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THE CHEMISTRY OF

DRUGS

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PREFACE TO THE THIRD EDITION

SINCE the publication of the second edition of *The Chemistry of Drugs* the changes in therapeutics may almost be described as revolutionary. While the most important of the new discoveries are undoubtedly the drugs that inhibit or destroy micro-organisms in the bloodstream (the antibiotics and the sulphonamides) a comparison of the chapter headings of the present edition with those of the second one shows that a number of completely new classes of drugs has been introduced. The activities of the synthetic chemist and of the pharmacologist are resulting in the production of new drugs on an ever-increasing scale; nor are the advances confined to synthetic compounds. Not only have new naturally occurring compounds been used in medicine—the antibiotics, tubocurarine and reserpine are examples—but new derivatives of natural compounds have been prepared and used and the chemical constitution of many of them has been elucidated and their synthesis accomplished.

The Chemistry of Drugs has therefore been completely rewritten. In order to confine the size of the book within reasonable limits only drugs that are actually used therapeutically have been included and many of the older drugs that are now not often used have been omitted.

N. E.
D. C.

PREFACE TO THE SECOND EDITION

THE rapid advances which have been achieved in the chemistry of drugs and the discoveries which have been made in certain fields since the first edition was published have necessitated a complete revision of this book.

Although few drugs have been found to which some addition has not been necessary, the developments which have taken place in the chemistry of the hormones and vitamins combined with the extension of their therapeutic applications in the last few years have made it necessary to include two new chapters on these subjects.

London, March, 1933 N. E.

PREFACE TO THE FIRST EDITION

IN preparing this work on *The Chemistry of Drugs*, I have endeavoured to give a description of substances used in medicine from the standpoint of pure chemistry —that is to say, the book is chiefly concerned with their chemical constitution and reactions, and the chemistry of the methods of manufacture of drugs obtained from natural sources or prepared by chemical synthesis. Drugs of natural origin, whose active principles are unknown, or from which no definite compounds of known constitution have been isolated, have been omitted or lightly touched on.

In describing methods of manufacture I have treated chiefly of the chemistry of the methods employed rather than of technical details or of details of plant. It is notorious that authors of textbooks do not describe methods of manufacture actually in use, or they omit the really important details of a process, because otherwise they would be giving away secrets of commercial value. However justified this criticism may be, it is felt that the book will be of more value to the student if manufacturing methods are regarded rather from the chemical than from the technical point of view. Methods of analysis have been excluded entirely. The analysis of drugs is matter sufficient for a textbook in itself, and is best treated as a separate branch of the subject.

The subject of essential oils used in medicine has been only cursorily treated, since it is fully dealt with in another book in this series, *The Chemistry of Essential Oils*, by H. Finnemore.

In the case of all drugs included in the British Pharmacopœia, or in the British Pharmaceutical Codex, the official name has been given first, although it may not be the one in common use—*e.g.*, 'Uradal' is given first, and the more common 'Adalin' as a synonym.

Solubilities are given except where otherwise stated as the weight of substance dissolved by 100 parts of the solvent at 15° C. Temperatures are given in degrees Centigrade, and specific gravities are at 15.5° C. compared with water at 15.5° C. The abbreviations of the names of journals should be intelligible without explanation.

I am indebted for much information to the following publications: *Organic Medicinal Chemicals* by Barrowcliff and Carr; *The Plant Alkaloids* by T. A. Henry; *The Chemistry of Synthetic Drugs* by Percy May; and *Organic Medicaments and their Preparation* by E. Fourneau (translated by Silvester).

My thanks are due to Mr. L. G. Timmis, M.Sc.Tech., A.I.C., for much assistance in the preparation of this work.

N. E.

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PART I

SYNTHETIC DRUGS

CHAPTER I

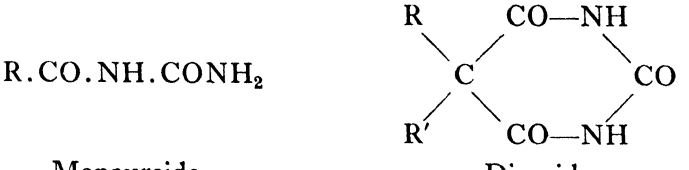
Hypnotics and Anticonvulsants

A HYPNOTIC may be defined as a drug used for the induction of sleep, and is thus one that has a depressant effect upon the central nervous system. The seizures of epileptic patients have their origin in the brain and the drugs used to control these seizures are included in this chapter. These drugs are known as anti-convulsants.

HYPNOTICS

The most important group of hypnotics is that containing the numerous derivatives of barbituric acid, of which the most commonly used is phenobarbitone. Thiobarbiturates are also important, thiopentone being a most valuable drug for the induction of unconsciousness before operations. Barbituric acid which was first synthesised in 1864 has almost no physiological activity. The 5-monoalkyl and monoacyl derivatives also show no hypnotic action. It is the 5-disubstituted barbituric acids which are physiologically active. 5-Alkyl-barbituric acids were prepared by Conrad and Guthzeit in 1882 and in 1903 Fischer and von Mering introduced 5 : 5-diethylbarbituric acid as a hypnotic. Since that date, a large number of barbiturates have been synthesised and the physician has now a wide range from which to choose. Thiobarbiturates are in general short acting, being rapidly decomposed in the body.

The barbiturates are diureides, i.e. the products formed by the condensation of urea with dibasic acids. When urea is condensed with a monobasic acid, a monoureide is formed. Certain members of the latter class have hypnotic properties, e.g. carbromal.



Monoureide Diureide

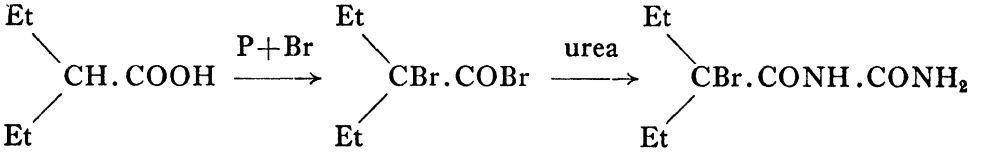
The introduction of the barbiturates was a milestone in medical history, but certain of the pre-barbiturate hypnotics are still in use. The most important of these compounds are—the opium derivatives and hyoscine (which are treated under alkaloids), paraldehyde and chloral hydrate.

In addition, certain new non-barbiturate sedatives have been introduced, e.g. the derivatives of glutarimide.

Carbromal. 1-Bromo-1-ethyl-butyrylurea. $C_7H_{13}BrN_2O_2$. (I).

Preparation. Diethylmalonic ester is converted to diethylmalonic acid which

is decarboxylated at 190° to yield diethylacetic acid. This is brominated in the presence of red phosphorus when 1-bromo-1-diethylacetyl bromide is formed and is purified by distillation. The required amount of urea is then added with constant stirring at a temperature controlled below 50°. Crude carbromal forms and is recrystallised from aqueous ethanol.

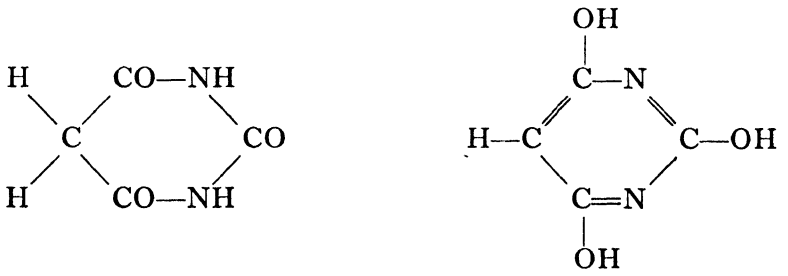


I

Properties. Carbromal is a white crystalline powder of m.p. 116° to 118°. It is slightly soluble in cold water and more soluble in hot water. It is also soluble in ethanol, ether and chloroform. When it is heated with aqueous sodium hydroxide it decomposes to yield ammonia and sodium bromide.

BARBITURATES

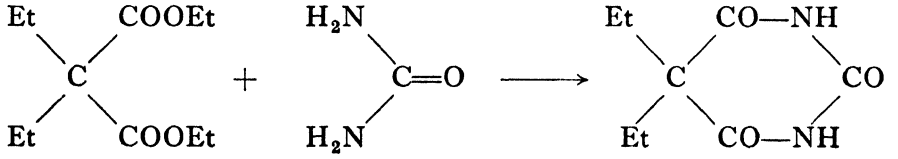
Barbituric acid (II) has the structure shown below and it may also be regarded as a tautomeric form of 2 : 4 : 6-trihydroxypyrimidine (III).



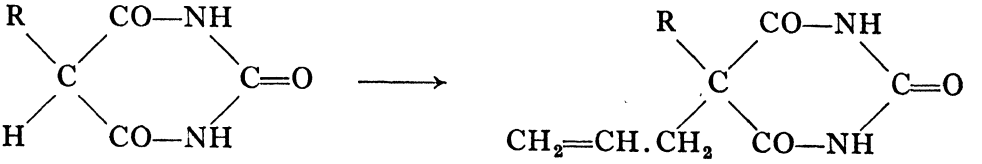
II III

The hydrogen atoms of the NH groups are easily split off as protons and give the compound its acidic character. Thus alkali metal salts of the barbiturates can be prepared (1). They are usually strongly alkaline in aqueous solution and are sometimes unstable (2).

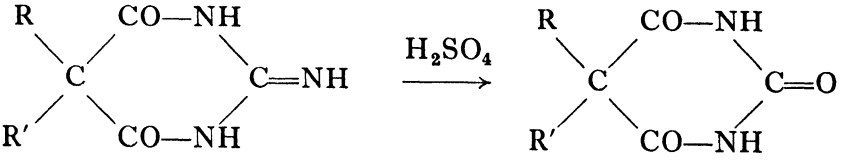
5 : 5-Dialkylated barbituric acids are commonly prepared by the condensation of the appropriate disubstituted malonic ester with urea in the presence of sodium alkoxide. Thus the preparation of barbitone is carried out as follows:



This method is used when both substituent groups are saturated. When unsaturated groups, such as allyl, are present, the monosubstituted barbituric acid may be first prepared and then allylated (3):

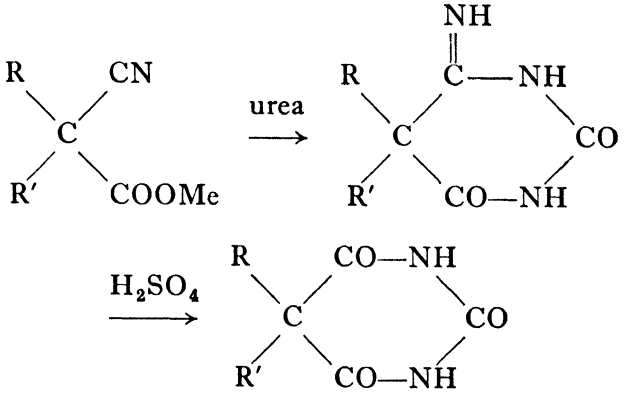


Substituted malonic esters may also be condensed with N-alkyl ureas to yield the N-alkylbarbituric acids or with thiourea to give thiobarbiturates. Guanidine leads to an imino derivative that can be hydrolysed by aqueous mineral acid to a barbiturate (4):



Substituted malonic esters can also be condensed with dicyandiamide, dicyandiamidine biuret and allophanates.

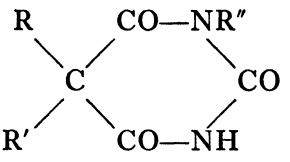
In the above procedures, malonic ester may be replaced by cyanoacetic ester. An iminobarbituric acid forms and on hydrolysis yields the required barbiturate (5):



An elegant method for the preparation of alkylcyanoacetates has been described (6) by Alexander and Cope.

Barbiturates containing an aryl group in the 5- position are obtained by condensation of the arylmalonic ester with urea. The substituted malonic ester required must be prepared by a special procedure as described under phenobarbitone.

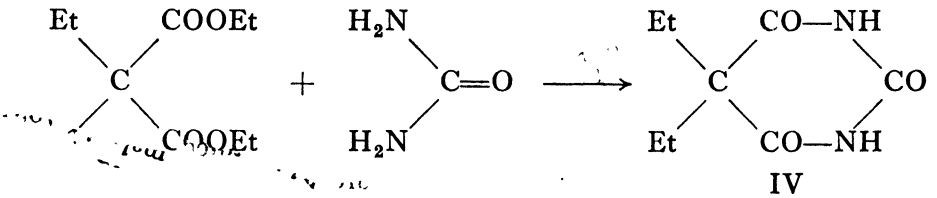
The most important barbiturates are listed on p. 18. Many other substituted barbituric acids not included here have been synthesised and claimed as hypnotics. Proprietary names are indicated thus: Nostal[P].



Name	R	R′	R″	M.p.°C
Allobarbitone	allyl	allyl	H	172–174
Amylobarbitone	ethyl	isoamyl	H	155–158
Aprobarbital	*iso*propyl	allyl	H	140–141·5
Barbitone	ethyl	ethyl	H	189–192
Butabarbital	*sec.*-butyl	ethyl	H	165–168
Butobarbitone	*n*-butyl	ethyl	H	122–124
Cyclobarbitone	ethyl	Δ^1-cyclohexenyl	H	171–176
Hexethal	ethyl	*n*-hexyl	H	122–125
Hexobarbitone	methyl	Δ^1-cyclohexenyl	Me	145–147
Methylphenobarbitone	ethyl	phenyl	Me	178–181
Nostal[P]	*iso*propyl	2-bromoallyl	H	179–180
Pentobarbitone	ethyl	1-methylbutyl	H	127–130
Pernoston[P]	*sec.*-butyl	2-bromoallyl	H	130–133
Phenobarbitone	ethyl	phenyl	H	173–177
Probarbital	ethyl	*iso*propyl	H	200–203
Quinalbarbitone	allyl	1-methylbutyl	H	96–100
Rutonal[P]	methyl	phenyl	H	221
Sandoptal[P]	*iso*butyl	allyl	H	138–139
Vinbarbitone	ethyl	1-methyl-Δ^1-butenyl	H	161–163
Thiobarbiturates				
Thiamylal	allyl	1-methylbutyl	H	131–133
Thialbarbitone	allyl	Δ^2-cyclohexenyl	H	148–150
Thiopentone	ethyl	1-methylbutyl	H	158–159

Barbitone. Barbital. 5 : 5-Diethylbarbituric acid. $C_8H_{12}N_2O_3$. (IV).

Preparation. Diethyl malonate is normally used and is condensed with urea in the presence of a sodium alkoxide. It has been suggested that yields are increased if the alkoxide is added as fast as it is used up in the reaction (7).



IV

The disubstituted dibutyl malonate (8), and methyl diethyl cyanoacetate (5) have also been employed in a similar condensation to yield barbitone. In a further variation methyl diethylcyanoacetate has been condensed with

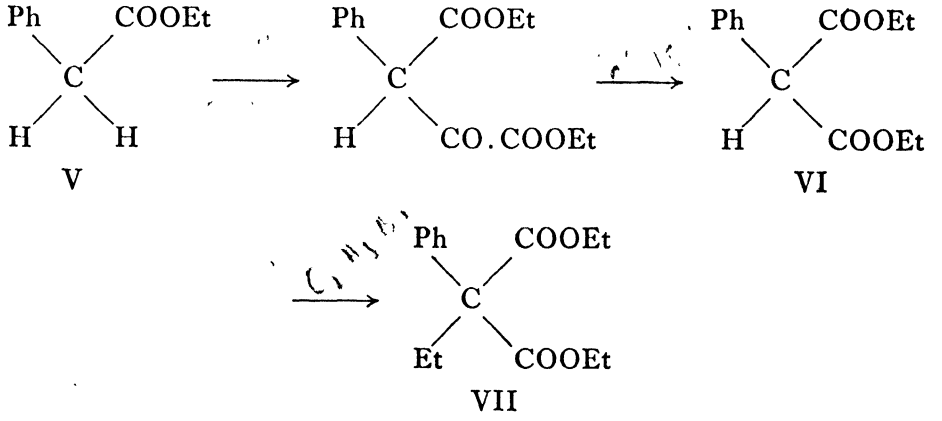
dicyandiamide and the iminobarbituric acid obtained converted to barbitone by acid hydrolysis (8).

Properties. Barbitone is a white crystalline powder of m.p. 189° to 192°. It has a bitter taste. Barbitone is slightly soluble in cold water and readily soluble in hot water, alcohol, ether and chloroform. It dissolves in dilute alkalis and the monosodium compound is water-soluble and liberates barbitone on the addition of acid. An aqueous solution acidified with nitric acid gives a gelatinous precipitate on addition of Millon's reagent. Mercuric perchlorate quantitatively precipitates barbitone from its solutions.

Phenobarbitone. Phenobarbital. 5-Ethyl-5-phenylbarbituric acid.

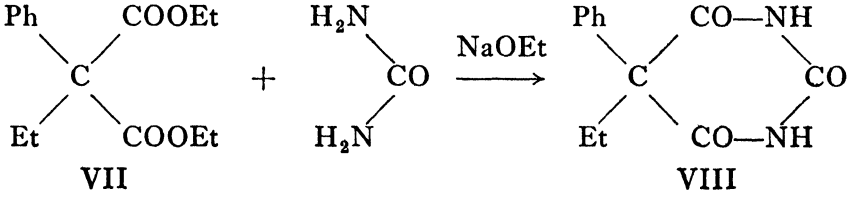
$C_{12}H_{12}N_2O_3$. (VIII).

Preparation. Whereas 5 : 5-dialkyl malonates are prepared by the step-wise alkylation of ethyl malonate, this procedure is not applicable to the preparation of an aryl malonic ester. Dimethyl ethylphenylmalonate is normally made by the following method (8). Benzyl cyanide is simultaneously hydrolysed and esterified to give methyl phenylacetate (V). This is condensed with diethyl oxalate and the resulting keto ester is decarbonylated at 180° to yield diethyl phenylmalonate (VI). Alkylation with ethyl bromide leads to the required ethylphenylmalonic ester (VII).



The same ester may be obtained by an alternative route whereby ethyl phenylacetate is condensed with diethyl carbonate and the resulting phenylmalonic ester alkylated by means of diethyl sulphate (9).

Phenobarbitone is obtained by the condensation of phenylmalonic ester with urea in absolute ethanol in the presence of sodium ethoxide. Phenyl butyramide is commonly present as an impurity in the reaction product (10).

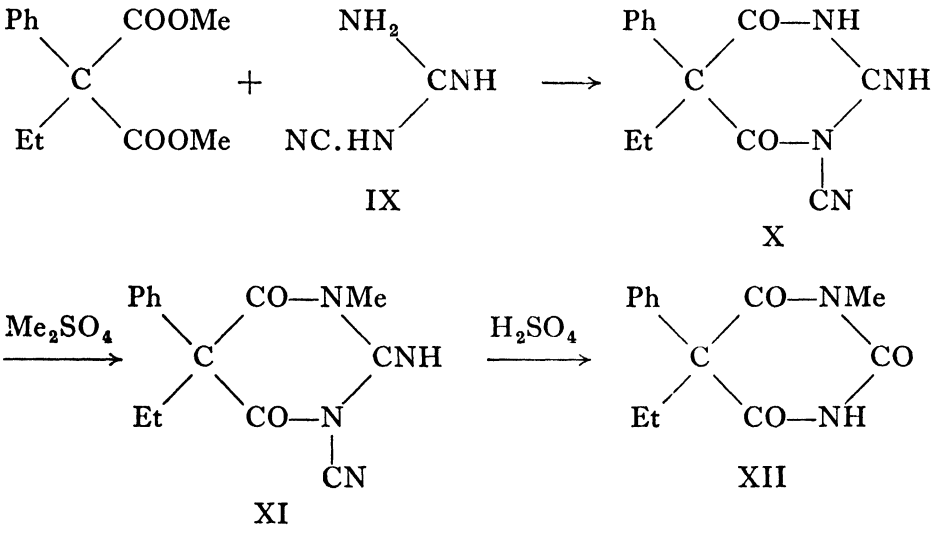


Properties. Phenobarbitone is a white powder with a bitter taste. It melts at 175·5°. It is slightly soluble in water and readily soluble in ethanol, ether, chloroform or solutions of alkalis. The solubility in different water - ethanol mixtures has been determined (11) as has the solubility in *iso*propanol (12). It gives a precipitate with Millon's reagent but may be distinguished from barbitone by the orange colour produced when a trace of sodium nitrite is added to a 10 per cent w/v solution in cold sulphuric acid.

Phenobarbitone is often used for the treatment of epilepsy.

Methylphenobarbitone. Phemitone. 5-Ethyl-5-phenyl-N-methylbarbituric acid. $C_{13}H_{14}N_2O_3$. (XII).

Preparation. Methylphenobarbitone may be made by the condensation of phenylethylmalonic ester with N-methylurea (13) or by the use of dicyandiamide (IX). In this method dimethyl phenylethylmalonate is condensed with dicyandiamide and the product (X) is methylated (XI) and then hydrolysed to give methylphenobarbitone (8, 14).



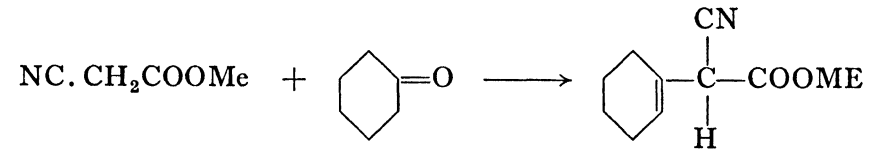
Properties. Methylphenobarbitone is almost insoluble in water, but is soluble in ethanol, ether, chloroform and solutions of alkalis. It melts at 178° to 181°. It gives a colour test with resorcinol. 0·1 g is mixed with an equal weight of resorcinol and four drops of sulphuric acid are added. The mixture is heated at 130° for 5 minutes and on cooling, a yellow colour appears, which becomes very pale green in ultra-violet light. On making the mixture alkaline, the colour becomes pale green and fluorescent and is then pale blue in ultra-violet light. No colour is given by barbitone or phenobarbitone.

Methylphenobarbitone is often used in the treatment of epilepsy.

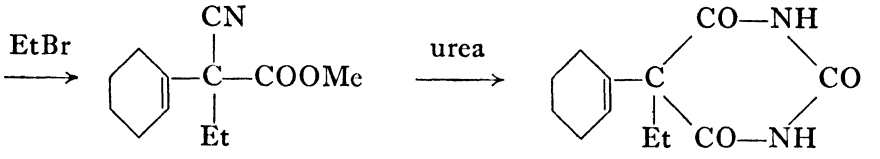
Cyclobarbitone. Cyclobarbital. 5-Δ^1-*cyclo*Hexenyl-5-ethylbarbituric acid. $C_{12}H_{16}N_2O_3$. (XIV).

Preparation. Methyl cyanoacetate is condensed with *cyclo*hexanone in the

presence of diethylamine to form methyl *cyclo*hexenylcyanoacetate (XIII). This is ethylated with ethyl bromide and the disubstituted ester is condensed with urea or with dicyandiamide (8, 15).



XIII



XIV

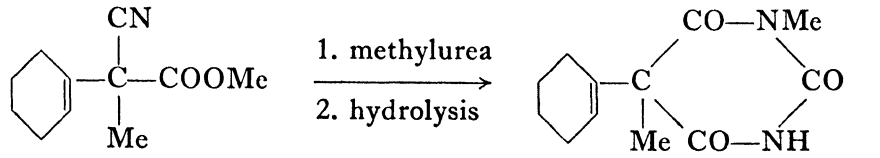
Properties. Cyclobarbitone is a white powder of m.p. 171° to 176°. It is slightly soluble in cold water and more soluble in hot water, ethanol, ether, chloroform and solutions of alkalis. It is unstable in air apparently due to the formation of a hydroperoxide (16). In the resorcinol test described under methylphenobarbitone, a blood-red colour forms that looks grey-green in ultra-violet light. On basifying this colour becomes wine-red and appears bright blue in ultra-violet light.

Cyclobarbitone is a short-acting barbiturate.

Hexobarbitone. Hexobarbital. 5-Δ^1-*cyclo*Hexenyl-5-methyl-N-methylbarbituric acid. $C_{12}H_{16}N_2O_3$. (XV).

Preparation. A similar process to that employed for the manufacture of cyclobarbitone from dicyandiamide may be used (8). An added step is the methylation of the imino group by means of dimethyl sulphate before hydrolysis.

Alternatively, Δ^1-*cyclo*hexenylmethylcyanoacetic ester can be condensed with N-methylurea (17) and the product hydrolysed:

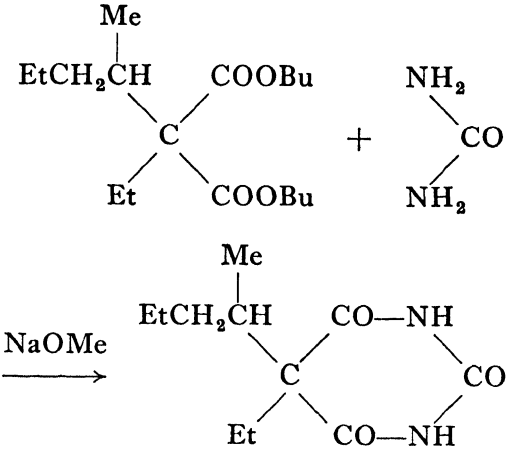


XV

Properties. Hexobarbitone melts at 145° to 147°. It is slightly soluble in water and more soluble in organic solvents and solutions of alkalis. The 4-nitrobenzyl derivative melts at 116° to 117°. Hexobarbitone gives the same colour reactions as cyclobarbitone. It is presumably as prone to aerial oxidation.

Pentobarbitone. Pentobarbital. 5-Ethyl-5-(1-methylbutyl)barbituric acid. $C_{11}H_{18}N_2O_3$. (XVI).

Preparation. An ethyl(methylbutyl)malonic ester is condensed in the normal manner with urea in the presence of a sodium alkoxide (18):

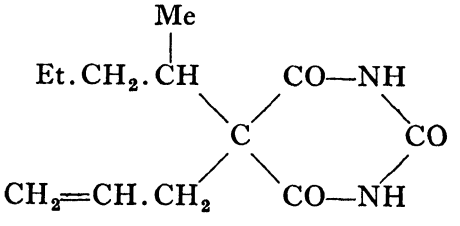


XVI

Properties. Pentobarbitone melts at 127° to 130°. It has the same solubility characteristics as hexobarbitone. In the resorcinol colour test described under methylphenobarbitone it gives an orange colour that becomes yellow on basifying and is then pale blue in ultra-violet light.

