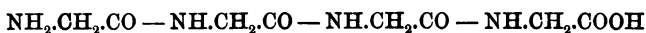


Glycylglycine.

This is the simplest representative of the polypeptides, as Fischer has termed these combinations of amino-acids. Continuing the process of substituting more glycyl radicals, we obtain glycylglycylglycine, or diglycylglycine, glycylglycylglycylglycine, or triglycylglycine :



Diglycylglycine.



Triglycylglycine.

and the chain can be lengthened to an infinite extent.

If we substitute other amino-acid radicals, *e.g.* alanyl, leucyl, tyrosyl, etc., in place of glycyl, and in various orders, we can obtain compounds such as alanylleucylglycine, glycylleucylalanine, tyrosylleucylalanylglycine, etc.

Nearly one hundred different polypeptides have already been prepared, the most complex being an octadeca-peptide, with eighteen amino-acid radicals joined together, and with a molecular weight of 1213.

It is in this way that the synthesis of proteins is now being carried out; there is a great difficulty in determining the order in which the amino-acids should be coupled together; and, further, all the proteins contain different amounts of the individual amino-acids (see tables). The number of permutations and combinations of twenty different amino-acids, taken 1, 2, 3, 4, etc. at a time, is enormous, and the problem looks as if it could never be solved; but there are two methods by which certain combinations only can be proved to occur in the protein molecule: (1) The action of ferments upon the polypeptides—some are attacked, some are not; (2) the isolation of complexes of amino-acids from the proteins. Both these methods have been frequently used, and the latter has only been successful since the properties of the individual synthetical polypeptides were studied. By carrying out the two processes of analysis and synthesis side by side a protein will, no doubt, ultimately be synthesised.

Another point to be particularly noticed is the optical activity of all the amino-acids, which has to be borne in mind in the process of synthesis.¹

¹ [A summary of Emil Fischer's work on the chemistry of the proteins is to be found in *Science Progress* for July 1907, in a paper entitled 'The Work of Emil

The result of the work on the chemistry of the proteins leads us to the conclusion that a protein molecule consists of a combination together of various amino-acids. We can imagine a child's box of bricks which is completely filled with bricks of various sizes accurately fitting together, from which smaller or larger portions can be taken away *en bloc*: four or five together, or even a whole layer. These portions again are also formed of the same irregular-sized bricks, also accurately fitting together, and can be still further divided into twos or threes, etc. The ultimate entity of each of these portions will correspond to an amino-acid in the complex protein molecule, which is represented by the entire box of bricks.]

An exact description of all the individual proteins, as well as their compounds with other organic substances, e.g. hæmoglobin, the nucleoproteins, the glycoproteins or mucins, belongs to physiological chemistry. The interest in these compounds grows in the study of the physiological functions in which they play a part.

The ferments, or enzymes, so often mentioned, probably belong to the group of the proteins. Many attempts have been made to isolate ferments from animal tissues and secretions, but only precipitates of protein have been obtained which still retained the ferment action, and it was thought that these precipitates were either the ferments themselves, or that they, on account of their protein-like properties, could not be separated from the proteins. An analogy between ferments and the proteins consists in the fact that ferment-containing solutions lose their activity on boiling. The albumins and globulins on boiling also lose their properties; they coagulate and alter their solubilities.

The chief difficulty in the isolation of ferments is that the ferment-containing precipitates become more inactive the more one tries to purify them, and Nencki, on this account, termed the ferments 'labile proteins,' considering that the ferment action was stopped by a rearrangement inside certain of the groups of the protein molecule.

Probably the poisonous metabolic products of pathogenic micro-organisms belong to the group of labile proteins; they have not yet been separated from protein, and consequently are called toxalbumins. Experiments made to isolate them have met with the further difficulty that the quantity of toxalbumin in all tissues and fluids is always extremely small. The toxalbumins are the deadliest poisons we

Fischer and his School on the Chemistry of the Proteins,' by R. H. Aders Plimmer.]

know. Vaillard and Vincent¹ grew the tetanus-bacillus in bouillon, and then filtered the bouillon through a clay filter. The bacteria-free filtrate contained only 0.025 gramme organic matter in a cubic centimetre, and of this organic matter only a small portion could be the poison; yet a cubic centimetre of this filtrate would have sufficed to kill a thousand guinea-pigs, or 100,000 mice.