Quinalbarbitone. 5-Allyl-5-(1-methylbutyl)barbituric acid. $C_{12}H_{18}N_2O_3$. (XVII).

Preparation. 5-(1-Methylbutyl)barbituric acid is reacted with allyl bromide in aqueous alcoholic potassium hydroxide and the crude product is recrystallised from a mixture of benzene and light petroleum (1).



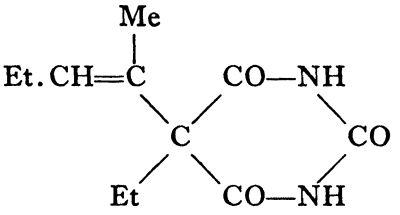
XVII

Properties. Quinalbarbitone melts at 96° to 100°. When 0·1 g is dissolved in 10 ml of a 10 per cent w/v solution of pyridine in water and 1 ml of a solution of copper sulphate in the same solvent added, a violet precipitate forms.

Vinbarbitone. 5-Ethyl-5-(1-methyl-Δ^1-butenyl)barbituric acid. $C_{11}H_{16}N_2O_3$. (XVIII).

Preparation. The ethyl ester of ethyl-(1-methyl-Δ^1-butenyl)cyanoacetic acid is prepared by ethylation of the corresponding monosubstituted ester in the usual manner (19) and the product is condensed in *iso*propanol with urea. The imino

derivative is hydrolysed and the crude vinbarbitone obtained is recrystallised from 50 per cent ethanol (20). Vinbarbitone melts at 161° to 163°.



XVIII

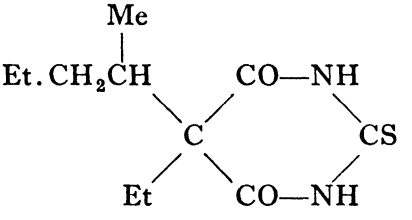
THIOBARBITURATES

The condensation of thiourea with a 5 : 5-dialkyl malonic ester under the conditions for the preparation of barbiturates leads to 5 : 5-dialkylthiobarbituric acids. A thiobarbiturate containing a 5-allyl group must be prepared from the corresponding allylmalonic ester. Attempts to allylate a monosubstituted thiobarbiturate lead to attachment of the allyl group to the sulphur atom (21). Similarly, an N-alkyl thiobarbituric acid is prepared with the N-alkyl group present before the final condensation is carried out, e.g. in the reaction between a substituted malonic ester and N-methylthiourea.

The thiobarbiturates have been recently reviewed (22) and a general article on the preparation and properties of thioureas has been published (23).

Thiopentone. Thiopental. 5-Ethyl-5-(1-methylbutyl)thiobarbituric acid. $C_{11}H_{18}N_2O_2S$. (XIX).

Preparation. Ethyl-(1-methylbutyl)malonic ester is condensed with thiourea in the presence of sodium ethoxide (24) or methoxide (25). The crude product is recrystallised from 50 per cent ethanol.



XIX

Properties. Thiopentone is a yellowish-white powder with a m.p. of 158° to 160°. It is slightly soluble in water and more soluble in organic solvents and solutions of alkalis. It is administered by injection as a solution of the soluble sodium salt. The latter is unstable and thiopentone for injection is sold as a mixture of the monosodium salt and anhydrous sodium carbonate, which is dissolved in water immediately before use.

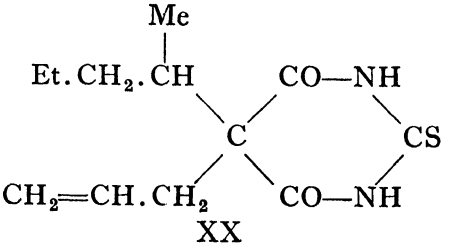
Thialbarbitone. 5-Allyl-5-Δ^2-*cyclo*hexenylthiobarbituric acid. $C_{13}H_{16}N_2O_2S$. (XX).

Preparation. Allylmalonic ester may be converted to its sodium derivative and reacted with 1-bromo-Δ^2-*cyclo*hexene. The resulting compound is condensed

with thiourea to give thialbarbitone of m.p. 148° to 150° (26). It is used as the monosodium derivative.

Thiamylal. 5-Allyl-5-(1-methylbutyl)thiobarbituric acid. $C_{12}H_{18}N_2O_2S$. (XX).

Preparation. Ethyl cyanoacetate is reacted with 1-methylbutyl bromide and the substituted ester so obtained is condensed with allyl bromide to yield allyl-(1-methylbutyl)cyanoacetic ester. This, on condensation with thiourea, gives an iminothiobarbituric acid that on hydrolysis leads to thiamylal, m.p. 131° to 133° (27).



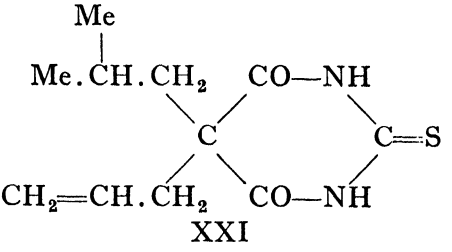
XX

VERY SHORT-ACTING BARBITURATES

The two compounds described below have been recently introduced as very short-acting thiobarbiturates. It is claimed that in addition to their short duration of hypnotic action they allow the patient to recover his normal level of faculties within a very short time.

Buthalitone. 5-Allyl-5-*iso*butylthiobarbituric acid. $C_{11}H_{16}N_2O_2S$. (XXI).

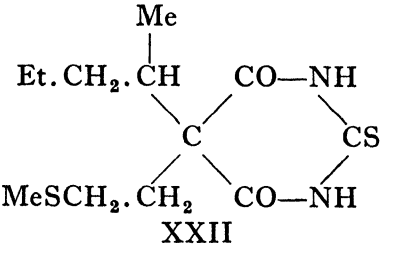
Preparation. This compound, which was made in 1936 (28) but not introduced into medicine until 1954, may be prepared by the usual condensation of thiourea and a substituted ester.



XXI

Methioturiate. 5-Methylthioethyl-5-(1-methylbutyl)thiobarbituric acid. $C_{12}H_{20}N_2O_2S_2$. (XXII).

Preparation. The appropriate disubstituted cyanoacetic ester is condensed with thiourea and the product hydrolysed to yield XXII of m.p. 79° to 81° (29).

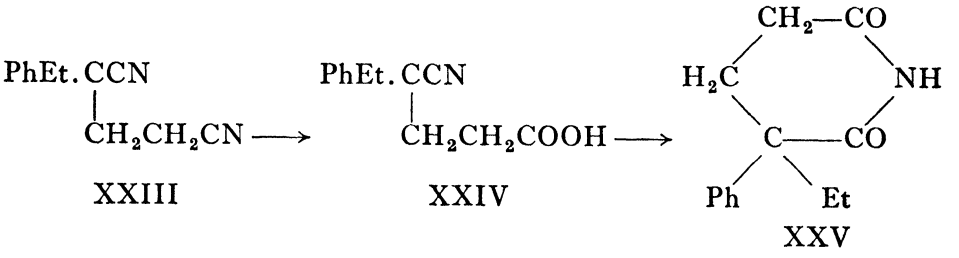


XXII

OTHER HYPNOTICS

Glutethimide. 2-Ethyl-2-phenylglutarimide. 3-Ethyl-3-phenyl-2:6-diketopiperidine. $C_{13}H_{15}NO_2$. (XXV).

Preparation. Ethylbenzyl cyanide was condensed with acrylonitrile and the resulting dinitrile (XXIII) was converted by alkaline hydrolysis to XXIV and thence to glutethimide (30). It has been prepared by other workers (31).

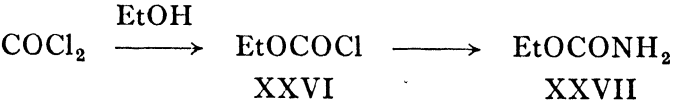


Properties. Glutethimide is a solid of m.p. 82° to 86°, when crystallised from ether or from a mixture of ethyl acetate and light petroleum. The monohydrate melts at 68° to 69°.

Glutethimide is a recently introduced hypnotic. It is of interest that 3-ethyl-3-methylglutarimide, i.e. bemegride (32, 33) (see p. 190) has no hypnotic properties and is in fact a barbiturate antagonist.

Urethane. Ethyl carbamate. $C_3H_7NO_2$. (XXVII).

Preparation. Ethanol is reacted with phosgene in the presence of a base such as dimethylaniline (34, 35) to give ethyl chloroformate (XXVI) which is added to excess aqueous ammonia solution to yield urethane.

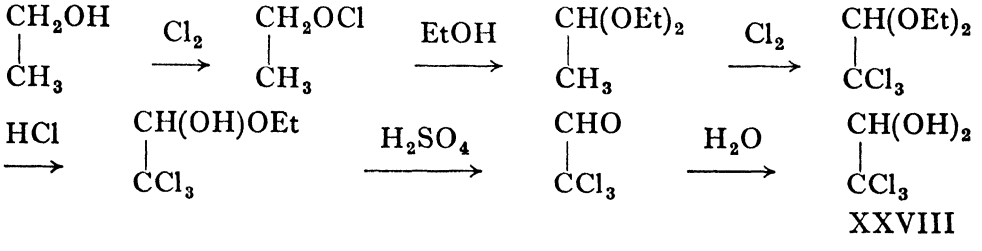


Properties. Urethane forms colourless prismatic crystals of m.p. 48° to 50°. It is easily soluble in water and in organic solvents. When heated with alkalis it evolves ammonia and when a solution is washed with sodium carbonate and a trace of iodine, iodoform is produced.

Urethane is a mild hypnotic that is not used extensively.

Chloral hydrate. Trichloroacetaldehyde hydrate. $C_2H_3Cl_3O_2$. (XXVIII).

Preparation. In one method the following reaction scheme is followed:



Chlorine is passed into ethanol and chloral alcoholate, $Cl_3CH(OEt)_2$, forms. Sulphuric acid is added and the mixture is heated until no more hydrogen

chloride is evolved. The mixture is then fractionated. Ethyl chloride comes off first, followed by ethanol and finally chloral is obtained. It is redistilled from calcium carbonate to produce chloral of b.p. 94°. On addition of the theoretical quantity of water, the hydrate is formed and may be recrystallised from ether, benzene, chloroform or light petroleum. Chloral may also be obtained by the direct chlorination of acetaldehyde (36).

Properties. Chloral is the oldest synthetic hypnotic, having been introduced in 1869, and is still regarded as one of the safest drugs of its kind. It is a colourless pungent liquid combining with water exothermically and readily soluble in ethanol and ether. It has b.p. 97·7° and weight per ml of 1·512 g at 20°.

Chloral hydrate forms colourless crystals, m.p. 57°. It is readily soluble in water or organic solvents. When warmed with caustic alkalis chloroform and sodium formate are produced.

Chlorbutol. Trichlorobutanol, $(CH_3)_2CCl_3.C.OH$.

Preparation. A mixture of dry acetone (500 g) and chloroform (1000 g) is cooled below 0° and finely powdered potassium hydroxide (325 g) is added gradually with constant stirring over a period of 60 hours. After standing for a further 36 hours the solid residue is filtered. The filtrate is fractionally distilled. Chlorbutol boils at 165°. It is washed with water and recrystallised from dilute ethanol.

Properties. Chlorbutol forms colourless crystals of m.p. 96° when pure. It is usually hydrated and then melts at 77° to 81°. It has a musty and somewhat camphoraceous odour. It is slightly soluble in water and readily soluble in ethanol, ether and chloroform. Chlorbutol gives the iodoform reaction and the odour of phenyl isocyanide is produced on warming with aniline and sodium hydroxide.

Amylene hydrate. *tert.*-Pentanol. $C_5H_{12}O$. (XXIX).

Preparation. Trimethylethylene is reacted with sulphuric acid and the sulphate so formed is hydrolysed with an alkali.

$$Me_2C{=}CHMe \xrightarrow{H_2SO_4} Me_2C(HSO_4)CH_2Me \xrightarrow{NaOH} Me_2COH.C_2H_5$$

XXIX

Properties. Amylene hydrate has mild hypnotic properties but its chief use is as a solvent for tribromomethyl alcohol to give the solution known as bromethol. This is used per rectum as a pre-operative anaesthetic.

It is a colourless liquid that forms colourless crystals of m.p. −13°. Weight per ml (20°), 0·808 to 0·811 g. It boils at 100° to 104°. It is miscible with water, ether, ethanol and chloroform.

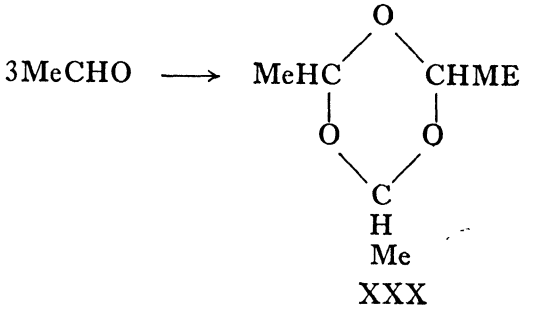
Tribromoethyl alcohol. $Br_3.C.CH_2OH$.

Preparation. Tribromoacetaldehyde is prepared in a way similar to that used for chloral and is then reduced by hydrogenation or by sodium amalgam.

Properties. A white crystalline powder of m.p. 79° to 81°. It is unstable in air and dissolves in water to give a solution that is unstable. Bromethol is a solution of tribromoethyl alcohol dissolved in amylene hydrate (2 : 1) and it is used as a basal anaesthetic.

Paraldehyde. Trimethyltrioxan. $C_6H_{12}O_3$. (XXX).

Preparation. Paraldehyde is a trimer of acetaldehyde. It is formed by the addition of a small quantity of mineral acid. The addition of 1 ml of hydrochloric acid to 1500 lb. of acetaldehyde is sufficient to start the reaction. Heat is produced and cooling is necessary. Further small quantities of acid are added until almost complete polymerisation has occurred. The reaction product is purified by fractional distillation.



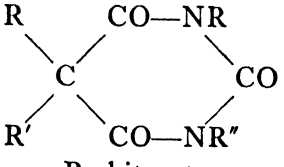
XXX

Properties. Paraldehyde which is a liquid of b.p. 123° to 126° and a m.p. of 11° is soluble in water. It has a weight per ml of 0·991 to 0·993 g at 20°. It is depolymerised by heating with dilute sulphuric acid. It reduces ammoniacal silver nitrate to give a silver mirror.

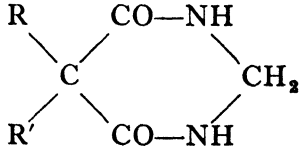
ANTICONVULSANTS

Anticonvulsants are drugs used in the treatment of epileptic seizures. These seizures are known as Grand Mal or Petit Mal according to the type and the anticonvulsants in use are often more active in one or other sort of seizure.

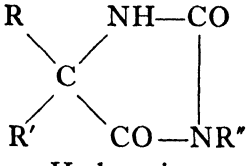
The principal anti-epileptic compounds used may be divided into the four chemical types shown:



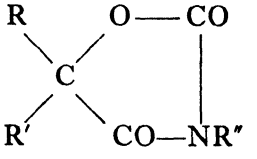
Barbiturates



Primidone



Hydantoins



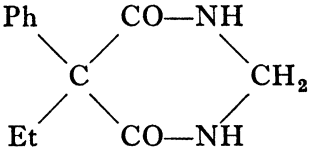
Oxazolidine-2:4-diones

Phenobarbitone and methylphenobarbitone are still the first substances to be considered in treating most types of epilepsy. Their synthesis has been described in the section devoted to barbiturates.

Primidone. 5-Ethyl-5-phenylhexahydropyrimidine-4:6-dione.

$C_{12}H_{14}N_2O_2$. (XXXI).

Preparation. Phenobarbitone or the corresponding thiobarbituric acid are reduced to primidone (37). Phenobarbitone, for example, may be electrolytically reduced with lead electrodes in sulphuric acid below 50°. The product is recrystallised from ethanol.

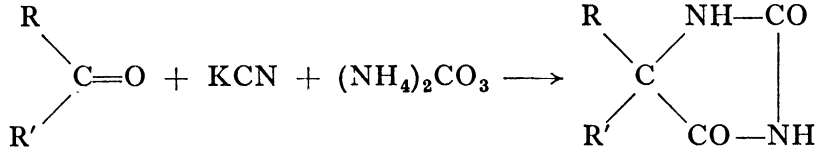


XXXI

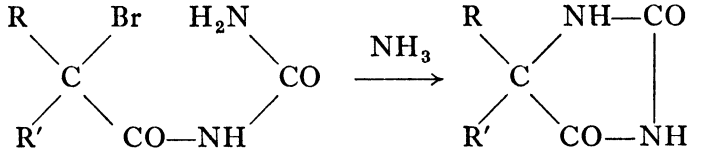
Properties. Primidone is a colourless crystalline solid of m.p. 281° to 282°. It is sparingly soluble in water and in most organic solvents. It has been used for the control of Grand Mal seizures.

HYDANTOINS

There are two general methods for the preparation of these compounds:

(1) 

In this method (38) a ketone is reacted with potassium cyanide and ammonium carbonate and, if necessary, the hydantoin formed can be alkylated on one of the nitrogen atoms.

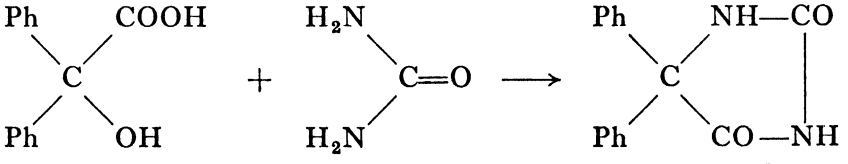
(2) 

Here a substituted bromoacetylurea is cyclised in alcoholic ammonia.

Phenytoin. Diphenylhydantoin. $C_{15}H_{12}N_2O_2$. (XXXII).

Preparation. Method (2) above is used (39).

A chemically simpler process has been described (40) in which benzilic acid is condensed with urea in the presence of acetic anhydride:



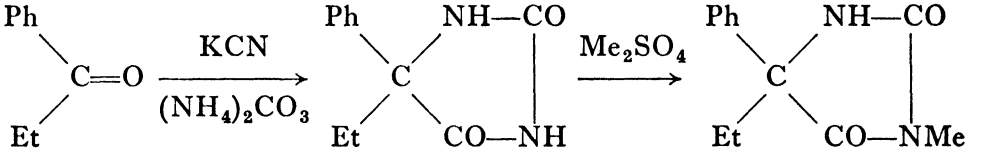
XXXII

The sodium salt is prepared by the addition of aqueous sodium hydroxide and evaporation to dryness.

Properties. Phenytoin forms white crystals, m.p. 295°. The sodium salt which is used in the treatment of Grand Mal is somewhat hygroscopic and on exposure to air absorbs carbon dioxide and forms phenytoin.

Methoin. 5-Ethyl-3-methyl-5-phenylhydantoin. $C_{12}H_{14}N_2O_2$. (XXXIII).

Preparation. Method (1) above is used. Benzene and propionyl chloride reacted together by the Friedel-Craft procedure give phenyl ethyl ketone and this in alcohol is treated in two stages in an autoclave with two successive quantities of potassium cyanide and ammonium carbonate in aqueous solution. The reaction mixture is concentrated to half volume and acidified, and the oil which is formed is extracted out and the solution is washed with aqueous sodium hydroxide. The aqueous solution now contains the hydantoin which is precipitated by addition of concentrated hydrochloric acid. It is methylated by methyl sulphate in aqueous alkali to methoin, which may be recrystallised from ethanol.



XXXIII

Properties. Methoin forms colourless lustrous plates, m.p. 137° to 138°. It is almost insoluble in water but is soluble in alkali hydroxides, in ethanol, ether and chloroform. A solution in aqueous sodium hydroxide, on being acidified with hydrochloric acid, gives a white precipitate insoluble in aqueous sodium carbonate or strong aqueous ammonia. This test distinguishes methoin and phenytoin.

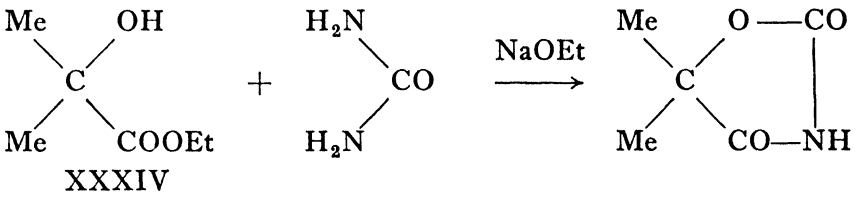
Methoin is used as the sodium derivative in the treatment of Grand Mal.

OXAZOLIDINE-2:4-DIONES

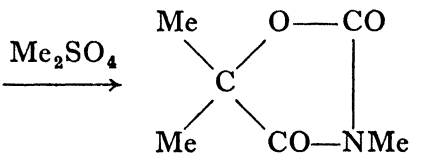
These compounds have recently been investigated as anticonvulsants. Three members of the group are important. They are troxidone, paramethadione and aloxidone.

Troxidone. Trimethadione. 3 : 5 : 5-Trimethyloxazolidine-2 : 4-dione. $C_6H_9NO_3$. (XXXV).

Preparation. The most useful method for the preparation of the therapeutically active oxazolidine-2 : 4-diones appears to be the Stoughton synthesis (41):



XXXIV



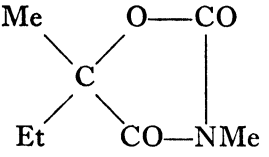
XXXV

Dimethylglycollic ester (XXXIV) which can be prepared from acetonecyanohydrin (42) is condensed with urea and the compound obtained is methylated to give troxidone which may be purified by fractional distillation (43).

Properties. Troxidone forms white granules with a camphor-like odour. It is soluble in water and freely soluble in most organic solvents, except petroleum spirit. M.p. 45° to 47°. Hydrolysis with sodium hydroxide yields N-methyl-1-hydroxy*iso*butyramide, m.p. 79° to 81°.

Paramethadione. Paradione. 5-Ethyl-3 : 5-dimethyloxazolidine-2 : 4-dione. $C_7H_{11}NO_3$. (XXXVI).

Preparation. The method is analogous to that used for the preparation of troxidone (43).

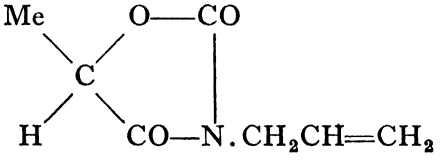


XXXVI

Properties. Paramethadione is a clear colourless liquid with an ester-like odour. It is sparingly soluble in water and soluble in organic solvents. The b.p. is 101° to 102° at 11 mm. It is used in the treatment of Petit Mal seizures.

Aloxidone. 3-Allyl-5-methyloxazolidine-2 : 4-dione. $C_7H_9NO_3$. (XXXVII).

Preparation. 5-Methyloxazolidine-2 : 4-dione is prepared by the Stoughton method described under troxidone and is allylated with allyl bromide to give aloxidone (44).



XXXVII

It is purified by distillation and boils at 129° to 132° at 18 mm. and 86° at 0·5 mm.

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CHAPTER II

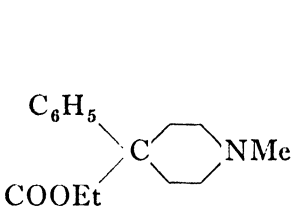
Analgesics and Antipyretics

ANALGESICS

ANALGESICS render a subject insensitive to pain. Hypnotics which induce sleep may thereby relieve pain, and many analgesics induce sleep in the absence of pain. Antipyretics have some analgesic activity. In addition, the analgesics—pethidine and morphine—might justifiably be regarded as anaesthetics. The division which has been made in this chapter must therefore be arbitrary, and is based upon the fact that the compounds described are used chiefly for the relief of pain.

The classical analgesic, morphine, is treated under alkaloids (p. 203).

Pethidine hydrochloride. Meperidine hydrochloride. Ethyl-1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride. $C_{15}H_{21}O_2N.HCl$.



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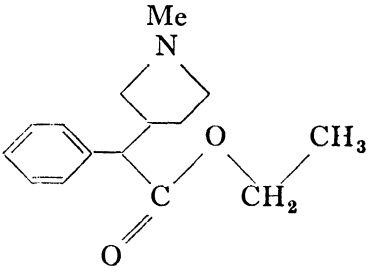
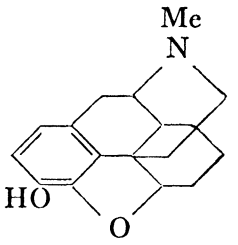


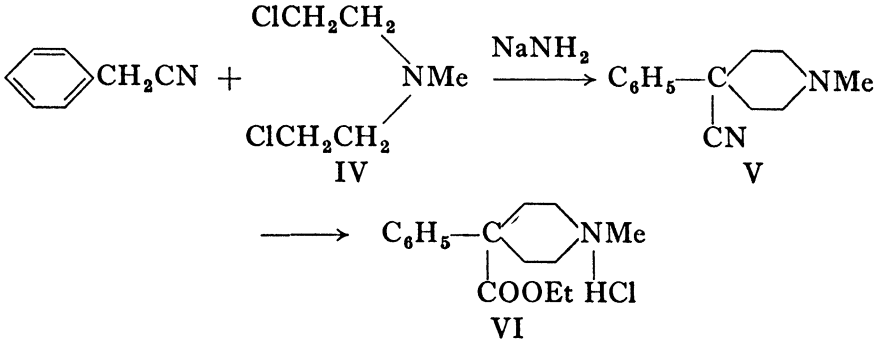
II



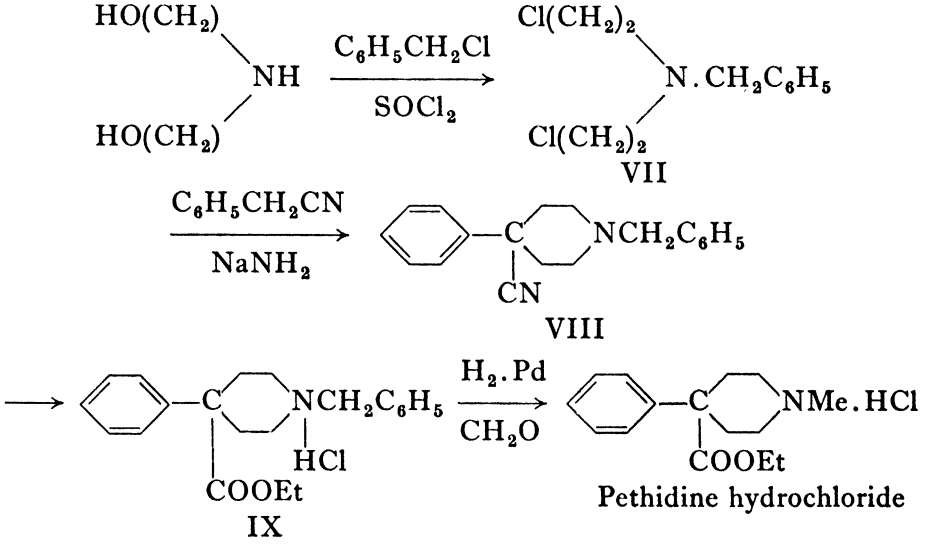
III

Pethidine (I) may be drawn as (II) thus showing its structural relationship to dihydrodeoxymorphine (III). This compound is used for illustration rather than morphine itself, as it is a powerful analgesic, and is simpler in structure.