These conditions show how great are the difficulties in the study of the proteins and ferments. Unfortunately the most distinguished investigators do not take up the subject, and the observation has often been made that the less a physiologist knows about chemistry, the greater is his inclination to work at the most difficult chemical subjects—the proteins and ferments. If even these subjects are not sufficiently obscure to him, he can study the phenomena of coagulation: we may suppose that in the coagulations in the tissues several proteins combine together. He feels perhaps most at home in the still more obscure subject of the pathology of coagulation, and of the ferments; it is good to fish in the dark! These authors have built up a literature which no one can become master of, and which is only a drag and a brake to science. The real chemist, however, does not easily take up the subject of the proteins. 'When a molecule contains more than 60 atoms of carbon,' a distinguished organic chemist was heard to say, 'then I will leave the investigation of that subject to others.'

In 1895 Adolph Baeyer, one of the greatest authorities in the realm of organic chemistry, said, in greeting a Medical Congress in Munich: 'As yet, there is no possibility of determining the nature of protein within a conceivable time. What shall we chemists do under these conditions? Shall we investigate subjects where solution seems very improbable, or shall we devote our energies to those subjects from which we are certain of reaping a rich, if even a modest, harvest? I believe that the latter is to be preferred. We, the representatives of pure science, continue to labour, nothing daunted, at the visible margin of an already conquered region, and look aloft with wonder at the results of modern medicine; though we cannot follow your keen flight with understanding, we wish success to your efforts, which bring blessings to mankind.'

It is therefore very gratifying that more recently Emil Fischer, another of the greatest authorities on organic chemistry, and a pupil

¹ L. Vaillard and H. Vincent, *Ann. de l'Inst. Pasteur*, 1891, vol. v. p. 15.

of Baeyer's, has devoted his entire energies to the study of the proteins. He has already brought light into the chemistry of the sugars and purines, just as Chevreul (1786-1889) did into the chemistry of the fats, and he will no doubt complete our knowledge of that third group of substances, which play the chief *rôle* in the processes of life. May he reach the age of Chevreul in unabated strength !

APPENDIX BY THE TRANSLATOR

METHODS

IN order that the student may comprehend the ordinary methods used in organic chemistry, to which frequent reference has been made in the foregoing pages, a short description of those several methods, in most constant use, is here given.

I. Recognition of an Organic Compound.

(a) *Detection of Carbon and Hydrogen.*—Whether an organic compound be gaseous, liquid, or solid, it generally contains both carbon and hydrogen. On heating such a solid compound in a dry test tube it will char, and drops of water will condense on the cooler parts of the tube; at the same time carbon dioxide will be given off, which can be detected by passing the gas into lime or baryta water.

The solid substance may, however, volatilise unchanged without charring, and, therefore, it is necessary to mix a little with finely powdered copper oxide and again heat. In the presence of copper oxide the substance will be decomposed, and will be oxidised to carbon dioxide and water, which can be detected as before.

Gaseous or liquid substances are burnt in a closed vessel, or the vapour evolved from a liquid passed over red-hot copper oxide, and then into lime or baryta water.

(b) *Detection of Nitrogen.*—The detection of nitrogen in an organic compound is carried out by one of two methods:

(i.) A small portion of the substance is thoroughly mixed with soda-lime, placed in a test-tube, and covered over with a thin layer of soda-lime. On heating the test-tube strongly ammonia may be evolved, which can be detected by smell, or by moistened red litmus paper.

(ii.) *Lassaigne's test*: A small portion of the substance is heated to redness with metallic sodium or potassium. Sodium or potassium cyanide is formed, which is detected by converting it into the ferrocyanide by boiling with ferrous sulphate in alkaline solution. The presence of ferrocyanide is then determined, by acidifying and adding a ferric salt, when a precipitate of prussian blue is obtained.

This second method is the one usually employed; the first method does not always succeed, since all nitrogenous compounds do not give off ammonia when heated with soda-lime.

(c) *Detection of Chlorine, Bromine, Iodine.*—Halogens in an organic compound cannot be detected in the same way as in an inorganic salt, since they do not, as a rule, react with silver nitrate. Some halogen-containing

organic compounds give a green tinge if they are placed in the outer zone of a non-luminous flame; or, on heating with copper, a green colouration appears. In all cases the organic compound must be finally destroyed and the halogen obtained in an inorganic state. This may be done by heating with lime, when calcium halide is formed, and the halogen can then be detected with silver nitrate in nitric acid solution. The halogens can also be detected by the method described under their estimation.