Preparation. Eisleb (1) prepared pethidine by several methods. The most direct method is that in which di(2-chloroethyl)methylamine (IV) is condensed with benzyl cyanide in the presence of sodamide and the resulting nitrile (V) is hydrolysed and esterified to give pethidine hydrochloride (VI).



However, compound IV is a nitrogen mustard and a vesicant, and its use often leads to dermatitis. In a second method, used by Eisleb (1) and described more fully by other workers (2), 2-chloroethylbenzylamine (VII) was employed as an intermediate, since it is less unpleasant to handle than IV. Benzyl chloride is reacted with diethanolamine and the diol obtained is converted to VII by the use of thionyl chloride. Then as in the previous method the chloroamine is condensed with the disodio derivative of benzyl cyanide to produce a nitrile (VIII), which again is hydrolysed and esterified to yield ethyl 1-benzyl-4-phenyl-piperidine-4-carboxylate hydrochloride (IX). To obtain pethidine hydrochloride, the compound (IX) must be debenzylated and then methylated. This is carried out by means of hydrogen in the presence of a palladium catalyst, which first debenzylates and then, on addition of formaldehyde, methylates the product.

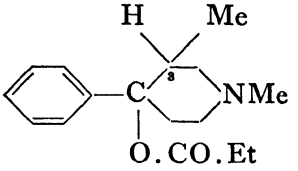


Many other routes for the preparation of pethidine have been explored (3, 4, 5, 6).

Properties. Pethidine hydrochloride is a colourless crystalline powder, soluble in water, methanol and ethanol, and slightly soluble in acetone and ether. It is also soluble in chloroform. M.p. 187° to 189°; the picrate melts at 189° to 190°. On adding an alkali to pethidine hydrochloride in water the base is obtained as

an oil which solidifies at 30°. Potassium mercuric iodide gives a cream-coloured precipitate. Pethidine was introduced in 1939 and since then the world production and consumption figures have approximated to those of morphine. It has been used to lessen the severity of withdrawal symptoms in morphine addicts undergoing treatment, but its employment is not without danger, for it can itself lead to addiction.

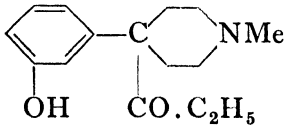
Alphaprodine (X) and **Betaprodine** (XI) are the *cis* and *trans* racemates respectively of 1 : 3-dimethyl-4-phenyl-4-propionoxypiperidine (7) and they are reversed esters, i.e. the —CO.OR grouping of pethidine (I) has been replaced by —O.CO.R. In addition, a methyl group has been introduced on the piperidine ring.



X = Hydrogen at position 3 and —O.CO.Et are *cis*
XI = Hydrogen at position 3 and —O.CO.Et are *trans*

Hydroxypethidine. Ethyl 4-*m*-hydroxyphenyl-1-methylpiperidine-4-carboxylate (8). This differs from pethidine only by the presence of a *m*-hydroxy group in the phenyl ring.

Ketobemidone (XII). 4-*m*-Hydroxyphenyl-1-methyl-4-propionylpiperidine.

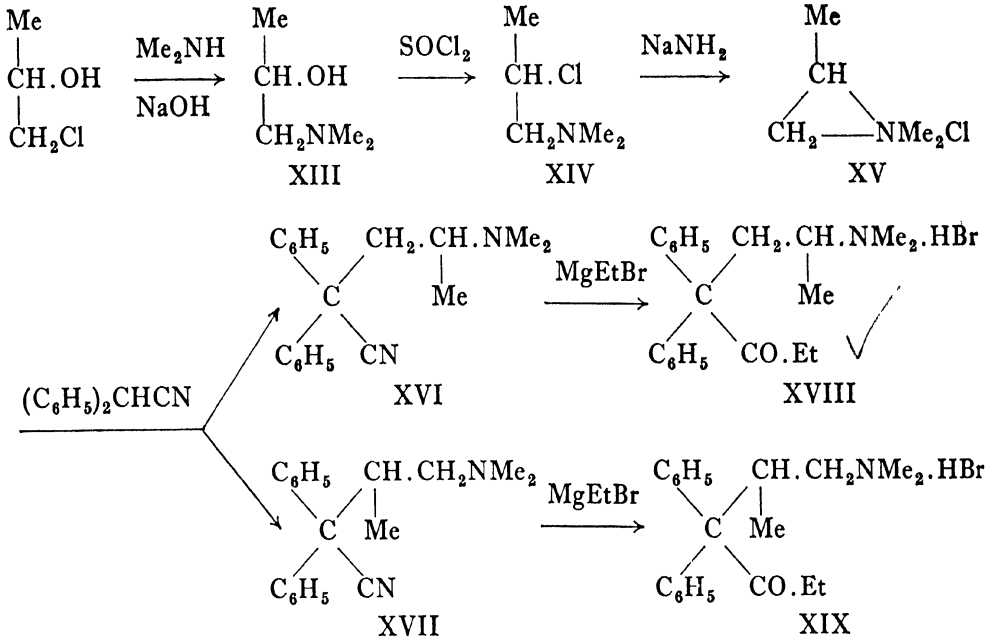


In this compound the ester group of hydroxypethidine has been replaced by $-COC_2H_5$, (8). Ketobemidone is more active than pethidine but is a powerful drug of addiction, being comparable with diacetylmorphine in this respect.

Methadone hydrochloride. 6-Dimethylamino-4 : 4-diphenyl-heptan-5-one hydrochloride. $C_{21}H_{27}ON.HCl$.

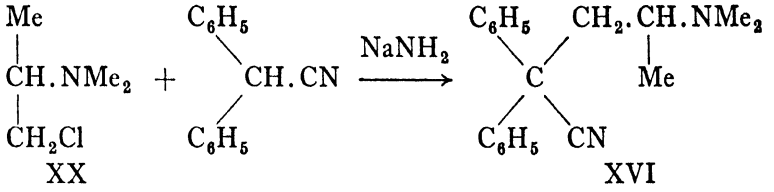
Preparation. Methadone was originally prepared by Bockmuhl (9) by the following method. 1-Dimethylaminopropan-2-ol (XIII), obtained by the condensation of dimethylamine with 1-chloropropan-2-ol in the presence of aqueous sodium hydroxide, was converted to the corresponding substituted alkyl halide (XIV) by reaction with thionyl chloride. XIV is condensed with diphenylacetonitrile in the presence of sodamide, and under these conditions it undergoes an intermediate cyclisation to the ethyleneimine (XV) which, on reaction, gives a mixture of the two possible nitriles XVI and XVII. These nitriles on treatment with ethylmagnesium bromide lead to the hydrobromides of methadone (XVIII) and isomethadone (XIX) respectively. Methadone hydrochloride is obtained by neutralisation of the hydrobromide and addition of ethanolic hydrogen chloride.

An alternative synthesis in which the quaternary ethyleneimine (XV) is employed has been used (10). In addition 1-chloro-2-dimethylaminopropane



(XX) has been used (11) in place of the 2-chloro-1-dimethylaminopropane of the original synthesis.

Methadone is a (±)-racemate and has been resolved by means of tartaric acid (12). The (−)-isomer is more active than the (+)-isomer. Isomethadone has also been resolved (13).



Properties. Methadone hydrochloride is a colourless crystalline powder which is soluble in water, alcohol or chloroform, but insoluble in ether. It has a m.p. 233° to 235° and its picrolonate melts at 160°. Methadone base has a m.p. of 78°.

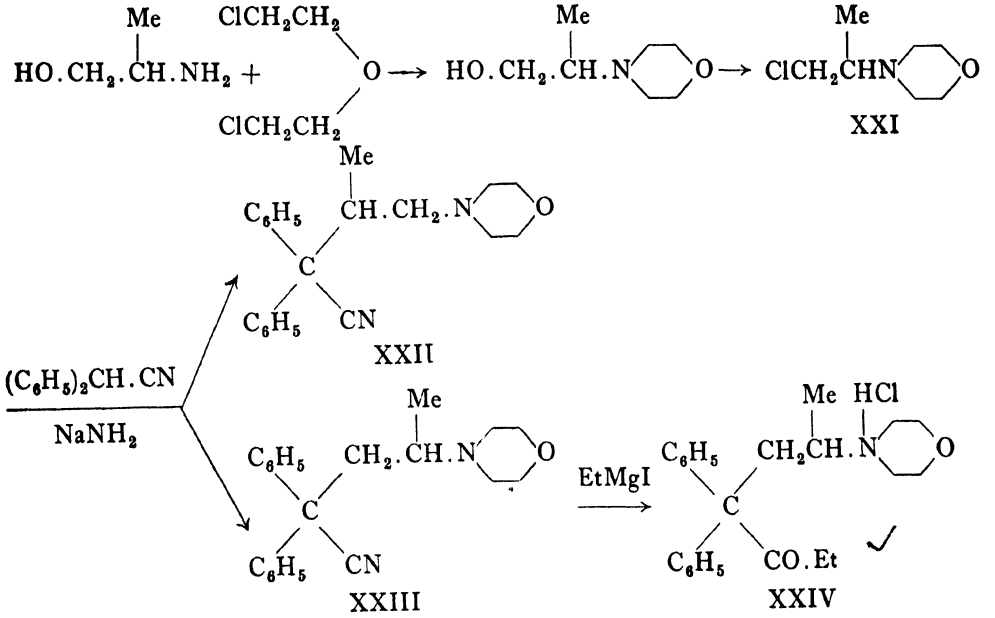
Methadol. α-(±)-6-Dimethylamino-4 : 4-diphenylheptan-3-ol. This compound is obtained by reduction of (±)-methadone (14) and is one of the two possible racemic mixtures.

Methadyl acetate. This is the acetyl ester of methadol (14). It has greater analgesic activity than methadone and shows some promise for clinical use.

Phenadoxone hydrochloride (XXIV). (±)-6-Morpholino-4 : 4-diphenylheptan-3-one hydrochloride. $C_{22}H_{27}O_2N.HCl$. Phenadoxone is methadone with the dimethylamino group replaced by morpholino.

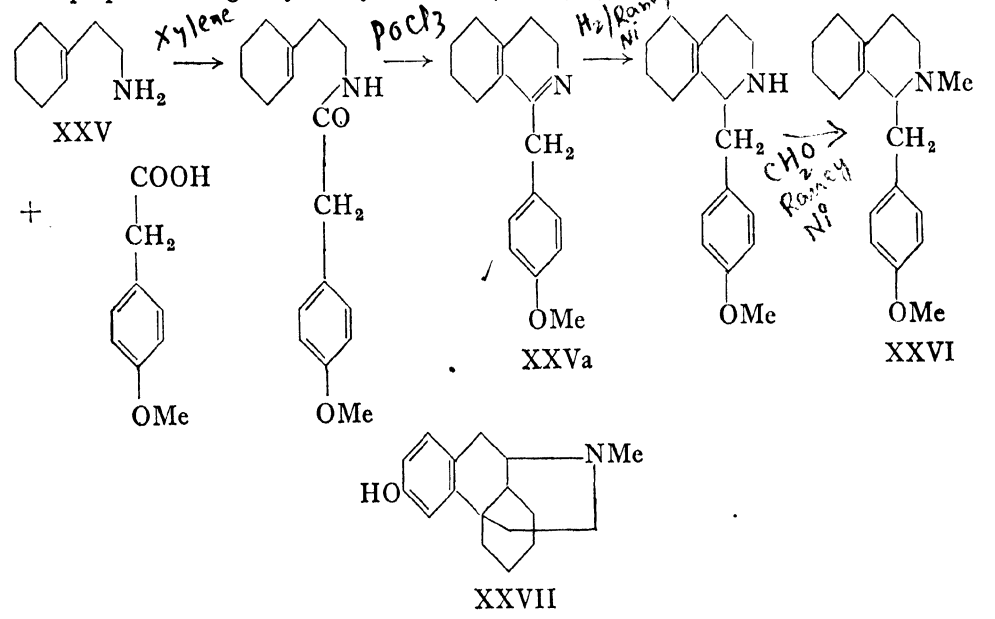
Preparation. The method of preparation used by Elks and his co-workers (11, 15) is basically that used by Bockmuhl for the preparation of methadone. 2-Aminopropan-1-ol is first condensed with di(2-chlorethyl) ether to give 2-morpholino-propan-1-ol which on treatment with thionyl chloride leads to the

required chloroamine, 1-chloro-2-morpholinopropane (XXI). This compound is condensed with the disodio derivative of diphenylacetonitrile to yield a mixture of isomeric nitriles (XXII and XXIII). On reaction with ethylmagnesium iodide XXIII gives phenadoxone which is converted to its hydrochloride (XXIV).



Methorphinan. (±)-3-Hydroxy-N-methylmorphinane. $C_{17}H_{23}ON$. (XXVII).

Preparation. Methorphinan was first prepared by Grewe during his fundamental studies upon compounds with morphine-like structures (16). It was later prepared in higher yield by Schnider (17, 18) by the following method:



*cyclo*Hexanone is reacted with cyanoacetic acid to give *cyclo*hexenylacetonitrile, which on reduction yields *cyclo*hexenylethylamine (XXV). The latter compound is then heated with *p*-methoxyphenylacetic acid in xylene and forms the amide which ring closes in phosphorus oxychloride to 1-(*p*-methoxybenzyl)-3 : 4 : 5 : 6 : 7 : 8-hexahydro*iso*quinoline (XXVa). This is reduced by means of hydrogen and Raney nickel, and the compound formed (after purification) is methylated by formaldehyde in the presence of Raney nickel to give 1-(*p*-methoxybenzyl)-2-methyl-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro*iso*quinoline (XXVI). Reaction with oxalic acid in acetone gives the oxalate of XXVI, which ring closes in 100 per cent phosphoric acid at 150° to 3-hydroxy-N-methylmorphinane (XXVII).

Properties. Methorphinan melts at 251° to 253°. The m.p. of the hydrobromide is 192° to 194°, and that of the tartrate 147°. Most of the analgesic activity of methorphinan resides in the (—)-isomer, and this appears to be usual amongst optically active analgesics (19). This (—)-isomer as its tartrate has been introduced for medical use and is known as levorphanol tartrate. It is a white powder with a bitter taste of m.p. 114° to 116°.

Methorphinan has been resolved into its two optical isomers by the use of (+)-tartaric acid (20). The (—) isomer known as *levorphanol* melts at 198° to 199° with $[\alpha]_D^{20}$ —56° (ethanol). The hydrobromide has $[\alpha]_D^{20}$ —27·5° (water). The tartrate melts at 206° to 208° and the dihydrate at 113° to 115° with $[\alpha]_D^{20}$ —13·8° (water). Levorphanol is a potent analgesic.

The (+) isomer, known as *dextrorphan*, has little analgesic action.

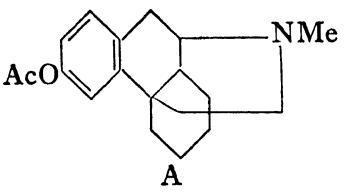
Levo- and Dextromethorphan. 3-Methoxy-N-methylmorphinane. $C_{18}H_{25}ON$.

Preparation. These two compounds are optical isomers of the methoxy compound formed by methylation of the hydroxy group in methorphinan (XXVII). (±)-Methorphan (racemethorphan) can be prepared by methylation of methorphinan with phenyltrimethylammonium chloride and, by resolution with (+)-tartaric acid, the two isomers are obtained. Alternatively the optically active compounds levorphanol and dextrorphan can be methylated by the same procedure (21).

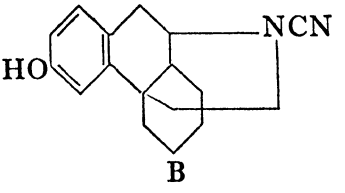
Properties. The racemic compound *racemethorphan* melts at 81° to 83° and the hydrobromide at 239° to 240° (anhydrous) or 92° to 94° (monohydrate). Levomethorphan melts at 108° to 111° and has $[\alpha]_D^{20}$ —49·3° (ethanol). The hydrobromide melts at 124° to 126° and has $[\alpha]_D^{20}$ —26·3° (water). Levomethorphan is an analgesic; dextromethorphan is used as an antitussive.

Levallorphan. (—)-3-Hydroxy-N-allylmorphinane. $C_{19}H_{25}ON$ (C).

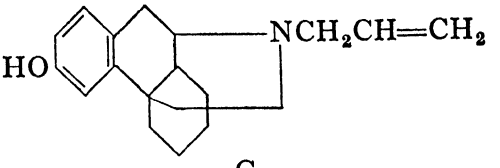
Preparation. In the same way that morphine is convertible to nalorphine (see p. 209) so levorphanol can be converted to levallorphan (22). Levorphanol is converted to its acetate (A) by reaction with acetic anhydride and the N-methyl group is then replaced by —CN by reaction with cyanogen bromide; the acetyl group is hydrolysed with ethanolic sodium hydroxide to give (—)-3-hydroxy-N-cyanomorphinane (B). The cyano group is removed and replaced by hydrogen by the action of dilute hydrochloric acid; alkylation with allyl bromide yields levallorphan (C).



A



B



C

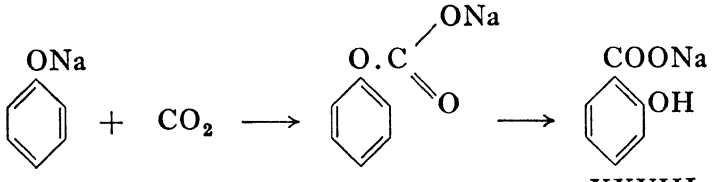
Properties. Levallorphan melts at 180° to 182° and has $[\alpha]_D^{20}$ −88·8° (methanol). It has been used as an antidote to the depressant activity of morphine-like analgesics on the respiration.

ANTIPYRETICS

Antipyretics are drugs which reduce the body temperature of persons with fever. The temperature of normal healthy persons remains almost unchanged. The compounds in this group have some analgesic and also some antiseptic action. Amongst them are found some of the earliest synthetic drugs. Phenazone was introduced in 1884, phenacetin in 1887 and acetylsalicylic acid in 1899.

Sodium salicylate. Sodium *o*-hydroxybenzoate. $C_7H_5O_3Na$. (XXVIII).

Preparation. Sodium salicylate is prepared by the reaction of carbon dioxide under pressure with sodium phenate (23). The method is the Schmitt modification of the original Kolbe reaction.



XXVIII

A mixture of phenol and sodium hydroxide solution is evaporated to dryness in a steam-jacketed rotary autoclave containing stirrer gear or steel balls to grind the sodium phenate formed. The temperature at the end of this stage is 190° to 195°, and is allowed to fall to 150°, when dry carbon dioxide is passed in. The gas stream is regulated so that the temperature remains at 159° to 160°, and then as the pressure rises, the temperature is allowed to reach 160° to 165°. After 48 hours the pressure is raised to 4·5 atmospheres and the temperature to 185° to 190°, and allowed to remain there for 4 hours. The pressure is then released, carbon dioxide is again blown in and any residual phenol is distilled. The recovered phenol is re-used. The residue in the autoclave is dissolved in water, neutralised with sulphuric acid, treated with zinc dust, sodium sulphite, sodium bisulphite and activated carbon and filtered. The filtrate is acidified at 75° and

the salicylic acid centrifuged off. The liquors are cooled and the second crop of salicylic acid is filtered and purified. The product is sublimed under vacuum and then melts at 158·5°.

It is converted to sodium salicylate by addition of sodium bicarbonate solution. The reaction mixture is not allowed to become alkaline, since then a brown coloration may develop. Iron must be excluded.

Properties. Sodium salicylate forms white crystals very soluble in water and in ethanol. It usually crystallises in the anhydrous condition, but from concentrated solutions, it may separate as large crystals containing six molecules of water of crystallisation. It gives a deep purple colour with ferric chloride solution. Sodium salicylate is the recognised treatment for acute rheumatic fever.

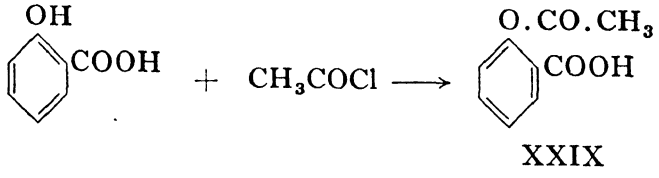
Salicylamide. *o*-Hydroxybenzoic acid amide. $C_7H_7NO_2$.

Preparation. Methyl salicylate is reacted with ammonia, preferably under pressure and in the presence of ammonium sulphite (24).

Properties. Salicylamide is a white crystalline powder of m.p. 141°. It was introduced in 1951 as a drug to relieve the pain associated with rheumatoid arthritis.

Acetylsalicylic acid. Aspirin. $C_9H_5O_4$. (XXIX).

Preparation. Acetylsalicylic acid is prepared by the action of acetyl chloride or acetic anhydride upon salicylic acid.



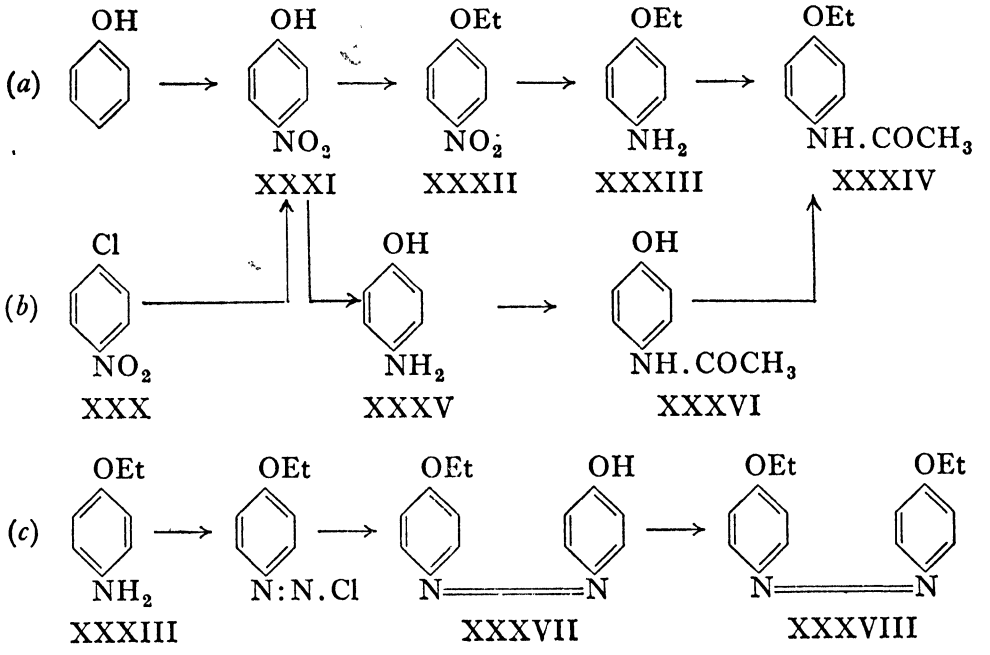
XXIX

An excess of acetylating agent is used and the temperature of the reaction mixture is kept as low as possible in order that the formation of salicylosalicylic acid, $HO.C_6H_4.COO.C_6H_4COOH$, may be avoided. When acetyl chloride is used as the acetylating agent, the plant may consist of a jacketed enamelled still connected to an earthenware condenser. The vapour passes to a scrubber containing acetic acid to absorb the excess of acetyl chloride, and finally hydrogen chloride evolved is absorbed by water trickling down a further absorption tower. The possibility of contamination by iron must be rigorously excluded. When the reaction is complete, the excess of acetyl chloride is distilled off and the reaction product is crystallised from benzene or other suitable solvent.

Properties. Aspirin is the most widely used of all the synthetic drugs, being a valuable antipyretic and analgesic. It is only slightly hydrolysed when passing through the stomach, and is therefore less irritating than salicylic acid, but it is rapidly decomposed on reaching the duodenum. Acetylsalicylic acid is a white crystalline powder, odourless, and with a slightly bitter taste. It is soluble in alcohol, chloroform, ether or benzene and slightly soluble in water in which it is slowly hydrolysed in the cold, and more rapidly on heating. In alkaline solutions it is rapidly decomposed. It dissolves in solutions of alkali citrates, but hydrolysis occurs on standing. The m.p. is 135° to 138°. Certain salts of acetylsalicylic

acid such as the calcium and magnesium salts are used medicinally but they are not very stable.

Phenacetin. Acetophenetidin. *p*-Ethoxyacetanilide. Acetyl-*p*-phenetidine. $C_{10}H_{13}O_2N$. (XXXIV).



Preparation. Phenacetin may be synthesised in several ways as is shown by the above scheme. (*a*) Monochlorbenzene is nitrated and the *p*-chloronitrobenzene (XXX) is separated. It is converted to *p*-nitrophenol (XXXI) by heating at 50° to 80° with alcoholic potassium hydroxide in the presence of potassium sulphite, further additions of the latter being made from time to time. An almost theoretical yield can be obtained (25). Conversion to *p*-nitrophenetole (XXXII) is effected by heating with ethyl chloride in an autoclave in the presence of caustic soda. One mole of *p*-nitrophenol is dissolved in the theoretical quantity of soda in a 10 per cent solution and one mole with a 10 per cent excess of ethyl chloride is added. The reaction is carried out at 100° for 8 hours in a lead-lined autoclave. The *p*-nitrophenetole is filtered off after cooling, washed with dilute soda and then with water. The conversion of *p*-chloronitrobenzene to *p*-nitrophenetole may be carried through in one stage by the controlled addition of alcoholic sodium hydroxide solution to *p*-chloronitrobenzene in alcohol. About 10 per cent of *p*-nitrophenol is not ethylated by this method and is again treated with ethyl chloride (26).