(d) *Detection of Sulphur*.—This can be most easily detected by fusing a small portion of the substance with metallic sodium. Sodium sulphide is formed, the presence of which is determined by its reaction with sodium nitro-prusside, or a lead salt, especially if the quantity of sulphur in the compound be considerable.

It may also be detected by the method described under detection of phosphorus, when inorganic sulphate is obtained.

(e) *Detection of Phosphorus*.—Phosphorus can only be found after the organic matter has been destroyed by oxidation. This is best done by heating with fusion mixture (a mixture of sodium carbonate and potassium nitrate), whereby the organic matter is converted into carbon dioxide, water, etc., and sodium or potassium phosphate remains, which is detected by ammonium nitro-molybdate etc.

Having found what elements are contained in an organic compound, it is necessary to determine the quantity of each, but before an exact analysis can be carried out, one must be first sure that the substance is pure. This should also be verified before finding out what elements it contains besides carbon and hydrogen, as these may be present as impurities.

II. Purification of an Organic Compound.

(1) *Solids*.—Most organic compounds can be obtained in a crystalline form, and they can be purified by crystallisation from a suitable solvent. If two or more substances be present, one of them may be soluble in a given solvent, but the others not; if they are all soluble in the same solvent, they can be separated by fractional crystallisation, since it generally happens that the substances are not of equal solubility.

A solution of the substance is made in the hot solvent, only just sufficient to dissolve it being used, and the clear solution is allowed to cool. When cold, the substance separates out in crystals. In the case of two substances, the more insoluble crystallises out first, and is filtered from the more soluble which still remains in solution, and is obtained by concentrating the solution by evaporation.

In some cases substances can be purified by sublimation; the substance is gently heated and it volatilises; its vapours are condensed upon a cold surface, such as an inverted funnel, or a cold watch-glass, from which it can easily be collected. The non-volatile substance or substances remain behind.

The purity of the substance is then ascertained by determining its *melting point*. A small quantity of the finely powdered substance is placed in a capillary tube (made by heating and drawing out a glass tube) sealed at one end. This is attached by a rubber ring, or by adhesion, to a thermometer, so that the substance is at the same level as the bulb. The thermometer is passed through a cork and placed in a small flask containing the liquid, (generally concentrated sulphuric acid), and this is gently heated by a small flame. At a certain temperature the substance, if pure, will melt suddenly within a range of 1 to 2 degrees. Just before this temperature is reached, the flame is removed, so that the temperature may rise quite slowly. If the substance be not pure it will not melt suddenly,

but will require a further rise of several degrees before it completely melts. A pure substance melts at a constant temperature. If after a second crystallisation the substance be found to melt at the same temperature as before, it can be assumed that it is pure. Often a substance must be recrystallised several times before its melting point becomes constant.

(2) *Liquids*.—The majority of organic liquids volatilise unchanged, without decomposition, and they can therefore be purified by distillation. They are heated in a flask with a side tube which is attached to a condenser (a glass tube by itself, or a glass tube surrounded by a jacket through which cold water can be circulated), in order to cool, and again liquefy, the vapours; the distilled liquid is collected in a receiver.

The purity of a liquid is known by its having a constant boiling point; this is determined during the distillation. A thermometer is placed in the neck of the distilling flask, so that the temperature indicated on it can be noted.

If two or more liquids are present, they are separated and purified by fractional distillation. This is carried out as before, except that the neck of the flask is made longer, by introducing between the flask and condenser a fractionating column, of which there are several kinds, e.g. a glass tube filled with glass beads. The two liquids will have different boiling points, as indicated by the thermometer, and are collected in separate receivers.

Some liquids will not distil at the ordinary atmospheric pressure without decomposition, but they may do so if the pressure be reduced. They are distilled *in vacuo*. The reduced pressure is obtained by connecting the whole distilling apparatus to a vacuum pump. Fractional distillation *in vacuo* necessitates a special method of arrangement, so that the distillation is not interrupted when it is necessary to change the receiver.

Distillation with steam is sometimes carried out in order to purify an organic compound. Steam is passed into a flask containing the substance, which is also heated, and the steam which now passes over takes the substance with it, and is condensed and collected as usual.