The *p*-nitrophenetole is reduced in a cast-iron vessel by means of iron filings and hydrochloric acid. It is mixed with twice its weight of water containing 1 per cent hydrochloric acid, and an equal weight of iron filings is added in portions, keeping the temperature at about 60°. The vessel is then heated to 90° until the reaction is complete. The aqueous liquid is siphoned off and the

p-phenetidine (XXXIII) distilled by super-heated steam at 150° to 180°. It distils as an oil which becomes discoloured if exposed to air.

The pure *p*-phenetidine is then boiled with an equal weight of glacial acetic acid in an enamelled still until no unaltered amine is found to be present. The operation takes about 10 hours, and then the excess of acetic acid is distilled off *in vacuo* and the phenacetin (XXXIV) is extracted from the residue with boiling water, decolorised by means of active carbon, allowed to cool and crystallise in the presence of a trace of sulphur dioxide to prevent oxidation (27). It may be recrystallised from water.

(*b*) *p*-Nitrophenol is reduced to *p*-aminophenol (XXXV) by being boiled with a solution of three times its weight of sodium sulphide in water for an hour. The product is poured into an excess of hydrochloric acid, boiled and filtered. *p*-Aminophenol hydrochloride crystallises on cooling. The base is then liberated from its hydrochloride by adding the required amount of soda, separated and treated with an equal weight of acetic anhydride, the latter being added slowly, keeping the temperature down to about 10°. After allowing the reaction mixture to stand for an hour, the solid acetyl compound (XXXVI) is filtered, washed and dried. It may then be ethylated by means of ethyl chloride as described in method (*a*).

(*c*) In this method one molecule of phenol with one molecule of *p*-phenetidine are converted to two molecules of the latter. *p*-Phenetidine is first diazotised with nitrous acid, and the solution of the diazo compound is added to the required quantity of phenol dissolved in aqueous sodium carbonate solution. *p*-Ethoxy-*p*-hydroxyazobenzene (XXXVII) crystallises out and is dissolved in alcoholic sodium hydroxide. Ethylation is then carried out as in method (*a*). *pp'*-Diethoxyazobenzene (XXVIII) is formed and is filtered off. It is reduced with tin and hydrochloric acid; after being made alkaline the reaction mixture is subjected to steam distillation to give *p*-phenetidine. It is converted to phenacetin by acetylation.

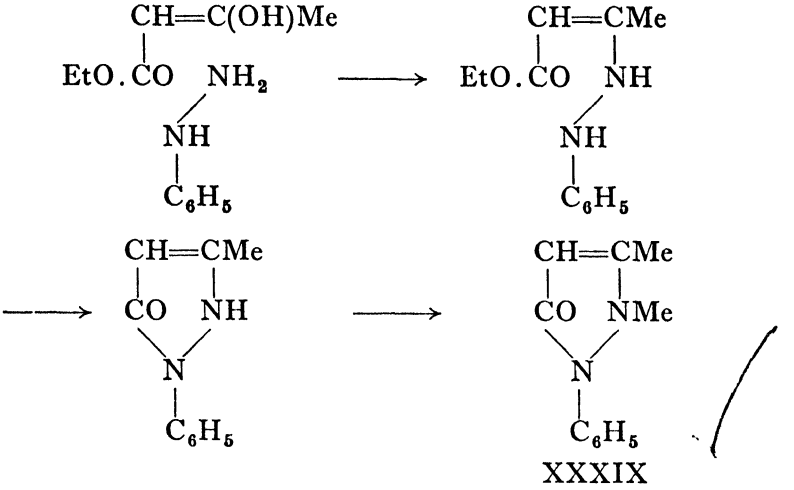
Properties. Phenacetin forms glistening white scales slightly soluble in cold water and fairly soluble in hot water. It is soluble in alcohol, ether or chloroform. The m.p. is 134° to 136°. On being warmed with hydrochloric acid and after addition of a drop of dilute potassium dichromate solution to the filtered acid solution, a violet colour appears which soon changes to ruby red. Phenacetin is frequently administered in an admixture with aspirin, or aspirin and caffeine.

Phenazone. Antipyrin. 2 : 3-Dimethyl-1-phenyl-5-pyrazolone. $C_{11}H_{12}ON_2$. (XXXIX).

Preparation. Phenazone was first made by Knorr in 1884 (28) and his method is still used. Phenylhydrazine is condensed with ethyl acetoacetate and the 3-methyl-1-phenylpyrazolone so formed is further methylated to yield phenazone. The reaction may be represented as shown on p. 42.

The first stage of the reaction involves the loss of water and takes place in the cold. The ring closure requires heat, and ethyl alcohol is eliminated. Phenylhydrazine in benzene solution is added to the ethyl acetoacetate dissolved in 10 per cent of its weight of ethyl alcohol. After a period at the boiling-point the solvents are distilled and the residue of 3-methyl-1-phenyl-5-pyrazolone is

dissolved in hot water, filtered and crystallised, and then recrystallised from ethanol. This compound may be methylated by means of a methyl halide, or by dimethyl sulphate (29). Caustic soda is not used since the reaction then goes too far. When methylation is complete, the liquid is made slightly alkaline with sodium carbonate and the solvent is distilled. The phenazone is recrystallised from benzene and then from water, after being decolorised by means of active carbon.

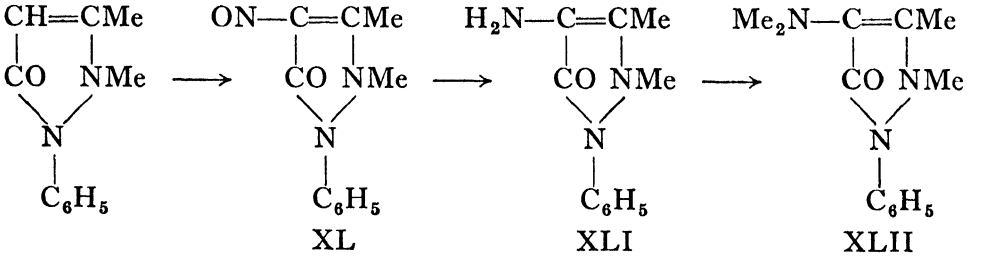


XXXIX

Properties. Phenazone crystallises in tabular crystals or lustrous scales. It is very soluble in water, alcohol and chloroform, and less soluble in ether. It is weakly basic in character and forms salts of which the most important is the salicylate. The m.p. is 111° to 113°. Phenazone gives a deep red colour with ferric chloride solution, and the red changes to light yellow on addition of sulphuric acid.

Amidopyrine. Aminopyrine. 2 : 3-Dimethyl-4-dimethylamino-1-phenyl-5-pyrazolone. $C_{13}H_{17}ON_3$. (XLII).

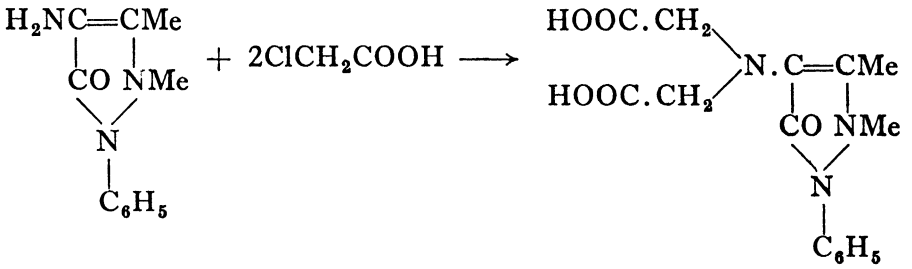
Preparation. Phenazone is the starting-point for the preparation of amidopyrine. Phenazone is reacted with nitrous acid to give the nitroso compound (XL) which on reduction and methylation leads to the amine (XLI) and amidopyrine (XLII). The reaction sequence is as follows:



XL XLI XLII

The preparation of the nitroso compound (XL) follows normal practice. The phenazone is dissolved in dilute mineral acid and sodium nitrite solution is

added. If the nitroso compound is reduced to the amine (XLI) by the use of sodium hydrogen sulphite the resulting compound may be methylated by formic acid and formaldehyde (29) or by dimethyl sulphate (30). Chloroacetic may also be used and the amino-acid (XLIII) formed is decarboxylated by being heated in an autoclave at 120° to 140° for 10 to 12 hours.



XLIII

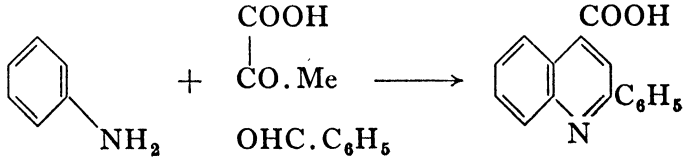
Phenazone may also be converted to amidopyrine by the following method (31). Phenazone (3·8 parts) is dissolved in 40 per cent sulphuric acid (10 parts) and water (50 parts) and a solution of sodium nitrite (1·55 parts) in water (15 parts) is added slowly with cooling and stirring. The nitroso compound separates out. Forty per cent sulphuric acid (40 parts) is then added and zinc dust (6 parts). The mixture is heated to 70° and a 10 per cent solution of formaldehyde (16 parts), zinc dust (12 parts) and a small quantity of copper sulphate solution are introduced. The mixture is stirred until hydrogen is no longer evolved and is then filtered and rendered alkaline. Crude amidopyrine is precipitated and is recrystallised from benzene.

Properties. Amidopyrine is a white crystalline powder which is soluble in water, alcohol or ether. It has a m.p. of 107° to 109°. With ferric chloride solution it produces a bluish-violet colour. Silver nitrate solution gives a deep violet colour and ultimately metallic silver is deposited.

The compounds which follow may be regarded as antipyretics, but are used for the treatment of rheumatic conditions.

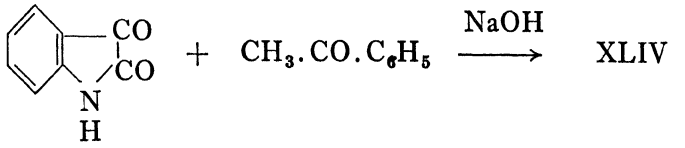
Cinchophen. Quinophan. 2-Phenylquinoline-4-carboxylic acid. $C_{16}H_{11}O_2N$. (XLIV).

Preparation. Cinchophen may be prepared by reacting together aniline and benzaldehyde, refluxing in ethanol until condensation is complete and then adding pyruvic acid. The cinchophen crystallises and is filtered off. It is purified by conversion to its sodium salt which is acidified (29). This is an example of the Döbner synthesis of quinoline-4-carboxylic acids.



XLIV

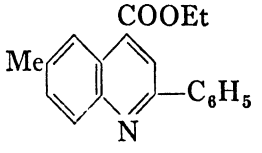
An alternative method of preparation uses the reaction between isatin and acetophenone (32). This is an example of the Pfitzinger reaction:



XLIV

Properties. Cinchophen is a yellowish-white crystalline powder with a bitter taste. It has a m.p. of 213° to 216°. It is insoluble in water, and moderately soluble in alcohol, ether or chloroform. It dissolves in solutions of alkalis. Cinchophen has been used for the treatment of gout and was introduced for this purpose in 1908.

Neocinchophen. 6-Methyl-2-phenylquinoline-4-carboxylic acid ethyl ester. $C_{19}H_{17}O_2N$. (XLV).



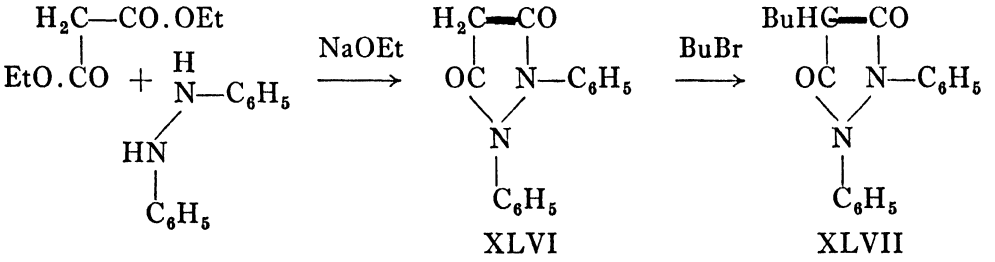
XLV

Preparation. The method used is analogous to that described for cinchophen, except that *p*-toluidine instead of aniline is reacted with benzaldehyde and pyruvic acid. The product is then esterified.

Properties. Neocinchophen is a white or pale yellow crystalline powder, odourless, and sensitive to light. It has the advantage over cinchophen of being almost tasteless. It is insoluble in water and soluble in hot alcohol, ether or chloroform. The m.p. is 74° to 77°.

Phenylbutazone. 4-*n*-Butyl-1 : 2-diphenylpyrazolidine-3 : 5-dione. $C_{19}H_{20}O_2N_2$. (XLVII).

Preparation. 1 : 2-Diphenylpyrazolidine-3 : 5-dione (XLVI) may be alkylated by means of 1-bromobutane in the presence of caustic soda to give phenylbutazone (33). 1 : 2-Diphenylpyrazolidine-3 : 5-dione has been prepared from diphenylhydrazine and diethyl malonate (34). Thus this route to phenylbutazone is as follows:



XLVI XLVII

Alternatively diphenylhydrazine (hydrazobenzene) may be condensed with diethyl-*n*-butyl-malonate (35) to give phenylbutazone.

Properties. Phenylbutazone is a white powder with a slightly bitter taste. It

is soluble in chloroform, benzene or ether, or aqueous alkali hydroxides, but is almost insoluble in water. The m.p. is 106° to 107°. Swiss workers in 1951 introduced a solution of amidopyrine in phenylbutazone for the treatment of rheumatoid diseases and in 1952 phenylbutazone alone was used for the same purpose. It has produced many toxic side-effects.

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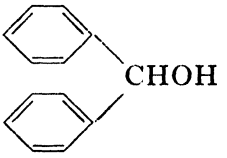
CHAPTER III

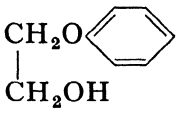
Tranquillisers

THE synthetic tranquillisers or ataraxics are drugs that induce a mental state free from agitation and anxiety. This group of drugs embraces many chemical compounds of widely differing structures. Many of these compounds such as chlorpromazine are phenothiazine derivatives and are thus closely related to antihistamines such as promethazine and antispasmodics such as ethopropazine. Further butylmercaptobenzhydryl-2-dimethylaminoethyl sulphide, whose preparation is described below, is similar in structure to the antihistamine diphenhydramine. Another group of tranquillisers represented by pipadrol, azacyclonal and benactyzine is derived from benzhydrol. Here there is a link with the antispasmodics such as benzhexol and trasentin. Many tranquillisers in common with antispasmodics have anticholinergic properties.

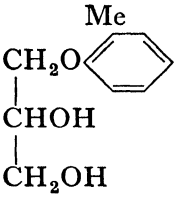


Benzhydrol

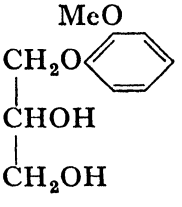
Mephenesin, one of the first tranquillisers to be introduced, was first used for its power of muscle relaxation. The discovery by Berger and Bradley (1) of its pharmacological properties was made in the course of a study of the side-effects of 2-phenoxyethanol, a compound used as a preservative in injections. They found that it possessed the power of muscle relaxation. Interest was thus aroused and further investigation showed that mephenesin was the most satisfactory compound of those tested. Its muscle-relaxant properties were due to an effect on the nervous system. Mephenesin is also structurally related to guaiacolglyceryl ether which was once used as a cough sedative.



Phenoxyethanol



Mephenesin

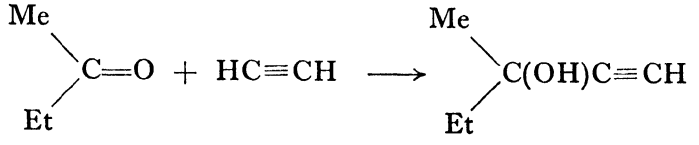


Guaiacolglyceryl ether

Methylpentynol, introduced by Margolin in 1951, is an acetylenic tertiary alcohol; a related saturated compound is amylene hydrate which is also used as a sedative.

Methylpentynol. 3-Methyl-1-pentyn-3-ol. Methylparafynol. $C_6H_{10}O$. (I).

Preparation. This compound is usually prepared by the reaction in a suitable solvent between ethyl methyl ketone and acetylene in the presence of a condensing agent.



I

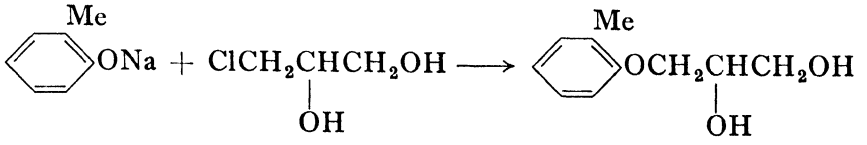
The condensing agent may be sodium in liquid ammonia (2, 3, 4), sodamide (5, 6, 7), an alkali metal alkoxide (8) or potassium hydroxide (9, 10, 11).

The chemistry of acetylenic alcohols has been reviewed by Johnson (12).

Properties. Methylpentynol melts at 30° to 31° and boils at 149° at 745 mm. and 78° at 150 mm. It has n_D^{20} 1·4318 and d^{20} 0·872. The acetate boils at 149° at 745 mm. and 52° at 13 mm. The hydrogen phthalate melts at 97° to 98°. Methylpentynol contains one asymmetric carbon atom and has been resolved into its optical isomers (13).

Mephenesin. 3-(2-Methylphenoxy)-1 : 2-propanediol. $C_{10}H_{14}O_3$. (II).

Preparation. The starting materials may be either allyl cresyl ether (14), glycerol (15, 16), an epoxide (17) or glyceryl monochlorohydrin (18, 19). In the last method the monochlorohydrin is reacted with cresol in hot aqueous sodium hydroxide solution.



II

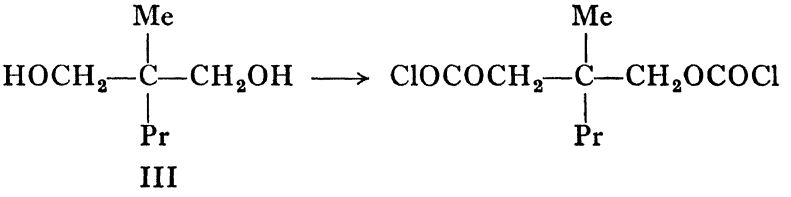
Excess of cresol is removed from the reaction solution by steam distillation. The mephenesin is extracted with benzene and the solution is evaporated; the crude residue is fractionally distilled.

Properties. Mephenesin is a white crystalline solid melting at 71° and boiling at 196° at 16 mm. It is soluble in ether, benzene, ethanol and boiling water and may be recrystallised from carbon tetrachloride. The monocarbamate melts at 93° (20).

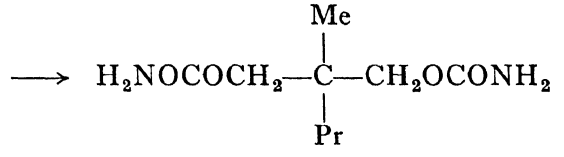
Meprobamate. 2-Methyl-2-propyl-1 : 3-propanediol dicarbamate. $C_9H_{18}O_4N_2$. (IV).

Preparation. 2-Methyl-2-propyl-1 : 3-propanediol (III) is obtained by reduction of either diethyl methylpropylmalonate (21) or of the condensation product of 2-methylvaleraldehyde and formaldehyde (22). The diol is then

converted by reaction with phosgene at a low temperature to the bischloroformate and this on addition of aqueous ammonia yields meprobamate (IV).



III



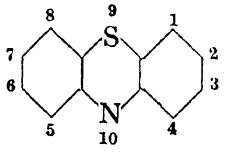
IV

Properties. Meprobamate is a white solid with a characteristic bitter taste. It melts at 105° to 106°; it is slightly soluble in water (0·34 g per 100 ml at 20°) from which it may be crystallised; it is soluble in most organic solvents. Although stable to cold dilute acids and alkalis meprobamate is decomposed by hot acids yielding ammonia, carbon dioxide and the diol.

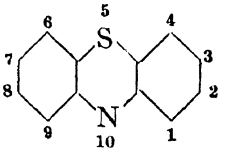
Meprobamate is a depressant of the central nervous system.

Chlorpromazine. 3 - Chloro - 10 - (3 - dimethylaminopropyl)phenothiazine. $C_{17}H_{19}N_2SCl$. (VII).

Phenothiazine is numbered differently in the British and American systems as shown below. The British system has been used in this book.



British
(Beilstein system)

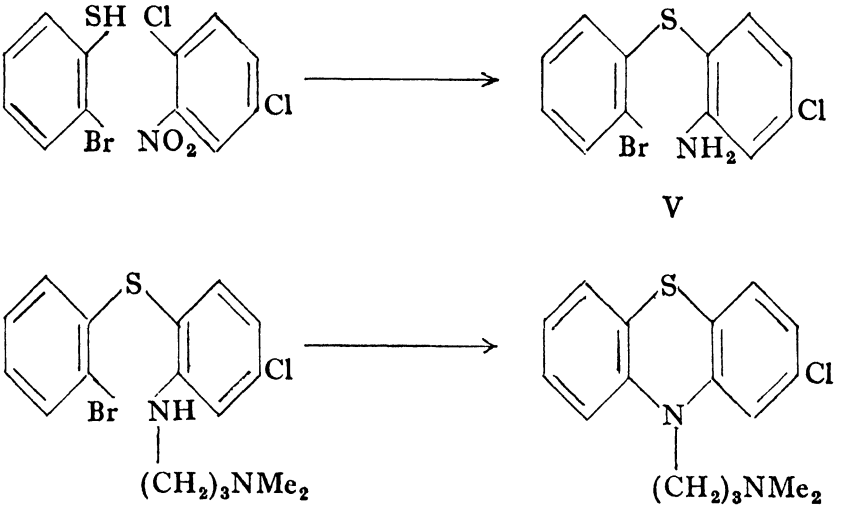


American
(Chemical Abstracts System)

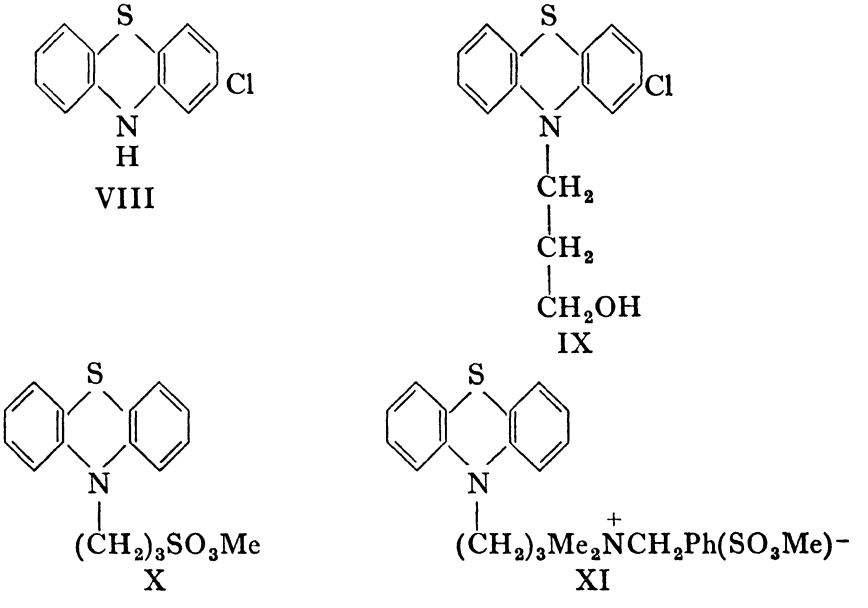
Preparation. The earlier methods for the preparation of phenothiazines involved the condensation of a diphenylamine derivative with sulphur; a mixture of 1- and 3-chloro derivatives is obtained by this method (23) and may be alkylated (24) by dimethylaminopropyl chloride to yield mainly the required 3-chloro compound.

An improved preparative method has been patented (25) in which 2-bromo-2′-amino-4′-chlorodiphenyl sulphide (V) is first obtained by condensation of 2 : 5-dichloronitrobenzene and 2-bromothiophenol and followed by reduction of the nitro group to an amine; the sulphide is then condensed with dimethyl-

aminopropyl chloride in xylene in the presence of sodamide to give 2-bromo-2′-(3″-dimethylaminopropyl)amino-4′-chlorodiphenyl sulphide (VI). This compound is ring closed by heating in dimethylformamide with sodium carbonate and copper powder yielding chlorpromazine (VII).



In another synthesis by Toldy and Fabricius (25a), 3-chlorophenothiazine (VIII) was transformed into 3-(3′-chlorophenothiazinyl-10′)propionic acid which was reduced with lithium aluminium hydride to 3-(3′-chlorophenothiazinyl)-propanol (IX); this was converted to the mesyl derivative (X) which when treated in acetone solution at room temperature with dimethylbenzylamine gave a product (XI) which was hydrogenated to chlorpromazine (VII).



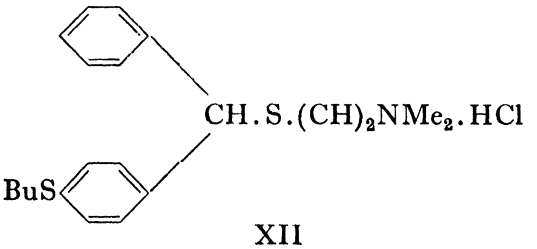
Properties. The free base is usually an oil boiling at 210° to 225° at 0·7 mm. but it has been obtained crystalline when it melts at 57° to 58° (25a). The hydrochloride melts at 192° to 195° and is a white crystalline powder soluble in water (1 in 25), ethanol and chloroform; insoluble in ether or benzene.

Other phenothiazine derivatives. The following compounds have also been introduced as tranquillisers:

3-chloro-10[3-(1-methyl-4-piperazinyl)propyl]phenothiazine (*prochlorperazine*); 10-(1-methyl-3-piperidylmethyl)phenothiazine (*mepazine*) and 10-(3-dimethylaminopropyl)phenothiazine (*promazine*).

Captodian. 4 - Butylmercaptobenzhydryl - 2 - dimethylaminoethyl sulphide hydrochloride. $C_{21}H_{29}NS_2.HCl$. (XII).

Preparation. Dimethylaminoethyl chloride is condensed with 4-butylmercaptobenzhydryl mercaptan in ethanol in the presence of sodium ethoxide; sodium chloride is filtered off and the solution on evaporation yields the crude base from which the hydrochloride is prepared (26).

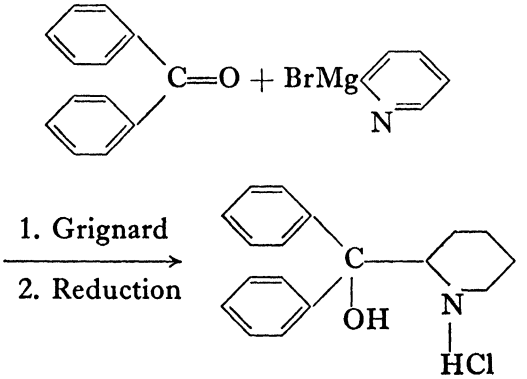


XII

Properties. The hydrochloride is a white solid melting at 131° to 132°. This compound bears a formal resemblance to antihistaminic benzhydryl ethers such as diphenhydramine.

Pipadrol hydrochloride. 2-Piperidylbenzhydrol hydrochloride. $C_{18}H_{21}ON.HCl.H_2O$. (XIII).

Preparation. The Grignard compound formed from 2-bromopyridine and magnesium is reacted with benzophenone and the diphenyl-2-pyridine methanol hydrochloride so obtained is reduced (27, 28) to pipadrol which is the corresponding piperidine compound (IX).



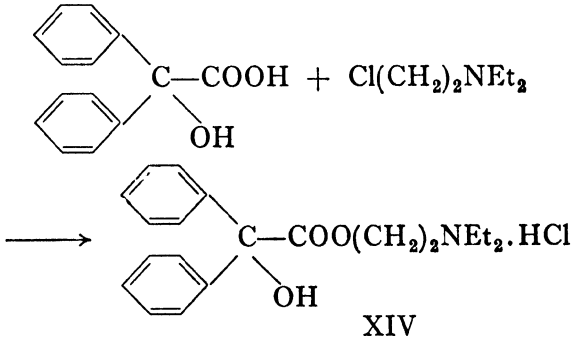
XIII

Properties. The hydrochloride is a white powder with a bitter taste. It melts at 308° to 309°; it is soluble in hot water (1 in 60) and in ethanol.

Pipadrol is a stimulant of the central nervous system. The corresponding 4-piperidyl isomer (azacyclonal) has also been used in medicine.

Benactyzine hydrochloride. Diethylaminoethyl benzilate hydrochloride. $C_{20}H_{25}O_3N.HCl$. (XIV).

Preparation. The ester may be prepared by transesterification of a benzilic acid ester with diethylaminoethanol (29); by the reaction between potassium benzilate and diethylaminoethyl chloride hydrochloride (30) or by the Horenstein-Pahlicke reaction (31 to 33). In the last method benzilic acid and diethylaminoethyl chloride are heated in boiling *iso*propanol for 2 hours and the benactyzine hydrochloride which forms is filtered off and recrystallised from *iso*propanol. This esterification technique is useful for the preparation of esters from acids, such as benzilic acid, which contain reactive functional groups.



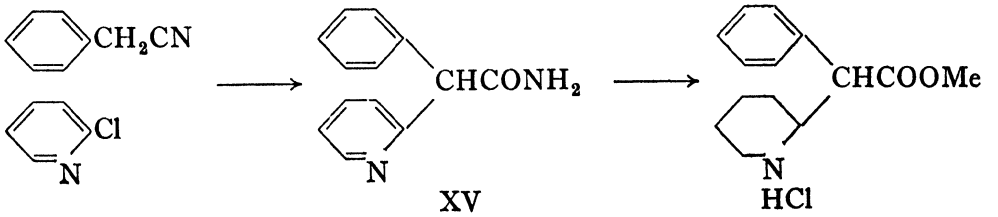
XIV

Properties. Benactyzine melts at 54° and boils at 149° to 151° at 0·01 mm. The hydrochloride which is a white crystalline solid sparingly soluble in water melts at 177° to 178°; the methobromide melts at 169° to 170° and the methochloride at 184° to 185°.

Methylphenidate. Methyl-(phenyl-2-piperidine acetate). $C_{13}H_{16}O_2N$. (XVI).

Preparation. Benzyl cyanide is condensed with 2-chloropyridine in toluene with sodamide as condensing agent (34) and the resulting nitrile is hydrolysed to phenyl-2-pyridineacetamide (XV) which is hydrogenated to a piperidine derivative and then hydrolysed by boiling hydrochloric acid to phenyl-2-piperidine acetic acid which is esterified (35) in the usual manner to the methyl ester hydrochloride (XVI).

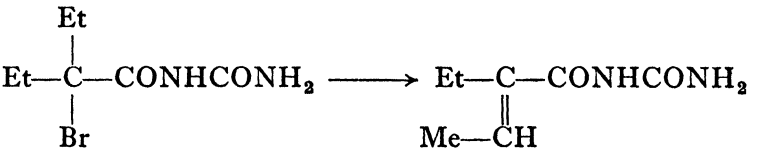
Methylphenidate hydrochloride melts at 208° and the ester base boils at 135° to 137° at 0·6 mm.



XV XVI

Ectylurea. 2-Ethylcrotonylurea. $C_7H_{12}O_2N_2$. (XVII).

Preparation. 2-Ethylcrotonylurea exists in *cis* and *trans* isomers; the higher melting form is the one required; it is prepared from carbromal (see p. 15) by the following method (36). Carbromal is dehydrohalogenated in *iso*propanol by means of silver oxide. The ectylurea obtained by concentration of the solution melts at 189° to 190·5°; recrystallisation from ethanol raises the melting-point to 197° to 198° (37).



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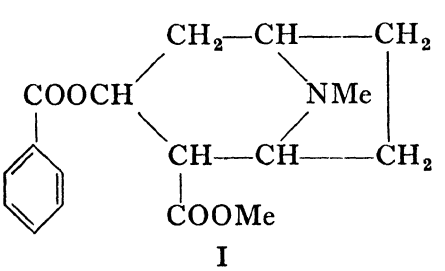
CHAPTER IV

Anaesthetics

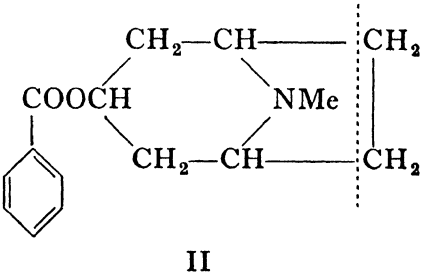
LOCAL ANAESTHETICS

LOCAL anaesthetics produce a localised insensitivity to pain. Surface anaesthesia may be produced by cold. Freezing may be effected by the evaporation of volatile liquids, and ethyl chloride is commonly used for minor operations on the tissues near the surface of the skin where a transient effect is all that is necessary. A more important group of local anaesthetics is that comprising the drugs which exert their paralysing effect on sensory nerve endings. These drugs when injected subcutaneously, anaesthetise an area round the site of injection, the effect lasting for an hour or more. They are thus particularly suitable for dental extractions. On the other hand, when they are injected into a central nervous organ, they block the transmission of impulses to or from the portion of the organ involved and thus regions of the body may be anaesthetised.

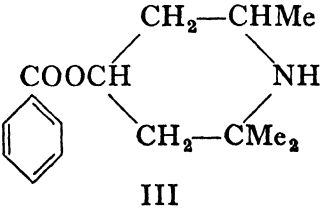
Many drugs have a local anaesthetic action. The alkaloid cocaine (I) (see p. 253) was the original drug used for this purpose and most synthetic local anaesthetics bear some relation to its structure. The removal of the carbomethoxy group from cocaine yields tropacocaine (II) which also has a powerful local anaesthetic action. Experiments with piperidine derivatives simulating the portion to the left of the dotted line in II led, in 1896, to the introduction of benzamine (i.e. eucaine) (III).



I

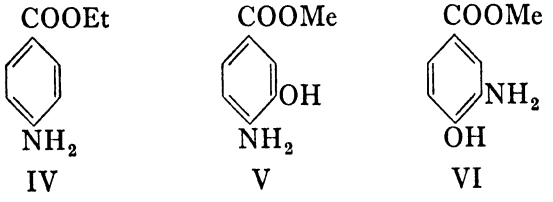


II



III

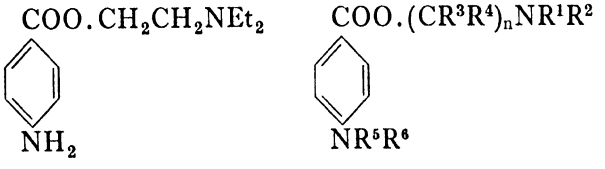
Meanwhile, the work of Einhorn led in 1897 to the introduction of benzocaine or ethyl 4-aminobenzoate (IV) and in 1898 to the introduction of Orthoform[P] (V) and Orthoform New[P] (VI) (now named Orthocaine).



IV V VI

On testing a number of *p*-aminobenzoates it was found that an increase of the length of the alkyl chain produced an increase in anaesthetic action and the butyl ester is still in use.

A more important discovery of Einhorn was that of the effectiveness of the dialkylaminoalkyl esters of *p*-aminobenzoic acid leading in 1905 (1) to the important drug, procaine (VII). A very large number of modifications of the structure of procaine has been made and tested and the most valuable are in clinical use. The table gives a list of the more important members of this series based upon the general formula (VIII).



VII VIII

Name	$-NR^1R^2$	$-(CR^3R^4)_n-$	$-OOC.C_6H_4.NR^5R^6$
Procaine	$-NEt_2$	$-(CH_2)_2-$	$-OOC.C_6H_4.NH_2$ (1 : 4)
Hydroxyprocaine	$-NEt_2$	$-(CH_2)_2-$	$-OOC.C_6H_3.(OH).NH_2$ (1 : 2 : 4)
Parethoxycaine	$-NEt_2$	$-(CH_2)_2-$	$-OOC.C_6H_4.OEt$ (1 : 4)
Amethocaine	$-NMe_2$	$-(CH_2)_2-$	$-OOC.C_6H_4.NH.Bu$ (1 : 4)
Hydroxy-methocaine	$-NMe_2$	$-(CH_2)_2-$	$-OOC.C_6H_3.(OH)NH.Bu$ (1 : 2 : 4)
Butacaine	$-NBu_2$	$-(CH_2)_3-$	$-OOC.C_6H_4.NH_2$ (1 : 4)
Butamin	$-NMe_2$	$-CH_2CHMeCHMe-$	$-OOC.C_6H_4.NH_2$ (1 : 4)
Butethamine	$-NHCH_2CHMe_2$	$-(CH_2)_2-$	$-OOC.C_6H_4.NH_2$ (1 : 4)
Larocaine	$-NEt_2$	$-CH_2CMe_2CH_2-$	$-OOC.C_6H_4.NH_2$ (1 : 4)
Amylocaine	$-NMe_2$	$-CH_2.C(Me)Et-$	$-OOC.C_6H_5$
Amydricaine	$-NMe_2$	$-CH_2.C(Et).CH_2NMe_2$	$-OOC.C_6H_5$
Apothesine[P]	$-NEt_2$	$-(CH_2)_2-$	$-OOC.CH=CH.C_6H_5$
Piperocaine	$-N.C_5H_9.Me$	$-(CH_2)_3-$	$-OOC.C_6H_5$

In addition to the above, we shall consider also the simple alkyl esters of 4-aminobenzoic acid and some compounds which do not fit into the above classification.

Many effective local anaesthetics are esters formed by the reaction of alcohols or amino-alcohols with benzoic or 4-aminobenzoic acid. The alcohols may be primary, secondary or tertiary. The amino group of the amino-alcohol may be secondary or tertiary, and may be attached to a simple or bridged ring system.

The preparation of amino-esters is not always simple, for the amino group tends to combine with the acid and with the esterification catalyst. Sometimes the amino group can be protected during the esterification by converting it to its hydrochloride:

$$R.COOH + HO(CH_2)_nNR'_2.HCl \longrightarrow R.COO(CH_2)_n.NR'_2.HCl + H_2O$$

When this reaction can be carried out in a solvent which dissolves the amino-alcohol hydrochloride, then high yields are obtained. Alternatively, a lower ester such as a methyl ester of the acid can be made first and this, on alcoholysis with the amino-alcohol, gives the amino-ester. The reaction is usually carried out in the presence of a sodium alkoxide.

$$R.COOMe + HO(CH_2)_nNR'_2 \xrightarrow{NaOMe} R.COO(CH_2)_nNR'_2 + MeOH$$

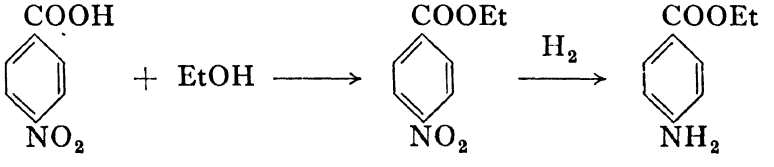
Often the acid is first converted to a chloro-ester which, on reaction with the appropriate amine leads to the required amino-ester.

$$R.COOH + HO(CH_2)_nCl \longrightarrow R.COO(CH_2)_nCl \xrightarrow{HNR'_2} R.COO(CH_2)_nNR'_2$$

An interesting method for the preparation of amino-esters involves the preparation of the salt of the acid with an amino-alkyl halide, which on being heated gives the amino-ester hydrochloride. This is known as the Horenstein-Pählicke reaction.

$$R.COOH + R'_2N(CH_2)_nCl \longrightarrow R.COO.HNR'_2(CH_2)_nCl \xrightarrow{heat} R.COO(CH_2)_nNR'_2.HCl$$

Where the acid to be esterified is an aromatic amino-acid, it can be esterified as a nitro-acid, and the nitro group reduced to the required amino group.



Examples of the above methods will be found in the preparative procedures for local anaesthetics.

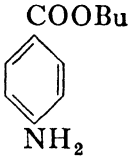
Benzocaine. Ethyl 4-aminobenzoate. $C_9H_{11}O_2N$. (IV).

Preparation. 4-Nitrobenzoic acid is the key intermediate required for the preparation of benzocaine and all other anaesthetics based on 4-aminobenzoic

acid. Toluene is nitrated with nitric acid to a mixture of 1- and 4- nitrotoluene and the 4- compound is separated and oxidised to 4-nitrobenzoic acid by sodium dichromate in 80 per cent sulphuric acid (2). Then the nitro acid is esterified with ethanol in the presence of sulphuric acid and finally the 4-nitro group is reduced to a 4-amino group. This reduction has been carried out catalytically (3), electrolytically (4), and by means of tin and hydrochloric acid (5). The method involving the use of iron filings and acetic acid is the most usual one (2, 6).

Properties. Benzocaine is soluble in alcohol, ether or chloroform and almost insoluble in water. It has a m.p. of 90°. A dilute solution in hydrochloric acid gives a precipitate with iodine solution but not with mercuric potassium iodide solution. Benzocaine is relatively insoluble and slowly absorbed, and is used therefore in dusting powders and ointments.

Butyl 4-aminobenzoate. $C_{11}H_{15}O_2N$. (IX).



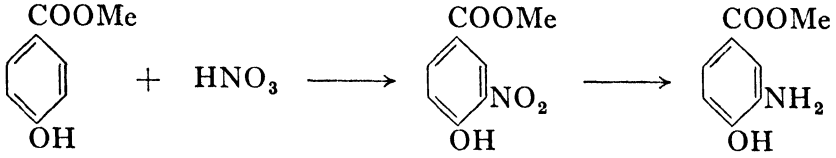
IX

This is the butyl ester corresponding to benzocaine and may be prepared by similar methods.

Properties. Butyl 4-aminobenzoate is soluble in alcohol, ether or chloroform and almost insoluble in water. It has a m.p. of 57° to 59°. On adding a solution of iodine to butyl 4-aminobenzoate in hydrochloric acid, a dark brown precipitate is formed, and slowly crystallises to give large brown prisms. The picrate (m.p. 109° to 110°) is also used as a local anaesthetic.

Orthocaine. Methyl 3-amino-4-hydroxybenzoate. $C_8H_9O_3N$. (X).

Preparation. Orthocaine is prepared by the reduction of the corresponding nitro compound, or by the reduction of 3-nitro-4-hydroxybenzoic acid and esterification of the product with methanol. Methyl 3-nitro-4-hydroxybenzoate is formed by nitration of methyl 4-hydroxybenzoate with dilute nitric acid.

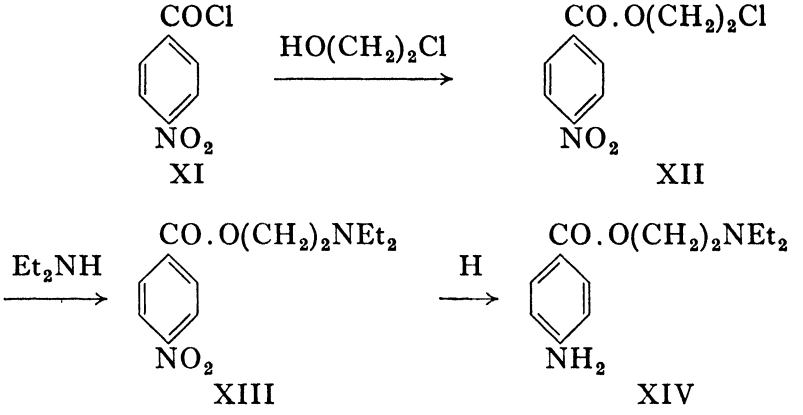


X

Properties. Orthocaine is slightly soluble in water and more soluble in ethanol. It has a m.p. of 141° to 143°. A solution in dilute hydrochloric acid gives no precipitate with a solution of iodine nor with a solution of mercuric potassium iodide, and it is thus distinguished from local anaesthetics of the procaine type, and from benzocaine.

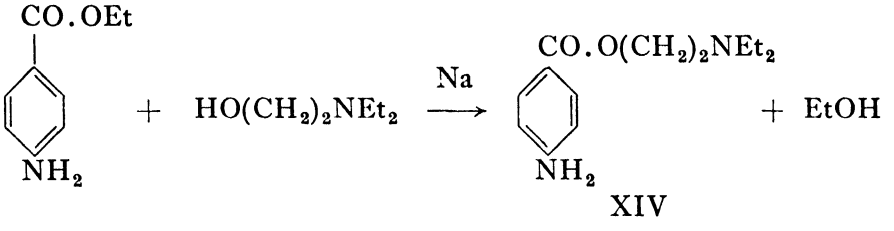
Procaine. 2-Diethylaminoethyl 4-aminobenzoate. $C_{13}H_{20}O_2N_2$. (XIV).

Preparation. Einhorn described the preparation of procaine in 1909 (7). It has been prepared (8) by the following method:



4-Nitrobenzoyl chloride (XI) is reacted with ethylene chlorhydrin and the resulting 2-chloroethyl ester (XII) reacted with diethylamine to give 2-diethylaminoethyl 4-nitrobenzoate (XIII). This, on reduction, yields procaine (XIV).

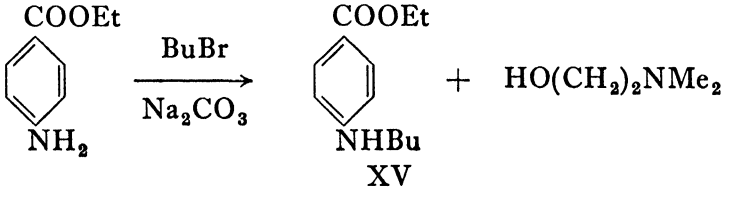
An alternative method using the ester-exchange reaction between benzocaine and diethylaminoethanol has been described (9) and follows the reaction scheme shown:

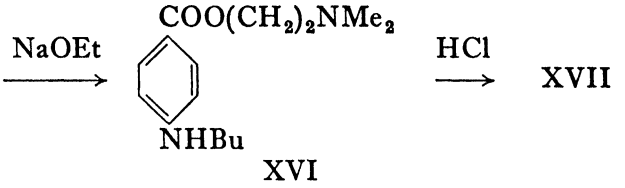


Properties. Procaine is chiefly used as the hydrochloride which has a m.p. of 154° to 156°. The base is precipitated by adding sodium hydroxide or sodium carbonate to a solution of the hydrochloride and when anhydrous it has a m.p. of 60° to 61°. A solution of the hydrochloride immediately decolorises potassium permanganate solution, and this test distinguishes procaine from cocaine. When diazotised and coupled with 2-naphthol, a scarlet azo compound is formed. Precipitates are formed on addition of either a solution of iodine or of mercuric potassium iodide to procaine hydrochloride.

Amethocaine hydrochloride. Tetracaine hydrochloride. 2-Dimethylaminoethyl 4-butylaminobenzoate hydrochloride. $C_{15}H_{24}O_2N_2.HCl$. (XVII).

Preparation. Einhorn's method (9) is as follows:



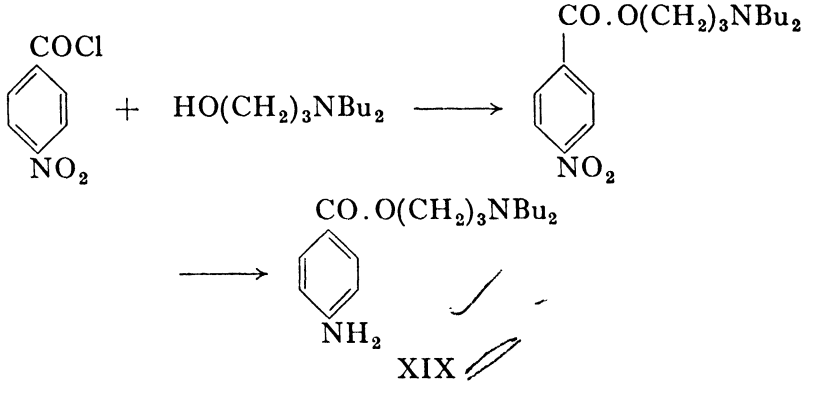


Benzocaine is alkylated by means of *n*-butyl bromide in the presence of sodium carbonate and a little copper powder, and the resulting 4-butylamino compound (XV) is then reacted with dimethylaminoethanol in the presence of sodium ethoxide to yield amethocaine (XVI) which is converted to the hydrochloride (XVII).

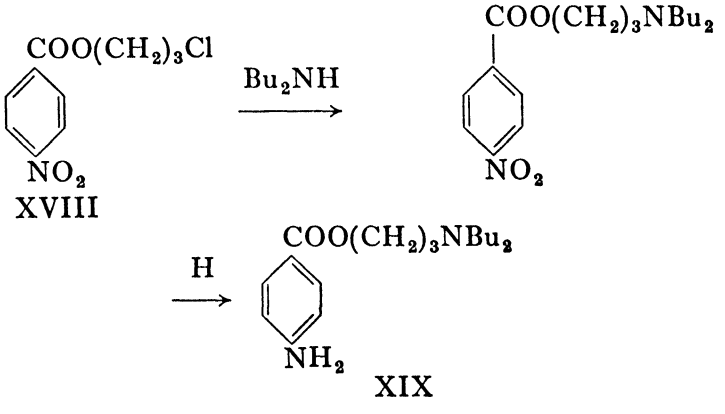
Properties. Amethocaine has a m.p. of 42° to 45°. The hydrochloride has a m.p. of 130° to 132°. When diazotised and coupled with 2-naphthol a white precipitate is formed. Solutions of the hydrochloride undergo decomposition when heated (10).

Butacaine. 3-Dibutylaminopropyl 4-aminobenzoate. $C_{18}H_{30}N_2O_2$. (XIX).

Preparation. It has been claimed (11) that butacaine may be prepared by the reaction of 4-nitrobenzoyl chloride with 3-dibutylaminopropanol and reduction of the nitro ester to the required amino ester. This reaction sequence is as follows:



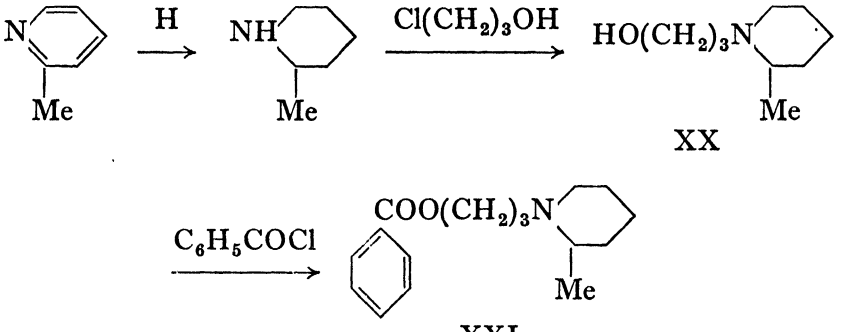
In a second method (12) the 3-chloro ester (XVIII) is made and reacted with dibutylamine to produce the 4-nitro compound corresponding to butacaine and on reduction the 4-amino compound is obtained.



Properties. Butacaine is an oil at ordinary temperatures. It is usually employed as the sulphate $B_2.H_2SO_4$ which has a m.p. of 100° to 103°. The hydrochloride melts at 104° to 105°. Solutions of butacaine salts give a white precipitate with potassium mercuric iodide and a red compound when diazotised and coupled with 2-naphthol.

Piperocaine. 3-(1-Methylpiperidyl)propyl benzoate. $C_{16}H_{23}O_2N$. (XXI).

Preparation. Piperocaine is made (13) by reacting together 2-methylpiperidine and 3-chloropropanol to give 3(1-methylpiperidyl)propanol (XX) which is then benzoylated with benzoyl chloride to produce piperocaine (XXI). 2-Methylpiperidine may be obtained by catalytic reduction of 2-methylpyridine.



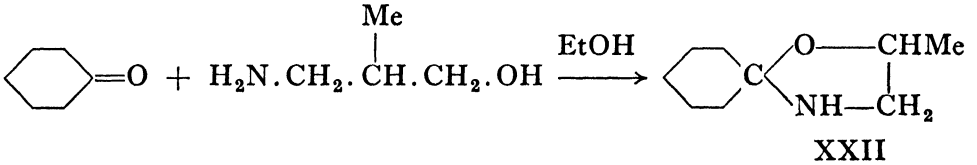
XX

XXI

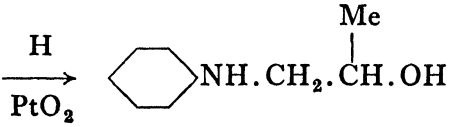
Properties. Piperocaine is used chiefly in the form of the hydrochloride which has a m.p. of 172° to 175°. In aqueous solution it gives precipitates with either iodide, mercuric potassium iodide, picric acid or gold chloride solutions. On addition of alkali to an aqueous solution of the hydrochloride the base separates as an oil.