3. *Gases*.—These are difficult to separate unless they can be condensed by cold to liquids, when they can be separated by distillation. Special chemical methods are otherwise required, and constant elementary composition can only determine when they are pure.

4. *Separation by Extraction*.—Two liquids if they are not miscible are easily separated from one another, e.g. by sucking up the lighter with a pipette, or by placing them in a separating funnel (which is a cylindrical or pear-shaped vessel with a glass tap), opening the tap and allowing only the heavier liquid to run out. If the liquids be miscible, they may not be both soluble in the same solvent, which again may not mix with the insoluble constituent, e.g. benzene and alcohol: alcohol is soluble in water and benzene is not, and it floats upon the alcohol and water mixture.

A mixture of two solids in a solution can also be separated by extraction; the solution is shaken up with a new solvent, the two liquids allowed to separate, and the substances obtained by evaporation of the respective solvents.

III. Quantitative Analysis.

1. *Carbon and Hydrogen*.—These are always estimated together. It was stated above that organic compounds, when burnt or heated with copper oxide, were converted into carbon dioxide and water. It is therefore only necessary to oxidise an accurately weighed quantity of the substance, and to collect and weigh the carbon dioxide and water produced.

Both the carbon dioxide and water are collected in special absorption

tubes, which are made in various forms. The water may be collected in a U-tube filled with calcium chloride, or in a tube containing pumice-stone wetted with sulphuric acid. A very special form of absorption tube, filled with caustic potash, is used for collecting the carbon dioxide. Both tubes are weighed before and after the experiment, and the difference in weight gives the respective amounts.

The oxidation of the weighed quantity of substance is carried out in a long combustion tube of hard glass, which is heated in a furnace. This long tube is filled to two-thirds of its length with coarse copper oxide, a small boat containing the substance, of suitable size, is introduced, and then a roll of oxidised copper gauze. This end of the tube is connected with a gasometer containing air (or oxygen), from which a current of air, freed from carbon dioxide and water by passing through potash and sulphuric acid, or calcium chloride, is passed through the combustion tube in order to drive out the products of the combustion, and to help in the oxidation. To the other end of the tube the absorption tubes are attached. This is the general principle; the details can only be learnt by practice, as they vary slightly, and may differ in detail for different substances.

2. *Nitrogen.*—(a) *Dumas' Method.*—When an organic substance containing nitrogen is oxidised in the presence of copper oxide, the whole of its nitrogen is given off as free nitrogen. Therefore it suffices to collect this gas and determine its volume, from which value its weight can be easily calculated. In practice several methods are again used. The accurately weighed substance is mixed with finely divided copper oxide, and introduced into a combustion tube, which contains coarse copper oxide, as in the estimation of carbon and hydrogen, except that at the other end it is necessary to place a roll of copper gauze, specially reduced to the metallic state, to convert any oxides of nitrogen, which may be formed in the process, into nitrogen. All the air must be expelled from the tube before the combustion is commenced, and this is done by passing through it a current of carbon dioxide from a generating apparatus, or by having the tube sealed at one end and magnesite introduced before the copper oxide, which on heating evolves carbon dioxide and displaces the air.

The nitrogen formed in the combustion is collected in a special form of apparatus, called Schiff's nitrometer, into which it is driven by the carbon dioxide produced by either of the above methods, and its volume, temperature, and pressure are measured.

b. *Kjeldahl's Method.*—In this method the substance is oxidised by concentrated sulphuric acid in an open flask. The nitrogen contained in the substance in this process is converted into ammonia, which combines with the sulphuric acid. When the oxidation is finished it is therefore only necessary to neutralise the sulphuric acid, make alkaline with soda, and distil off the ammonia, which is collected in standard acid, and titrated.

3. *Halogens.*—These can only be estimated after the organic matter has been oxidised to carbon dioxide and water, when they are obtained in the inorganic state, and can be estimated by the ordinary methods. A known weight of substance in a narrow tube is placed in a stout walled tube sealed at one end, a few cubic centimetres of fuming nitric acid are added, and then some crystals of silver nitrate. The other end of the tube is then sealed and it is placed in a hot-air furnace at 200° C. for several hours. It is then allowed to cool, the contents washed out, and the silver halide weighed. This is Carius's method.

4. *Sulphur.*—This element is estimated, in a similar way to the halogens, in a sealed tube, when the sulphur is converted into sulphuric acid and is then precipitated as barium sulphate, and weighed.