Hexylcaine hydrochloride. 1-*cyclo*Hexylamino-2-propyl benzoate hydrochloride. $C_{16}H_{23}O_2N.HCl$. (XXIV).

Preparation. The 1-*cyclo*hexylamino-propan-2-ol (XXII) required for the synthesis of hexylcaine has been made (14) by the following method:

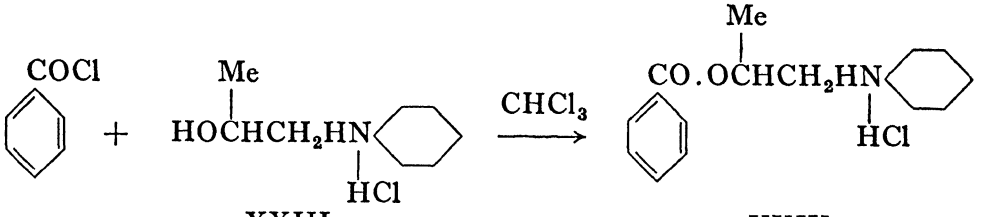


XXII



XXIII

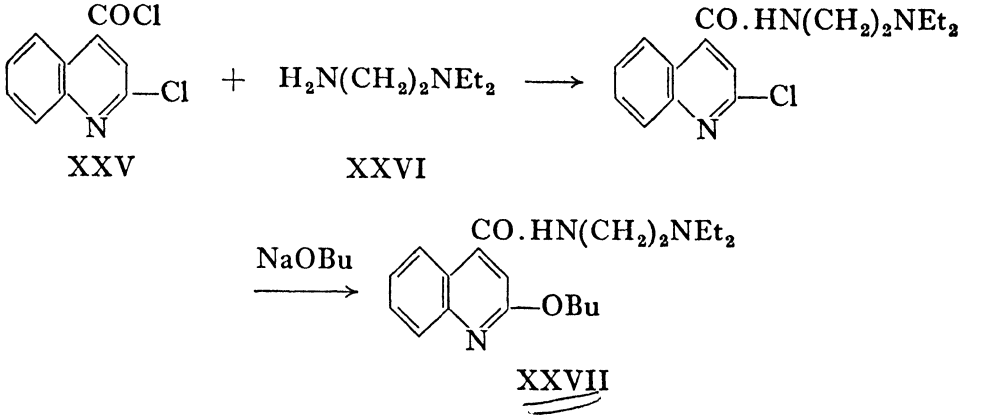
*cyclo*Hexanone and 3-amino-2-methylbutan-1-ol are mixed in absolute ethanol and the oxazolidine (XXII) formed is reduced with hydrogen in the presence of Adam's catalyst to give the required amino-alcohol (XXIII). This amino-alcohol is then converted in chloroform solution to its hydrochloride and benzoyl chloride in chloroform is added and the mixture warmed (15). Hexylcaine hydrochloride (XXIV) is so obtained and can be converted to hexylcaine:



XXIII XXIV

Cinchocaine. Dibucaine. 2-Diethylaminoethylamide of 2-butyloxycinchoninic acid. $C_{20}H_{29}O_2N_3$. (XXVII).

Preparation. 2-Chlorocinchoninic acid chloride (XXV) is condensed with *asym.*-N-diethylethylenediamine (XXVI) and the product is treated (16) with sodium butoxide to yield cinchocaine (XXVII).



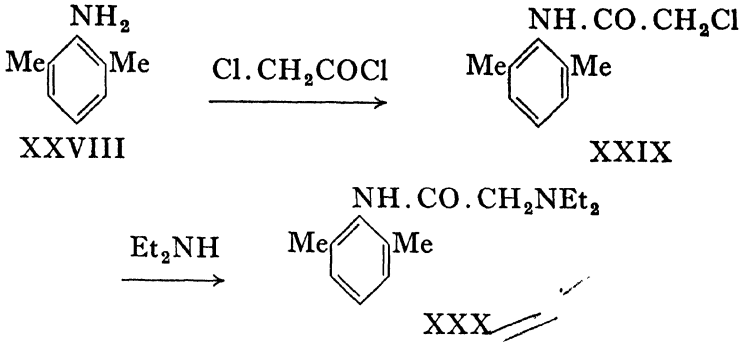
XXV XXVI XXVII

Properties. Cinchocaine is a little unusual since, instead of being an amino ester like the other local anaesthetics described above, it is an amide of an aromatic acid with an aliphatic amine. It is used as the hydrochloride B.HCl, which occurs as colourless hygroscopic crystals which are very soluble in water. Cinchocaine base melts at 64° and the hydrochloride at 95° to 100°. The perchlorate has a m.p. of 132°.

Lignocaine. Lidocaine. Diethylamino-2 : 6-xylidide. $C_{14}H_{22}ON_2$. (XXX).

Preparation. This compound was introduced as a result of the work of Löfgren (17). It is prepared in the following manner (18). 2 : 6-Xylidine (XXVIII) is dissolved in cooled glacial acetic acid and chloroacetyl chloride is added with vigorous stirring. Sodium acetate or some other neutralising agent is added and the product (XXIX) is filtered and dried. It is then reacted with

diethylamine in benzene solution and the lignocaine (XXX) formed is isolated and purified by distillation *in vacuo*.



XXVIII XXIX XXX

In an alternative procedure (19), diethylaminoacetyl chloride (XXXI) prepared from the corresponding acid is condensed with 2 : 6-xylidine:

$$SOCl_2 + Et_2N.CH_2COOH \longrightarrow Et_2N.CH_2.COCl$$

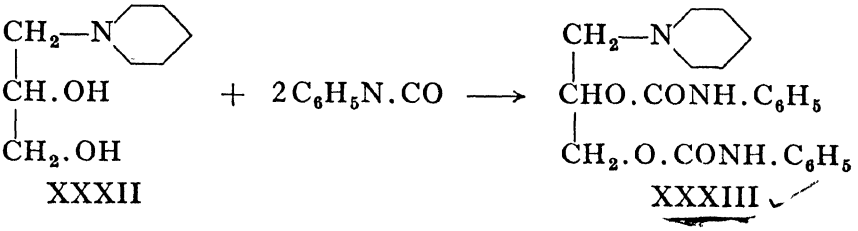
XXXI

Properties. Lignocaine base is a white crystalline solid of m.p. 67° to 68° and b.p. 183°/4 mm. Its hydrochloride has a m.p. of 128° to 129° and its monohydrate melts at 77° to 78° (20). The picrate melts at 231° to 232°.

Like cinchocaine, lignocaine is also an amide, but in a reverse sense, for it is an amide of an aliphatic acid and an aromatic amine.

Diperodon. 3-Piperidylpropanediol diphenylurethane. $C_{22}H_{27}O_4N_3$. (XXXIII).

Preparation. 3-Piperidylpropan-1 : 2-diol (XXXII) is reacted with phenyl *iso*cyanate in an inert solvent to yield diperodon (XXXIII).



XXXII XXXIII

Properties. Diperodon is used as the hydrochloride B.HCl which has a m.p. of 195° to 200°. The base is an oil at ordinary temperatures.

GENERAL ANAESTHETICS

Ether. Diethyl ether. $C_4H_{10}O$.

Preparation. Ethyl alcohol vapour is passed into a heated mixture of sulphuric and ethylsulphuric acids:

$$C_2H_5OH + H_2SO_4 \longrightarrow C_2H_5.HSO_4 + H_2O,$$

$$C_2H_5.HSO_4 + C_2H_5OH \longrightarrow C_2H_5.O.C_2H_5 + H_2SO_4$$

A mixture of 30 parts by weight of sulphuric acid with 20 parts of 85 per cent ethyl alcohol is heated to 120° in a copper still. Ethyl alcohol vapour from a second vessel is then blown in, and the temperature of the reaction is carefully regulated at 128°. The vapour from the reaction consists of a mixture of diethyl ether, ethanol and water. It is passed into a scrubber containing a solution of caustic soda, and then through a fractionating column where ethanol and water are condensed and the ether vapour passes to a condenser and cooler and is collected.

Ether is also obtained as a by-product in the hydration of ethylene to ethanol.

Ether that is to be used for anaesthetic purposes needs to be rigorously purified by careful fractionation. The chief impurities are water, ethanol, aldehydes, ketones, vinyl alcohol and ethyl peroxide.

Properties. Diethyl ether is a very volatile colourless liquid with a characteristic odour. It boils at 34·9° and has a wt. per ml of 0·7135 g at 20°. Ether is a valuable solvent for organic compounds. It is soluble in water and 1 part of ether dissolves in 10 of water; conversely 3 parts of water dissolve in 100 of ether. Diethyl ether is miscible with chloroform or ethanol and concentrated hydrochloric or sulphuric acids. On standing, especially when exposed to light, ether forms peroxides. These compounds are highly explosive and dangerous accidents have occurred when ether which has been stored for too long has been distilled. Therefore, ether is stored in amber bottles and a small quantity of stabiliser such as diphenylamine is added. The B.P. allows the addition of not more than 0·002 per cent w/v of the stabiliser.

Ether has the advantage in anaesthesia that it induces muscular relaxation as well as causing unconsciousness.

Vinyl ether. Divinyl ether. C_4H_6O.

Preparation. 2 : 2′-Dichlorodiethyl ether is reacted with caustic potash and the product is purified.

$$ClCH_2.CH_2.O.CH_2.CH_2.Cl + 2KOH \longrightarrow CH_2{=}CH.O.CH{=}CH_2 + 2KCl + 2H_2O$$

Properties. Divinyl ether was first prepared in 1887 and its anaesthetic properties were discovered in 1930. It was introduced into clinical anaesthesia in 1933. It has a b.p. of 28° to 31° and a wt. per ml at 20° of 0·770 to 0·778 g. Divinyl ether is a volatile, colourless, inflammable liquid with a characteristic odour. It is miscible with ethanol, diethyl ether and with chloroform. For use as an anaesthetic it contains about 4 per cent of anhydrous ethanol and 0·01 per cent of phenylnaphthylamine to prevent oxidation. It is stored in amber bottles. When warmed with dilute sulphuric acid, divinyl ether yields acetaldehyde.

Methyl propyl ether. $C_4H_{10}O$.

Preparation. Williamson's ether synthesis may be used. Propanol is reacted with sodium to give sodium propoxide which is then reacted with methyl iodide. Methyl propyl ether and sodium iodide are obtained.

$$CH_3.CH_2.CH_2.ONa + CH_3I \longrightarrow NaI + CH_3.OCH_2.CH_2.CH_3$$

Properties. Methyl propyl ether is a colourless inflammable volatile liquid with a b.p. of 39° and wt. per ml at 16° of 0·726 g. 100 ml of water dissolves 5 ml of the ether. It was introduced as a general anaesthetic in 1946.

Cyclopropane. Trimethylene. C_3H_6.

Preparation. 1 : 3-Dibromopropane may be treated with zinc dust in 75 per cent ethanol at 50° to 60°.

*Properties. cyclo*Propane is a colourless inflammable gas which at normal temperatures has a b.p. at 760 mm. of −34·5°. Therefore it is supplied under pressure in cylinders. One volume is soluble in 2·7 volumes of water at 15°. It is very soluble in alcohol, ether and chloroform, and is absorbed by sulphuric acid.

Chloroform. Trichloromethane. $CHCl_3$.

Preparation. For the production of chloroform for anaesthetic purposes the reaction between ethanol and bleaching powder may be used. It is a complex reaction in which the ethanol is oxidised to acetaldehyde which is then converted to chloral and hydrolysed. Acetone is commonly used in place of ethanol.

$$C_2H_5OH \xrightarrow{} CH_3CHO \xrightarrow{Cl_2} CCl_3CHO \xrightarrow{H_2O} CHCl_3 + H.COOH$$

Properties. Chloroform is a colourless, heavy, volatile liquid with a characteristic odour and a sweet burning taste. When pure, it has a b.p. of 61·2° and a wt. per ml at 20° of 1·489 g. It is liable to decompose on exposure to air and light and the poisonous phosgene $COCl_2$ is formed. Therefore Chloroform B.P. contains 2 per cent v/v ethanol and has a wt. per ml of 1·474 to 1·479 g and boils chiefly at 60° to 62°. When warmed with aniline and alcoholic potassium hydroxide, chloroform gives the powerful and objectionable odour of phenyl *iso*cyanide. This test which is called the carbylamine reaction is given by many compounds with compositions similar to that of chloroform.

Chloroform is a toxic substance and greatly weakens the heart; because of its disadvantages it is seldom used.

Nitrous oxide. N_2O.

Preparation. Ammonium nitrate is decomposed by heat to give water and nitrous oxide.

$$NH_4NO_3 \xrightarrow{} N_2O + 2H_2O$$

The decomposition begins at a temperature below 200° and the reaction is exothermic. If heated above 250°, the salt may explode. The gas is purified from nitric oxide by passage through a solution of potassium permanganate and from chlorine with caustic soda. It is liquefied by compression and stored in steel cylinders.

Properties. Nitrous oxide is a colourless gas with faint sweetish odour and taste. 1 volume of water at 20° dissolves 0·67 volume of nitrous oxide and 1 volume of ethyl alcohol dissolves 3·025 volumes of nitrous oxide. The b.p. of liquid N_2O is −88·7°. It supports combustion more vigorously than air.

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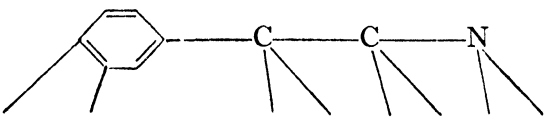
CHAPTER V

Sympathomimetics and Adrenergic Blocking Agents

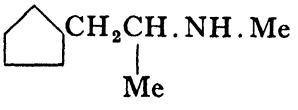
SYMPATHOMIMETICS

THE sympathomimetics are drugs which induce bodily responses similar to those following stimulation of the sympathetic nervous system. They are thus autonomic drugs. The substances adrenaline (I), noradrenaline (II), and ephedrine (IX) are natural products and are treated in Part II. Noradrenaline is now known to be the chemical mediator of sympathetic impulses, as acetylcholine is of parasympathetic impulses. Isoprenaline (III) or a very similar compound has also been detected in the body (1).

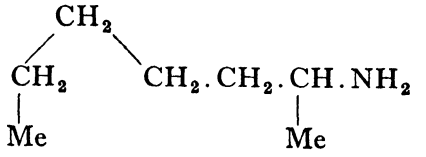
The aromatic sympathomimetics are derivatives of phenylethylamine and may be classified into those with two, one and no benzenoid hydroxyl groups. The last class includes compounds such as amphetamine, which are central stimulants.



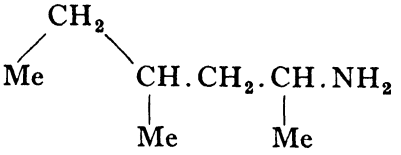
I.	Adrenaline	OH	OH		H	OH	H	H	H	Me
II.	Noradrenaline	OH	OH		H	OH	H	H	H	H
III.	Isoprenaline	OH	OH		H	OH	H	H	H	$CHMe_2$
IV.	Deoxyadrenaline	OH	OH		H	H	H	H	H	Me
V.	Tyramine	H	H		H	H	H	H	H	H
VI.	Phenylephrine	H	OH		H	OH	H	H	H	Me
VII.	Hydroxyamphetamine	OH	H		H	H	H	Me	H	H
VIII.	Pholedrine	OH	H		H	H	H	Me	H	Me
IX.	Ephedrine	H	H		H	OH	H	Me	H	Me
X.	Phenylpropanolamine	H	H		H	OH	H	Me	H	H
XI.	Methoxamine	H	OMe	2—OMe	H	OH	H	Me	H	H
XII.	Amphetamine	H	H		H	H	H	Me	H	H
XIII.	Methamphetamine	H	H		H	H	H	Me	H	Me
XIV.	Phenylpropyl-methylamine	H	H		H	Me	H	H	H	Me
XV.	Methoxyphenamine	H	H	2—OMe	H	H	H	Me	H	Me



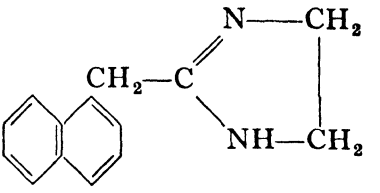
XVI. Cyclopentamine



XVII. Tuaminoheptane



XVIII. Methylhexaneamine



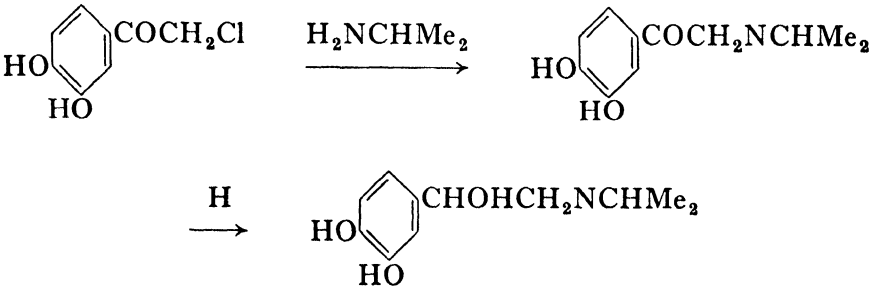
XIX. Naphazoline

There are also aliphatic amines which have sympathomimetic action. In general, these drugs relax the tone of smooth muscle, constrict peripheral blood vessels and stimulate the heart.

The methods of preparation are fairly simple and generally follow the same pattern. The table shows the relationship between the chemical structures of the compounds described in this chapter.

Isoprenaline. Isoproterenol. Isopropylarterenol. 1 - (3 : 4 - Dihydroxyphenyl)-2-isopropylaminoethanol. $C_{11}H_{17}NO_3$. (III).

Preparation. Catechol is converted to 4-chloroacetylcatechol by reaction with chloroacetyl chloride in boiling benzene in the presence of phosphorus oxychloride (2). The 4-chloroacetylcatechol is condensed with isopropylamine and the compound is reduced to isoprenaline (3). An alternative route via 3 : 4-diacetoxyacetophenone has been described (4).



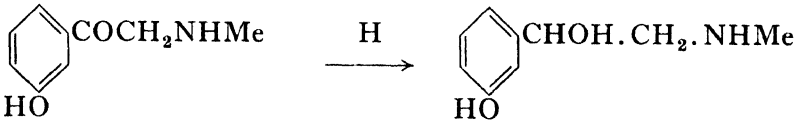
III

Properties. Isoprenaline hydrochloride is a white crystalline solid with a m.p. of 170° to 172°. It is soluble in water and in ethanol, and slightly soluble in benzene or ether. An aqueous solution becomes pink on standing. The sulphate has a m.p. of about 128° (dec.); it is hygroscopic, whereas the hydrochloride is not.

This drug was introduced in 1940. Its salts when administered sublingually or by oral inhalation are effective in the treatment of asthma, for they are effective bronchodilators and cause little rise in blood pressure.

Phenylephrine. (−)-1-(3-Hydroxyphenyl)-2-methylaminoethanol. $C_9H_{13}NO_2$. (VI).

Preparation. 3-Hydroxymethylaminoacetophenone hydrochloride which may be obtained by a six-stage synthesis from acetophenone (5) is reduced with hydrogen in the presence of palladium to (±)-phenylephrine (6).



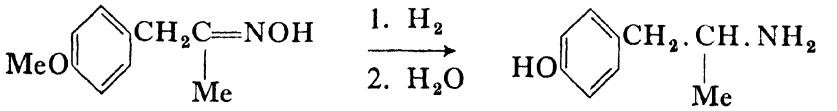
VI

The racemate may be resolved by means of (+)-tartaric acid (5) or with bromocamphorsulphonic acid (7). It is of interest that the (+)-base bitartrate obtained by the former method is converted to the required (−)-compound by refluxing with acetic anhydride. A Walden inversion occurs and the (−)-acetate so obtained can be converted to the hydrochloride.

Properties. Phenylephrine hydrochloride is a white crystalline powder which gives an acid solution in water. It has a m.p. of 141° to 144°, and gives a purple colour with ferric chloride solution. This drug is active on injection or when administered orally. It is a vasopressor that has no effect upon the central nervous system, and it is one of the safest drugs for use during spinal anaesthesia. It has also been employed for symptomatic relief of hay-fever.

Hydroxyamphetamine. 2-(4-Hydroxyphenyl)*iso*propylamine. $C_9H_{13}NO$. (VII).

Preparation. 4-Methoxybenzylmethyl ketoxime is reduced and the methoxy group hydrolysed (8).



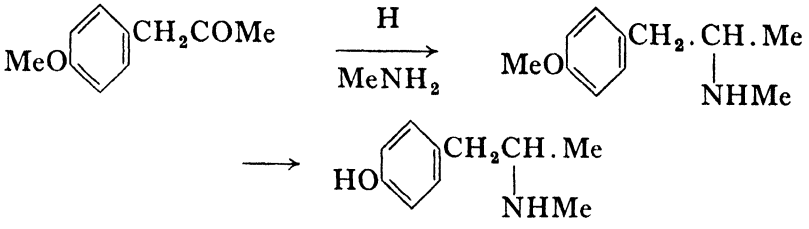
VII

Properties. Hydroxyamphetamine base melts at 127° to 129°. The drug is employed in the form of its hydrobromide which is a white crystalline solid melting at 189° to 192°. It gives a purple colour with ferric chloride solution. Hydroxyamphetamine has no central stimulatory action and is used for its peripheral effect as a mydriatic.

Pholedrine. 2-(4-Hydroxyphenyl)-N-methylisopropylamine. $C_{10}H_{15}NO$. (VIII).

Preparation. Anisylacetone is reductively aminated by methylamine in the

presence of activated aluminium and the methoxy group is then hydrolysed to give pholedrine (9).



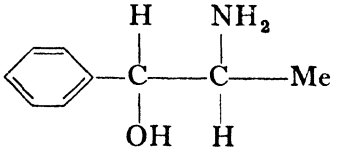
VIII

Anisylacetone is obtained in a five-step synthesis from anisole (10).

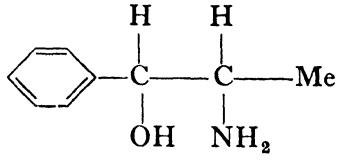
Properties. Pholedrine base melts at 162° to 163° and its picrate at about 155°. The sulphate which is used therapeutically has a m.p. of 320° to 323°. It has been employed as a circulation stimulant following surgical shock, and in the treatment of central depression.

Phenylpropanolamine. (±)-Norephedrine. (±)-2-Amino-1-phenylpropanol. $C_9H_{12}NO$. (X).

Preparation. 2-Amino-1-phenylpropanol has two asymmetric carbon atoms and therefore exists in two racemic forms. These correspond to the threo and erythro forms of chloramphenicol. Nor*pseudo*ephedrine (IX) is the threo and norephedrine is the erythro compound.

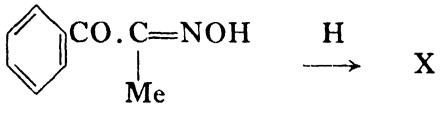


Threo form
(±)-Nor*pseudo*ephedrine
IX



Erythro form
(±)-Norephedrine
X

Phenylpropanolamine alone is obtained when *iso*nitrosopropiophenone is reduced either with palladium on charcoal and hydrogen (11, 12) or with nickel-aluminium alloy and caustic soda (13).



Other methods of preparation (14, 15) lead to a mixture of the two racemates which may be separated by fractional crystallisation of their hydrochlorides (16).

Properties. Phenylpropanolamine has a m.p. of 104° to 105° and the hydrochloride a m.p. of 194°. The latter compound is soluble in alcohol or water and is insoluble in benzene, chloroform or ether. It gives a yellow colour with ferric

chloride solution. Phenylpropanolamine benzoate melts at 143°. The hydrochloride is used as a vasoconstrictor. It is applied locally and by producing constriction of the capillaries leads to shrinking of the swollen mucous membranes.

Methoxamine. 2 : 5-Dimethoxynorephedrine. 2-Hydroxy-2-(2 : 5-dimethoxyphenyl)*iso*propylamine. $C_{11}H_{17}NO_3$. (XI, see table, p. 66).

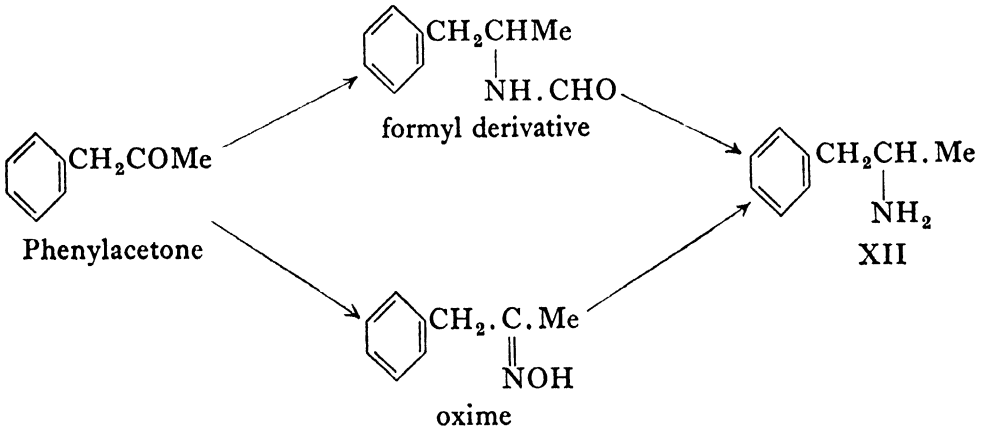
Preparation. The method of preparation is similar to that described for phenylpropanolamine. 2 : 5-Dimethoxy*iso*nitrosopropiophenone is reduced to methoxamine (17, 18).

Properties. Methoxamine diacetate melts at 119° to 120° and the hydrochloride at 215°. The latter compound is a white crystalline powder that is freely soluble in water and slightly soluble in ether and ethyl acetate. It is a vasopressor, i.e. it causes peripheral vasoconstriction, and it has been used to maintain blood pressure during surgery. It has no cerebral-stimulating action.

Amphetamine. (±)-2-Amino-1-phenylpropane. $C_9H_{13}N$. (XII).

Preparation. Amphetamine was first made in 1887 by Edeleanu (19) by a Hofmann degradation of the corresponding amide. Modern syntheses start with benzyl methyl ketone (phenylacetone), which has been prepared in a variety of ways (20, 21, 22). It may be reductively aminated to amphetamine by means of hydrogen in the presence of ammonia and a catalyst (23) or with ammonium formate (22, 24). In the latter case the formyl derivative is obtained as an intermediate and on hydrolysis yields amphetamine.

Alternatively phenylacetone is converted to its hydrazide (21) or oxime (11, 25) and reduced to amphetamine.



Properties. Amphetamine is a liquid of b.p. 209° to 210°. It readily adsorbs carbon dioxide from the air. The hydrochloride melts at 146° and the picrate at 128°. The phosphate, $C_9H_{13}N.H_3PO_4$, is sometimes used in medicine, but the sulphate, $(C_9H_{13}N)_2.H_2SO_4$, is more commonly employed. It is a white powder of m.p. 315° (dec.) and is freely soluble in water and slightly soluble in ethanol.

Amphetamine has a stimulating effect upon the central nervous system.

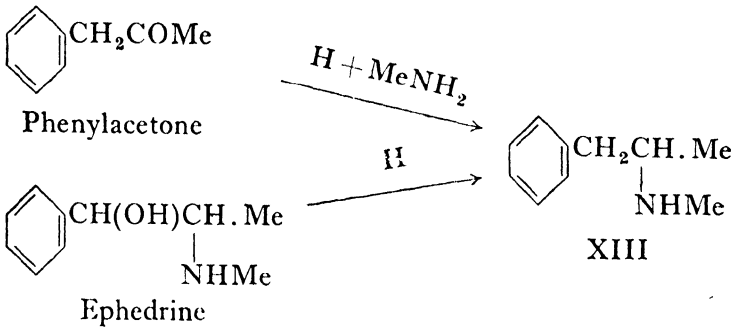
Dexamphetamine. (+)-2-Amino-1-phenylpropane. $C_9H_{13}N$. (XII).

Preparation. Amphetamine may be resolved with (+)-tartaric acid (24, 26). The sulphate has a specific rotation of +21·8°.

Properties. Dexamphetamine is unusual in being a (+)-isomer which is more active pharmacologically than the corresponding (−)-isomer. The reverse is usually the case.

Methamphetamine. (+)-Deoxyephedrine. (+)-2-Methylamino-1-phenylpropane. $C_{10}H_{15}N$. (XIII).

Preparation. The method is similar to that used for the preparation of amphetamine. Phenylacetone is reduced in the presence of methylamine to give the (±)-compound (27). This is resolved through the tartrate (28, 29). Since methamphetamine is deoxyephedrine, it may also be obtained (30, 31) by reduction of ephedrine.

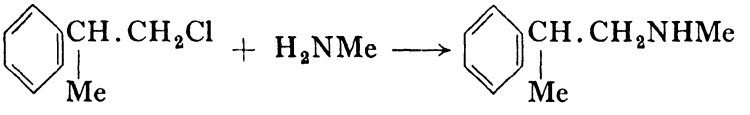


Properties. Methamphetamine has a b.p. of 212° to 215°. The hydrochloride melts at 182°, the picrate at 144° to 145° and the aurochloride at 127° to 128°.

The hydrochloride which has a specific rotation of +16° to +18°, has the ability to stimulate the central nervous system and is therefore used to combat depressive conditions. It is a vasopressor.

Phenylpropylmethylamine. (±)-1-Methylamino-2-phenylpropane. $C_{10}H_{15}N$. (XIV).

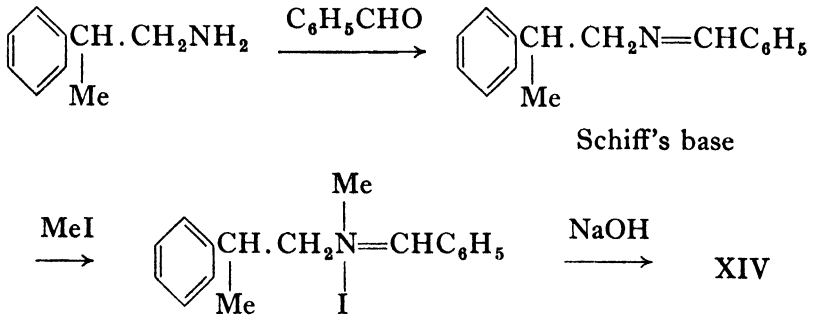
Preparation. 2-Phenylpropyl chloride is condensed with methylamine in methanol at 130° under pressure (32).



XIV

The 2-phenylpropyl chloride has been made by a reaction between allyl chloride and benzene (33) and indeed it has been claimed that benzene and N-methylallylamine may be reacted together in the presence of aluminium chloride to give phenylpropylmethylamine directly (34).

An alternative procedure (35) is that in which 2-phenylpropylamine is converted to its Schiff's base, methylated, hydrolysed and basified to give phenylpropylmethylamine.



Properties. Phenylpropylmethylamine is a liquid of b.p. 205° to 210° which is soluble in ethanol, benzene or ether and slightly soluble in water. An aqueous solution is alkaline. The hydrochloride melts at 148° to 149° and the picrate at 155°. The base is used by inhalation to produce nasal constriction. It has little effect upon the central nervous system.

Methoxyphenamine. 1-(2-Methoxyphenyl)-2-methylaminopropane.

$C_{11}H_{17}NO$. (XV, see table, p. 66).

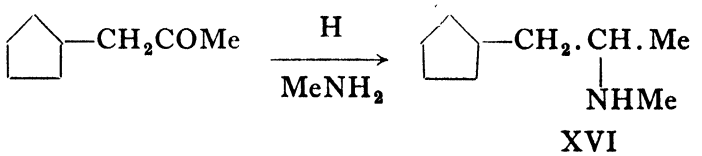
Preparation. The method is analogous to that employed for the preparation of phenylpropylmethylamine (35). 2-(2-Methoxyphenyl)*iso*propylamine is reacted with benzaldehyde to give the Schiff's base which is methylated and hydrolysed.

Alternative methods have been published (46, 47).

Properties. Methoxyphenamine boils at 100° to 102° and its hydrochloride has a m.p. of 137° to 138°. The latter substance is freely soluble in ethanol, chloroform or water and is slightly soluble in ether or benzene. It is a bronchodilator and has been found beneficial in cases of asthma.

Cyclopentamine. 1-*cyclo*Pentyl-2-methylaminopropane. $C_9H_{19}N$. (XVI).

*Preparation. cyclo*Pentylacetone is reductively aminated (40). It is reduced by means of hydrogen and Raney nickel at 150° and 200 atmospheres in the presence of methylamine.



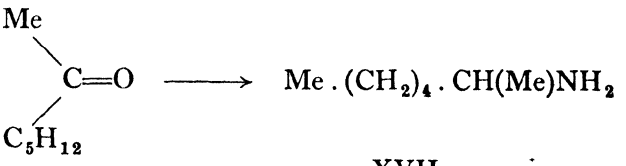
XVI

Alternatively the reaction between 1-*cyclo*pentyl-2-bromopropane and methylamine may be employed.

Properties. The free base is a liquid of b.p. 169° to 173°. Its hydrochloride which melts at 113° to 116° is soluble in water, ethanol or chloroform and is slightly soluble in benzene or ether. It has little effect upon the central nervous system and is a vasopressor that is used as a nasal decongestant.

Tuaminoheptane. (±)-2-Heptylamine. 1-Methylhexylamine. $C_7H_{17}N$. (XVII).

Preparation. Racemic tuaminoheptane is prepared by the reductive amination of heptan-2-one.



XVII

The reaction may be carried out by means of hydrogen in the presence of Raney nickel and ammonia or with ammonium formate (36). In the latter case a formylamino compound $R_1R_2NH.CHO$ is obtained, and on hydrolysis with mineral acid yields the hydrochloride of the amine.

In an alternative approach, the oxime of heptan-2-one is first prepared and is reduced either chemically (36, 37) or electrolytically (38) to tuaminoheptane.

Properties. Tuaminoheptane is a liquid of b.p. 142° to 143°. The hydrochloride melts at 133°. The sulphate which is a monohydrate has no definite melting-point but softens above 250°. Tuaminoheptane has a powerful vasoconstrictor action and it is employed as a nasal decongestant.

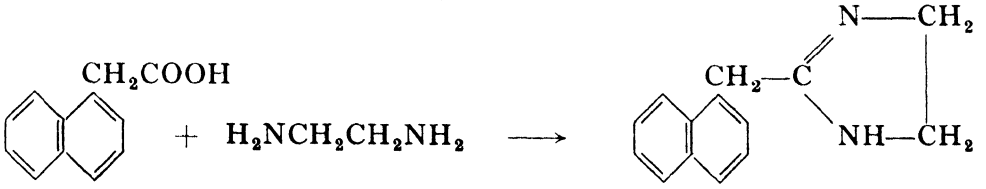
Methylhexaneamine. (±)-4-Methyl-2-hexylamine. $C_7H_{17}N$. (XVIII, see p. 67).

Preparation. The methods used are analogous to those described above for tuaminoheptane (39).

Properties. Methylhexaneamine is a liquid of b.p. 130° to 135°. It is readily soluble in ethanol, chloroform, ether and dilute mineral acids, and is slightly soluble in water. It is used as an inhalant for decongestion of nasal mucous membranes.

Naphazoline. 2-(1-Naphthylmethyl)-2-imidazoline. $C_{14}H_{14}N_2$. (XIX).

Preparation. Naphazoline is prepared by a reaction between naphthyl-1-acetic acid and ethylenediamine (41).



XIX

The corresponding nitrile (42, 43), acid chloride (44) or thioamide (45) may also be used.

Properties. Naphazoline has a m.p. of 120° and the hydrochloride a m.p. of 258° to 259°. The latter is a white crystalline powder which is soluble in ethanol or water, slightly soluble in chloroform and insoluble in ether. It is a potent vasoconstrictor which is used for its local effects in hay-fever and coryza.

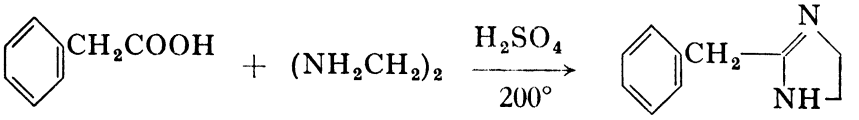
ADRENERGIC BLOCKING AGENTS

The effects caused by adrenaline in the body may be antagonised or prevented in several ways. When the effects of circulating adrenaline are neutralised, the drug used is called an adrenolytic whilst if it prevents the normal response of tissue receptors to the impulses from the sympathetic nervous system it is called a sympatholytic. If the sympathetic nervous system is blocked, then the compound is a ganglionic blocking agent. By a different mechanism parasympathomimetics are antagonists of adrenaline, for they simulate the effects caused by the parasympathetic nervous system.

Ganglionic blocking agents which are linked chemically and historically to the muscle relaxants are treated together with those compounds in Chapter VII. Some alkaloids have an adrenergic blocking action amongst which are certain ergot alkaloids and yohimbine. These are treated in Part II.

Tolazoline. 2-Benzyliminazoline. 2-Benzyldihydroglyoxaline. $C_{10}H_{12}N_2$. (XX).

Preparation. The general methods for the preparation of 2-iminazolines such as naphthazoline (q.v.) apply to tolazoline. It may be obtained from the reaction between phenylacetic acid and ethylenediamine in the presence of concentrated sulphuric acid at 200° (48).



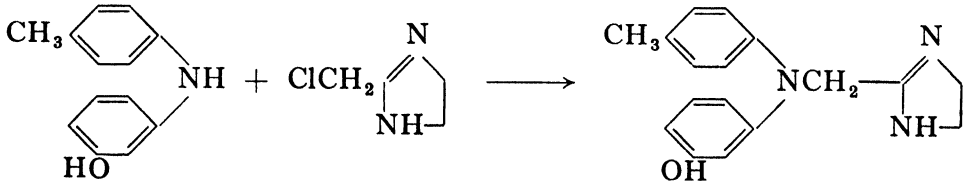
XX

Benzyl cyanide may also be used as a starting material (42, 49).

Properties. Tolazoline has a b.p. of 125° at 2 mm. and a m.p. of 66° to 68°. The picrate melts at 148·5° and the toluene-*p*-sulphonate at 91°. The hydrochloride which melts at 172° to 176° is a white powder that is soluble in water, ethanol and chloroform. It is used as a vasodilator, mainly in peripheral vascular disorders, and is active orally.

Phentolamine. 2 - N - (3 - Hydroxyphenyl) - *p* - toluidinomethyliminazoline. $C_{17}H_{20}N_3O$. (XXI).

Preparation. The general 2-iminazoline method (50) employing the substituted diphenylaminoacetonitrile and ethylenediamine may be used or, alternatively, N-(3-hydroxyphenyl)-*p*-toluidine can be condensed with 2-chloromethyliminazoline.

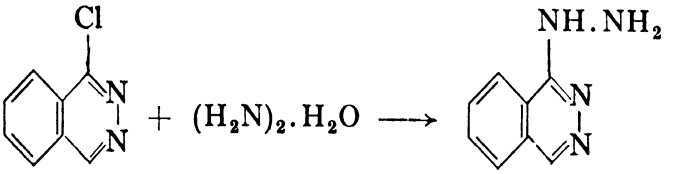


XXI

Properties. The base melts at 174° to 175° and its hydrochloride at 239° to 240°. The latter compound which is a white powder is soluble in water to give an unstable solution. It is slightly soluble in ethanol and chloroform. It is a vasodepressor and has been found to be beneficial in the treatment of peripheral vascular disorders. It is active orally. Phentolamine salts are used for the diagnosis of pheochromocytoma.

Hydrallazine. 1-Hydrazinophthalazine. $C_8H_8N_4$. (XXII).

Preparation. 1-Chlorophthalazine and hydrazine hydrate are condensed together in boiling ethanol (51).

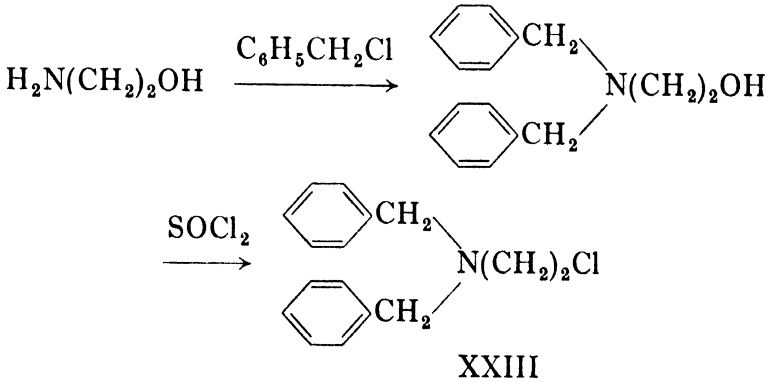


XXII

Properties. Hydrallazine is a yellow powder of m.p. 172° to 173°. Its hydrochloride which is white and has a m.p. of 273° (dec.) is soluble in water and slightly soluble in ethanol. It is a vasopressor and has been employed for the control of essential hypertension.

Dibenzylaminoethyl chloride. $C_{16}H_{17}N$. (XXIII).

Preparation. Benzyl chloride is condensed with aminoethanol and the 2-dibenzylaminoethanol hydrochloride obtained is neutralised and distilled *in vacuo*. The product is reacted with thionyl chloride to give dibenzylaminoethyl chloride (52, 53).



XXIII

Properties. The base has a b.p. of 182° to 184° at 5 mm. and the hydrochloride has a m.p. of 194° to 195°. This compound is related chemically to the nitrogen mustards and is of interest because its adrenergic blocking effect is irreversible. It must be administered by injection.

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CHAPTER VI

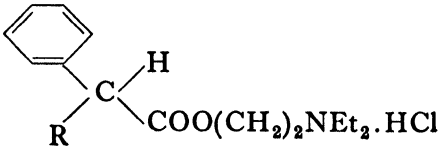
Antispasmodics

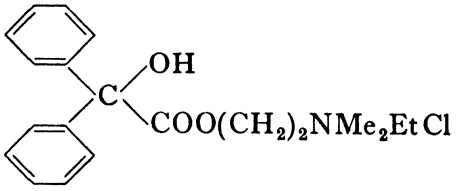
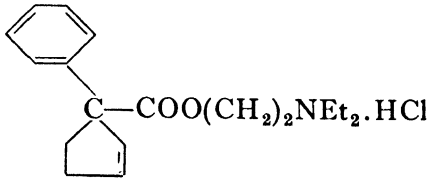
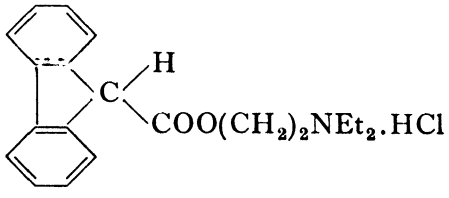
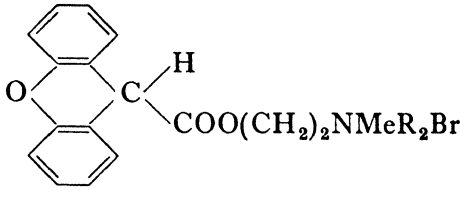
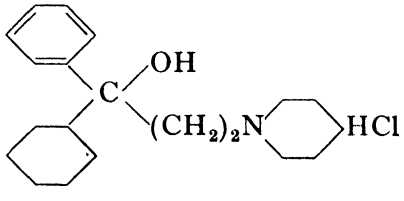
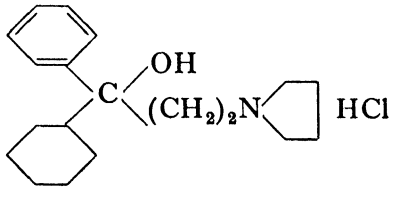
ANTISPASMODICS or spasmolytics are drugs which abolish spasms occurring in the involuntary muscles innervated by the autonomic nervous system. This system is formed of sympathetic and parasympathetic nerves. The sympatholytics such as tolazoline hydrochloride which abolish the effects of adrenaline in the body are not discussed in this chapter. The parasympatholytics interfere with the action of acetylcholine, and again a division must be made. Acetylcholine has two types of effect in the body, which are termed nicotinic and muscarinic. The blocking of the nicotinic activity causes relaxation of the voluntary muscles or ganglionic block and drugs which produce these effects are described in Chapter VII, as their clinical use is quite different from that of the antispasmodics. It is the abolition of the muscarinic effect that prevents spasm of involuntary muscle, and the drugs causing it are called neutropic antispasmodics. Atropine is the prototype of this group of compounds. In addition, some antispasmodics act directly upon the muscle cells irrespective of innervation, and these drugs, of which papaverine is a typical example, are termed musculotropic antispasmodics.

Since histamine has a direct stimulating action upon involuntary muscle cells, antihistaminic compounds are antispasmodics, but they are described in Chapter VIII.

Although spasmolytic activity is not confined to one class of compound, the substances described in this chapter and listed in the table have a certain structural similarity. Possibly they all derive ultimately from attempts to prepare a synthetic atropine-like compound. Atropine is an ester formed from the amino-alcohol, tropine, and the substituted phenylacetic acid, tropic acid, and the antispasmodic Trasentin[P] is an ester of diethylaminoethanol and diphenylacetic acid. Pavatrine and methantheline are condensed ring systems closely allied to Trasentin[P] in form.

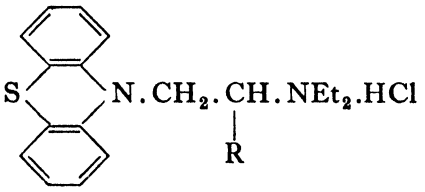
It is of interest that pethidine hydrochloride, which is now employed as an analgesic, has a strong antispasmodic action, and was first developed for that purpose.

Name	*Formula*
Trasentin. R=Phenyl Trasentin H. R=*cyclo*Hexyl	

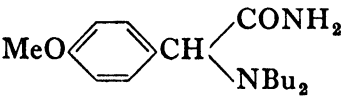
Name	*Formula*
Lachesine chloride	
Caramiphen hydrochloride	
Pavatrine hydrochloride[P]	
Methanthelinium bromide R=Ethyl Propantheline bromide R=*iso*Propyl	
Benzhexol hydrochloride	
Procyclidine hydrochloride	

Name *Formula*

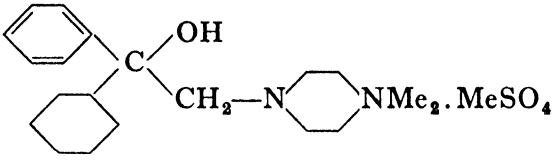
Diethazine hydrochloride
R=H.
Ethopropazine hydrochloride
R=Methyl



Ambucetamide

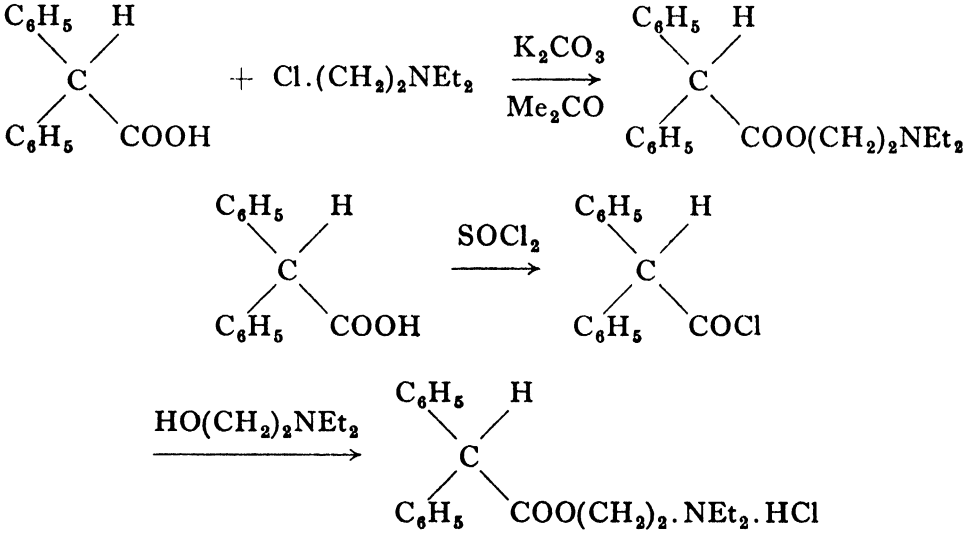


Hexacyclium methylsulphate



Trasentin[P]. 2-Diethylaminoethyl diphenylacetate hydrochloride pentahydrate.

Preparation. Two alternative methods of preparation have been used: (*a*) diphenylacetic acid may be reacted with 2-diethylaminoethyl chloride in warm acetone in the presence of potassium carbonate, or (*b*) diphenylacetic acid may be converted to the corresponding carbonyl chloride which is reacted with diethylaminoethanol in chlorobenzene.



Properties. Hydrochloride, m.p. 114°. Picrate, m.p. 144° to 145·5°. Trasentin was introduced in 1936. It was used to relieve spasm of the gastro-intestinal tract, but has been superseded by more potent compounds.

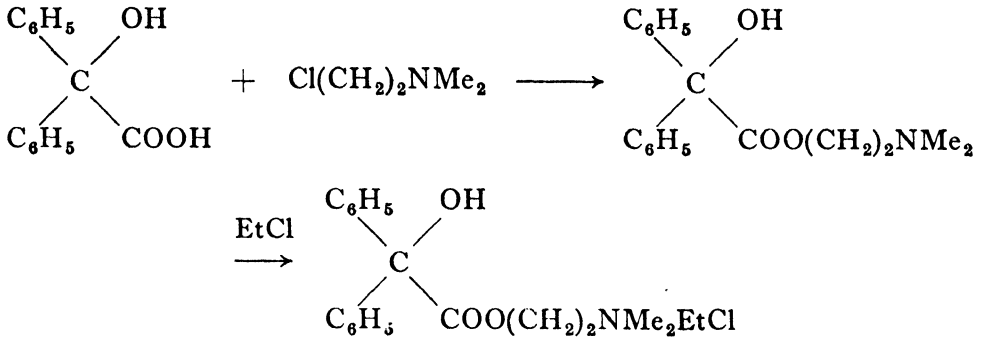
Trasentin H[P]. 2-Diethylaminoethyl *cyclo*hexylphenylacetate hydrochloride.

Preparation. Trasentin[P] is hydrogenated in the presence of Adam's catalyst in acetic acid solution (1).

Properties. M.p. 146·7°. Trasentin H is more active than Trasentin.

Lachesine chloride. 2-Benziloyloxyethyldimethylethylammonium chloride. $C_{20}H_{26}O_3NCl$.

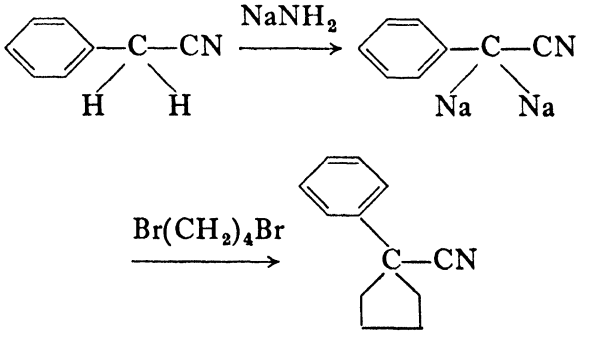
Preparation. It may be prepared by reaction of benzilic acid with dimethylaminoethyl chloride (2) and then quaternisation of the product by means of ethyl chloride.



Properties. Lachesine chloride was introduced in 1945 (3). It is used in solution as eye-drops for its mydriatic effect. It is soluble in water, and ethanol, but is insoluble in acetone, chloroform and ether. The m.p. is 212° to 216°. The aurichloride melts at 147° to 149°.

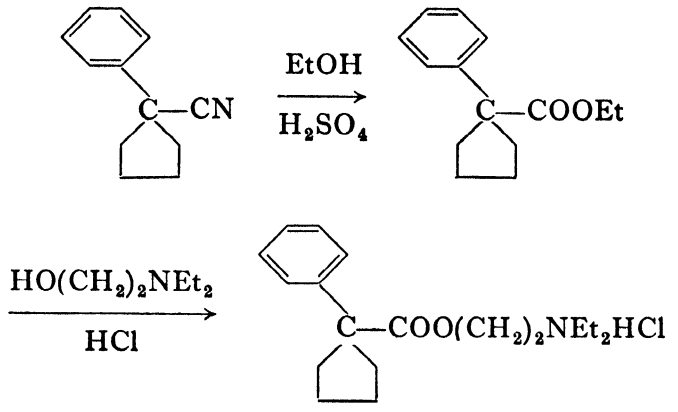
Caramiphen hydrochloride. 1-(2′-Diethylaminoethyl)-1-phenyl*cyclo*pentane carboxylate hydrochloride. $C_{18}H_{26}O_2N.HCl$.