5. *Phosphorus.*—Phosphorus may be estimated in the same way as sulphur, and the resulting phosphoric acid determined by the usual methods.

It may be estimated by fusing the substance with fusion mixture, as in the qualitative test, or by the recent method of Neumann,¹ wherein the substance is oxidised in an open flask with a mixture of nitric and sulphuric acids, the phosphoric acid produced precipitated as ammonium phosphomolybdate, and this then estimated by solution in standard caustic soda, and subsequent titration.

It is impossible, in so general a statement of methods, to give all the practical details for carrying out any of these processes; an exposition of the principles being only the point aimed at.

We have now determined the quantities of the various elements contained in an organic compound, and from these figures the percentage composition, the amounts of C, H, N, P, etc. given by 100 grammes of substance, can be calculated. The amount of O is found by difference, as there are no methods for estimating oxygen directly.

The formula of the compound is then obtained by dividing the percentages by the atomic weights of the elements, which gives the ratio of the number of atoms to each other, thus:

$$\begin{aligned} \text{C } \frac{19.05}{12} &= 1.59 \div 1.59 &&= 1 \\ \text{H } \frac{5}{1} &= 5 \div 1.59 &&= 3.1 = 3 \\ \text{O } \frac{75.95}{16} &= 4.74 \div 1.59 &&= 2.9 = 3 \end{aligned}$$

The empirical formula is therefore CH_3O_3 . Only a difference of 0.2-0.3 per cent. is allowed between the values found in a determination and that calculated from the percentage given by the formula CH_3O_3 .

As has been shown in Professor Bunge's book, several substances can have the same empirical formula; they may be isomers, or polymers; in the latter case the formula might be $\text{C}_2\text{H}_6\text{O}_6$ or $\text{C}_3\text{H}_9\text{O}_9$, both of which give the same figures on elementary analysis, because the ratio of C : H : O is the same.

IV. Molecular Weight Determination.

(a) In order to find out which of these formulæ is the correct one, the molecular weight of the substance must be determined, i.e. the weight of its molecule compared with that of an atom of hydrogen. This depends on Avogadro's law (p. 18).

Several methods can be employed, and that by Victor Meyer is perhaps the most frequently used, when the substance can be vaporised without decomposition. A known weight of substance is rapidly vaporised at a temperature 40-50° C. above its boiling-point, in a special piece of apparatus; the air contained in the tube is displaced by the vapour, collected in a graduated cylinder, and its volume measured; this corresponds to the volume occupied by the substance, after making corrections for temperature and pressure.

(b) In cases where the substance cannot be vaporised without decomposition, recourse may be had to the freezing-point method; the freezing-point of a given liquid is lowered the same number of degrees when different substances are dissolved in it, the weights of these necessary to do

¹ A. Neumann, *Z. f. physiol. Chem.* 1902, vol. xxxvii. p. 129; R. H. A. Plimmer and W. M. Bayliss, *Journ. Physiol.* 1906, vol. xxxiii. p. 439.

this being proportional to their molecular weights. A factor for each solvent is therefore first necessary ; these have all been determined, and the figures are given in the larger text-books. The molecular weight is expressed by the formula

$$M = \frac{100 \times C \times w}{dW},$$

where C is the constant, w the weight of the substance, W the weight of the solvent, and d the depression of the freezing-point.

This is Raoult's method, which has been made easily practical by Beckmann's apparatus.

Similarly, a rise in the boiling point of a solvent produced by the substance serves also for the determination of the molecular weight.

(c) In certain cases, when the substance is an acid or a base, the molecular weight can be determined by chemical methods.

In the case of an acid, the number of hydrogen atoms replaceable by metal can be obtained by estimating the amount of metal. The ratio of metal to salt is that of the atomic weight of the metal to the molecular weight of the salt. The silver salts are those most usually employed.

In the case of a base, the property that they have in common with ammonia, of forming chloroplatinates with platinic chloride, is made use of. The amount of platinum in such a compound is estimated, from which the molecular weight of the platinum compound is calculated, and therefrom that of the base.

Only an attempt has been made here to indicate the general principles underlying the commoner methods of finding out the constituents of an organic compound, its purification, elementary analysis, and molecular weight. The precise details can only be learnt by actual practice and performance.

R. H. ADERS PLIMMER.

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