Preparation. The method of preparation of caramiphen is interesting (4). Benzyl cyanide is converted to its di-sodio derivative by means of sodamide and is reacted with tetramethylene dibromide. Ring closure occurs and 1-phenyl-*cyclo*pentyl cyanide is obtained.



The cyanide is then simultaneously hydrolysed and esterified by a mixture of ethanol and concentrated sulphuric acid. The ethyl ester is converted to the

diethylaminoethyl ester on being heated with diethylaminoethanol. The amine is converted to its hydrochloride on addition of ethanolic hydrogen chloride.



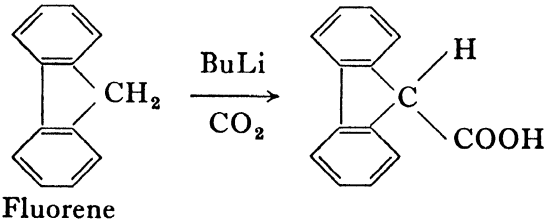
Caramiphen hydrochloride

The preparation of caramiphen from 1-phenyl*cyclo*pentanecarbonyl chloride or from the carboxylic acid has also been described by other workers (5).

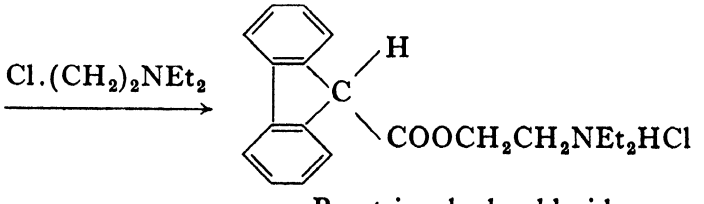
Properties. The m.p. of caramiphen hydrochloride is 142° to 144°. It is soluble in methanol and ethanol and insoluble in ether. It has been used to relieve the spasms of Parkinsonism.

Pavatrine hydrochloride[P]. 2-Diethylaminoethyl fluorene-9-carboxylate hydrochloride. $C_{18}H_{23}O_2N.HCl$.

Preparation. Fluorene-9-carboxylic acid required for the synthesis of Pavatrine may be obtained by the interaction of aluminium chloride and benzilic acid, or by reaction of fluorene with an organoalkali followed by carbonation (2). The latter method is preferred. Butyllithium is made from *n*-butyl chloride and lithium in ether, and to it is added fluorene. Butane is evolved and the mixture is poured into solid carbon dioxide. The acid so obtained is esterified by reaction with 2-diethylaminoethyl chloride in *iso*-propanol.



Fluorene

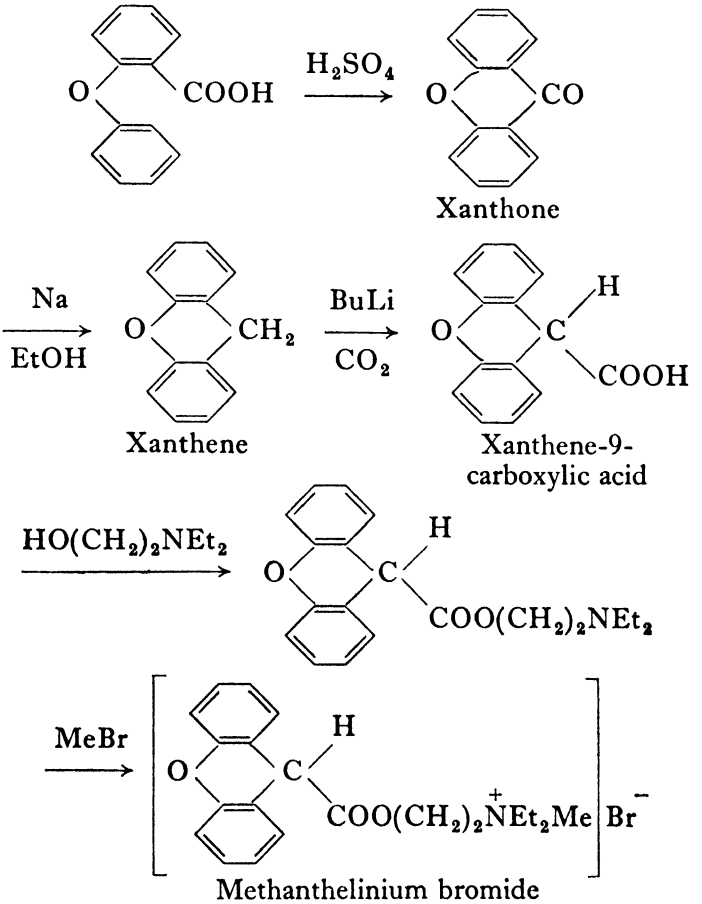


Pavatrine hydrochloride

Properties. Pavatrine hydrochloride melts at 143° to 144°. Burtner prepared compounds of this type allied to Trasentin, because in previous studies upon local anaesthetics it had been found that cyclisation of certain polynuclear carboxylic acid derivatives occasionally led to enhanced activity and therefore the cyclised or bridged forms of Trasentin-type compounds were made.

Methanthelinium bromide. 2′-Diethylaminoethyl-xanthene-9-carboxylate methobromide.

Preparation. This compound is made by esterifying xanthene-9-carboxylic acid with 2-diethylaminoethanol (6). The carboxylic acid is prepared from *o*-phenoxybenzoic acid. The latter is first converted to xanthone by heating with concentrated sulphuric acid and then on reduction with sodium in alcohol the xanthone yields xanthene. By the procedure detailed above for the preparation of fluorene-9-carboxylic acid, the xanthene is converted to the corresponding acid which is esterified with 2-diethylaminoethanol and then the tertiary amine is quaternised with methyl bromide to yield methanthelinium bromide.



Methanthelinium bromide

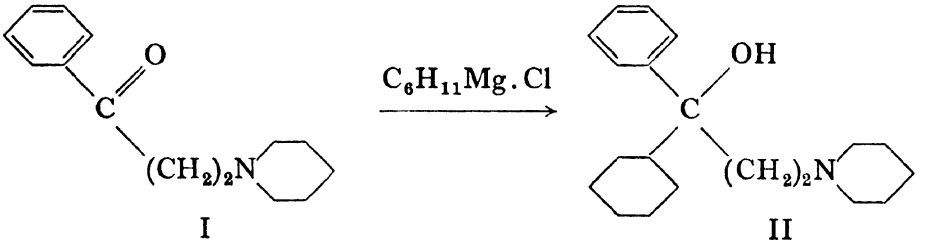
Properties. Methanthelinium bromide is a white crystalline powder with a very bitter taste. It melts at 172° to 177° and is soluble in water and ethanol, but not in ether. It is used to inhibit spasms of the gastro-intestinal tract.

Propantheline bromide. 2′-Di-*iso*propylaminoethyl-xanthene-9-carboxylate methobromide.

Preparation and properties. Similar to methanthelinium methobromide.

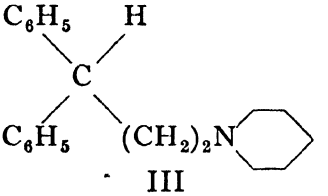
Benzhexol hydrochloride. Trihexyphenidyl. 1-*cyclo*Hexyl-1-phenyl-3-piperidinopropan-1-ol hydrochloride. $C_{20}H_{31}ON.HCl$.

Preparation. Three teams of workers have reported upon the preparation of this compound which, as may be seen by comparison of the formulae, is akin to Trasentin H. Denton *et al.* (7) first obtained 2-piperidinopropiophenone (I) by a Mannich reaction between piperidine hydrochloride, formaldehyde and acetophenone and then reacted it with *cyclo*hexylmagnesium chloride to produce benzhexol (II).



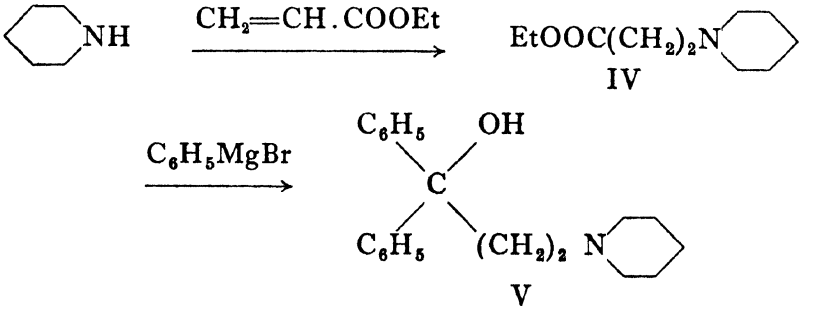
I II

Ruddy and Buckley (8) prepared benzhexol hydrochloride by reaction of a Grignard reagent with a Mannich base as one of a series of compounds having structures based upon that of 1 : 1-diphenyl-3-piperidinopropane (III) which was a spasmolytic compound described in 1942 (9); its method of preparation was later published (10).



III

Adamson *et al.* used a different method (11). Ethyl acrylate was reacted with piperidine and the ethyl 2-piperidinopropionate (IV) obtained was reacted with the Grignard reagent prepared from bromobenzene to give crude 1 : 1-diphenyl-3-piperidinopropan-1-ol (V).



IV

V

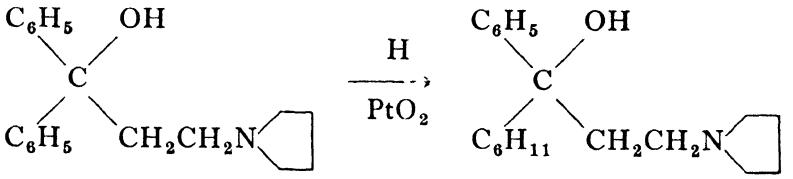
The diphenylamino-alcohol was then partly reduced in glacial acetic acid solution by hydrogen in the presence of Adam's catalyst to give the 1-*cyclo*hexyl-1-phenyl-3-piperidinopropan-1-ol required. The addition of hydrogen chloride led to benzhexol hydrochloride which was recrystallised from ethyl alcohol.

Properties. Benzhexol hydrochloride is a white crystalline powder of m.p. 250° (dec.); it is slightly soluble in cold water and more soluble in ethanol and methanol. When a solution in warm methanol is made just alkaline to litmus paper with sodium hydroxide benzhexol of m.p. 114° to 115° is obtained. The methiodide has m.p. 204·5° to 206·5° and the ethiodide m.p. 179° to 180° (dec.).

Benzhexol hydrochloride is an acetylcholine antagonist and has been used in the treatment of Parkinsonism (paralysis agitans). It was introduced in 1949.

Procyclidine hydrochloride. 1-*cyclo*Hexyl-1-phenyl-3-pyrrolidinopropan-1-ol hydrochloride. $C_{19}H_{29}ON.HCl$. (VII).

Preparation. 1 : 1-Diphenyl-3-pyrrolidinopropan-1-ol (VI) is reduced in the presence of Adam's catalyst to the cyclohexyl compound (VII).



VI VII

The base on addition of hydrogen chloride gives the hydrochloride which may be recrystallised from a mixture of ethanol and ethyl acetate.

Properties. Procyclidine hydrochloride is a white powder of m.p. 226° to 227° (dec.) with a methiodide m.p. 204° to 205° (dec.) and ethiodide m.p. 158° to 159° (dec.). It has been used for the treatment of Parkinsonism and was introduced in 1952.

Diethazine hydrochloride. N(2-diethylaminoethyl)phenothiazine hydrochloride. $C_{18}H_{22}N_2S.HCl$. (X, R=H).

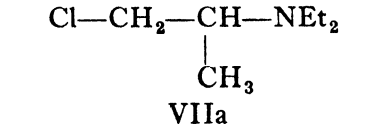
Preparation. To a boiling solution of phenothiazine in xylene containing sodamide is added 1-chloro-2-diethylaminoethane. After a further period at the boiling-point, the mixture is cooled and dilute mineral acid is added. The aqueous layer is separated and basified in the presence of an immiscible solvent, from which is obtained the base that after distillation and acidification yields diethazine hydrochloride (12).

Properties. Diethazine hydrochloride has a m.p. of 186°. It has been employed in the symptomatic treatment of Parkinsonism.

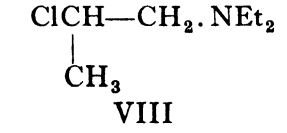
Ethopropazine hydrochloride. N-(2-diethylaminopropyl)phenothiazine hydrochloride. $C_{19}H_{24}N_2S.HCl$. (X, R=Me).

Preparation. Fundamentally the method used is the same as that used for diethazine. However, either 1-chloro-2-diethylaminopropane (VIIa) or 2-chloro-1-diethylaminopropane (VIII) may be condensed with phenothiazine

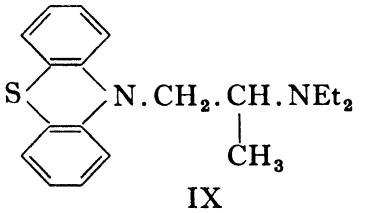
and in each case ethopropazine (IX) is obtained (13). When 2-chloro-1-diethylaminopropane is employed, then N-(2-diethylamino-*iso*propylphenothiazine (X) is obtained as an impurity.



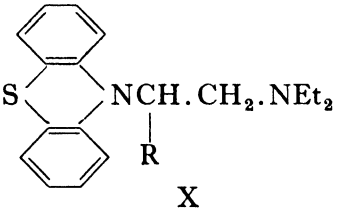
VIIa



VIII



IX



X

The fact that (IX) may be formed from (VIII) shows that during the condensation of phenothiazine with the chloroamine a partial transfer of the methyl group takes place.

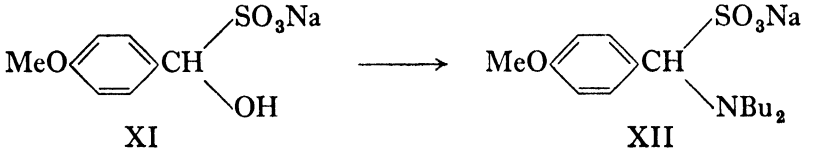
Properties. Ethopropazine hydrochloride is a white crystalline material with a bitter taste. It darkens on exposure to light. Its m.p. is 225° (dec.) and its picrate melts at 148° to 149°. It is not very soluble in water, but is more soluble in ethanol or in chloroform. It has been used for the treatment of spasms in Parkinsonism.

Structurally, ethopropazine is very similar to promethazine which is the corresponding N-(2-dimethylamino) compound. Promethazine is an antihistamine; diethazine and ethopropazine also have slight antihistaminic properties. It is of interest that ethopropazine, like many other antispasmodics, contains an active carbon atom, and therefore occurs as two optically-active forms. This mixture has been resolved (14) by means of (+)-tartaric acid, and the (—) base was found to be twice as active in nicotinolytic action as the (+) form.

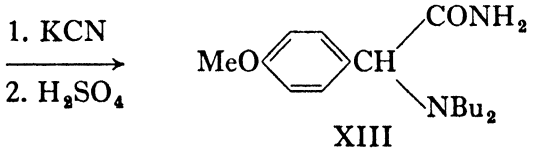
Ambucetamide. 2-(4-Methoxyphenyl)-2-dibutylaminoacetamide.

$C_{15}H_{24}N_2O_2$. (XIII).

Preparation. Anisaldehyde is converted to its bisulphite compound (XI) which reacts with dibutylamine to yield (XII). Potassium cyanide converts the SO_3Na group to CN and sulphuric acid hydrolyses this to ambucetamide (XIII). The product is recrystallised from 95 per cent ethanol (15, 16).



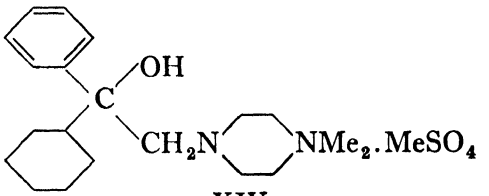
XI XII



XIII

Properties. Ambucetamide is unique among the antispasmodics described in this chapter in containing the amide grouping. It has a specific use as a uterine antispasmodic in dysmenorrhoea. It melts at 128°.

Hexacyclium methylsulphate. 1-(2-*cyclo*Hexyl-2-hydroxyphenylethyl)-4 : 4-dimethylpiperazinium methylsulphate. $C_{21}H_{36}O_5N_2S$. (XIV).



XIV

Properties. This compound, which is used for the treatment of peptic ulcer, is soluble in one part of water, slightly soluble in chloroform and insoluble in ether. It melts at 200° to 210°.

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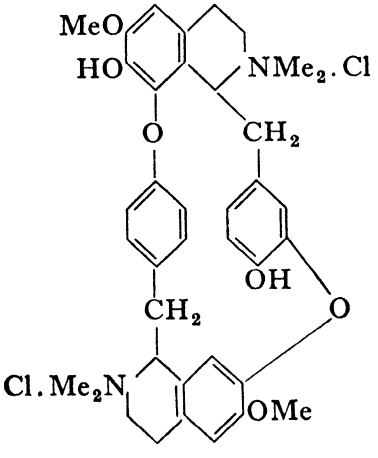
CHAPTER VII

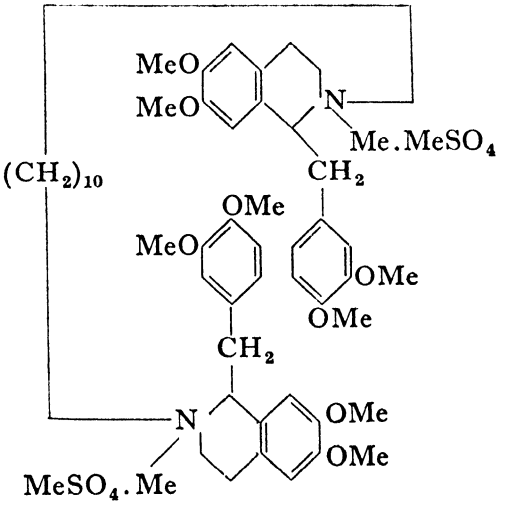
Neuromuscular and Autonomic Blocking Agents

INTRODUCTION. Curare has been of interest for many years. It was known in the early sixteenth century to be the material used by the natives of South America for coating the tips of their poisoned arrows. During the following years a certain amount was learned about its physiological action. It was discovered that (+)-tubocurarine chloride (see p. 252) causes relaxation of the voluntary muscles and the effects of this in a conscious human being have been graphically described by later workers (1, 2). (+)-Tubocurarine became one of the routine adjuncts to general anaesthesia for major surgery first in Canada (3) and the U.S.A. (4) and then in Britain (5).

An inevitable result has been an intensive search for better and cheaper muscle relaxants and certain of these are now in use. The molecule of (+)-tubocurarine (I) contains two quaternary nitrogen atoms and the investigation of the pharmacological properties of quaternary nitrogen compounds has led to the discovery of new neuromuscular and autonomic blocking agents. This work has been reviewed (6, 7).



I



II

$IMe_3N(CH_2)_{10}NMe_3I$

III

It was discovered by Brown and Fraser in 1868 that quaternary ammonium salts possess curare-like activity, but it was not until after the use of (+)-tubocurarine as a muscle relaxant that synthetic compounds were introduced for this purpose. In 1948 Barlow and Ing (8) and Paton and Zaimis (9, 10) found decamethonium iodide (III) to be a potent curarising agent. It is not now widely used in this country. A synthetic compound more closely resembling tubocurarine (I) in structure was laudexium (II) prepared by Taylor in 1951 (11).

Bovet and his collaborators were responsible for the introduction of gallamine triethiodide and suxamethonium chloride. The latter short-acting muscle relaxant is a diester that is readily hydrolysed in the body to the relatively inactive half ester.

The physiological activity of the muscle relaxants renders them potentially dangerous and antidotes are available for tubocurarine, laudexium and gallamine. The alkaloid physostigmine was originally used, but has been replaced by the synthetic compounds neostigmine and edrophonium.

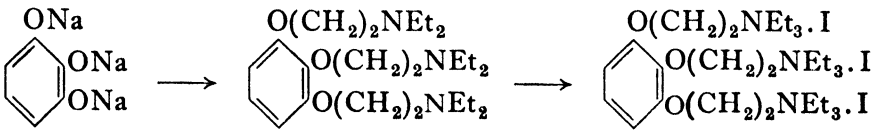
Whereas the curarising agents block the transmission of impulses from the nerves to the skeletal muscles, the autonomic blocking agents paralyse the ganglia of the autonomic or involuntary nervous system. Their chief effect is a fall in blood pressure due to blockade of the sympathetic ganglia. Thus they are hypotensives. Carbachol or neostigmine may be used as antidotes.

Tetraethylammonium chloride was the first ganglionic blocking agent to be used in the treatment of hypertension. Hexamethonium salts followed soon after. Pentolinium tartrate and mecamylamine are recent introductions.

NEUROMUSCULAR BLOCKING AGENTS AND THEIR ANTAGONISTS

Gallamine triethiodide. 1 : 2 : 3-tris(2-Diethylaminoethoxy)-benzene triethiodide. $C_{30}H_{60}I_3N_3O_3$. (IV).

Preparation. Trisodium pyrogallate, which is made by reacting pyrogallol with sodium methoxide, is condensed with 2-chloroethyldiethylamine. The resulting tritertiary amine is then alkylated (12) by the use of ethyl iodide to yield gallamine triethiodide (IV).



IV

Properties. Gallamine triethiodide is a white hygroscopic powder that melts at 230° to 235° when dry and at 152° to 153° if crystallised from aqueous solvents. It is soluble in ethanol and water. A 2 per cent aqueous solution has a pH of 5·8. It is antagonised by neostigmine and edrophonium.

Suxamethonium chloride. Bis(2-dimethylaminoethyl)-succinate bis-methochloride dihydrate. $C_{14}H_{30}Cl_2N_2O_4.2H_2O$. (VII).

Preparation. This compound was first prepared by Hunt and Taveau in 1911 (13). It was due to the work of Bovet and his colleagues, however, that it was accepted for medical use (14). Fusco has listed the possible methods for the preparation of suxamethonium compounds (15).

Glick (16) and Walker (17) obtained suxamethonium bromide by reacting bis(2-bromoethyl) succinate with trimethylamine. The corresponding bis(2-iodoethyl) succinate (V) has been used as an intermediate in a patented approach (18). It is condensed with dimethylamine in benzene and after filtration of precipitated dimethylamine hydriodide, the benzene is evaporated and the product distilled to yield bis(dimethylaminoethyl) succinate (VI). Alkylation with methyl chloride in acetone then gives suxamethonium chloride (VII).

$$\begin{matrix} CH_2COO(CH_2)_2I \\ | \\ CH_2COO(CH_2)_2I \end{matrix} \quad \xrightarrow{HNMe_2} \quad \begin{matrix} CH_2.COO(CH_2)_2NMe_2 \\ | \\ CH_2.COO(CH_2)_2NMe_2 \end{matrix}$$

V VI

$$\xrightarrow{MeCl} \quad \begin{matrix} CH_2COO(CH_2)_2NMe_3.Cl.H_2O \\ | \\ CH_2COO(CH_2)_2NMe_3.Cl.H_2O \end{matrix}$$

VII

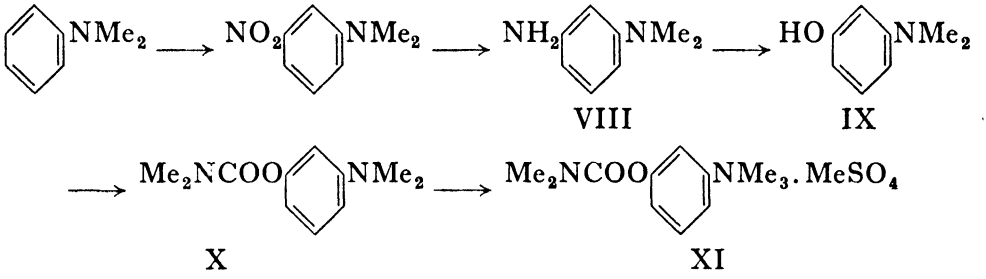
Properties. Suxamethonium chloride is a white powder possessing a slightly bitter taste. As normally prepared, it is a dihydrate of m.p. 163° to 165°. When this is dried at 135° *in vacuo*, the anhydrous solid of m.p. 191° to 193° is obtained. Suxamethonium chloride is soluble in water and methanol and slightly soluble in ethanol. 100 ml of ethanol dissolve 0·42 g at room temperature. A 2 per cent aqueous solution has pH of 3·0 to 4·5. Prolonged contact with hydroxylic solvents causes progressive hydrolysis.

Suxamethonium chloride is not antagonised by neostigmine or edrophonium. The bromide which is slightly hygroscopic melts at 225° and the methosulphate at 171°.

Neostigmine methylsulphate. 3-Dimethylcarbamoxyphenyl trimethyl-ammonium methylsulphate. $C_{13}H_{22}N_2O_6S$. (XI).

Preparation. Dimethylaniline is nitrated and the 3-nitrodimethylaniline obtained is separated from its 4-nitro isomer and reduced with iron and hydrochloric acid to 3-aminodimethylaniline (VIII). This is diazotised and heated to give 3-dimethylaminophenol (IX). Reaction with dimethylcarbamoyl chloride in the presence of sodium hydroxide then leads (19) to 3-dimethylamino-phenyl dimethyl carbamate (X). This is purified by distillation and boils at 195° at 20 mm. It is alkylated (20) with dimethyl sulphate to give neostigmine

methylsulphate (XI) or with methyl bromide to yield the quaternary bromide. Other methods of preparation have been published (21).



VIII IX

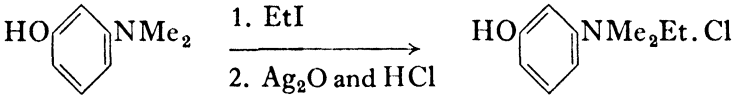
X XI

Properties. Neostigmine methylsulphate is a white crystalline powder of m.p. 147°. It is freely soluble in water and gives a neutral solution. It is also soluble in ethanol. The bromide melts at 167°.

Neostigmine methylsulphate is used as an antagonist to tubocurarine and gallamine. It is often administered together with atropine which nullifies its unwanted muscarinic effects.

Edrophonium chloride. Ethyl(3-hydroxyphenyl)dimethylammonium chloride. $C_{10}H_{16}ClNO$. (XII).

Preparation. 3-Dimethylaminophenol (IX) as used above for the preparation of neostigmine is converted to its ethiodide by reaction with ethyl iodide in hot acetone. The edrophonium iodide obtained is recrystallised from *iso*propanol and then melts at 113° to 115°. It is reacted with silver oxide to give the quaternary hydroxide and addition of hydrochloric acid leads (22) to the required chloride (XII).



IX XII

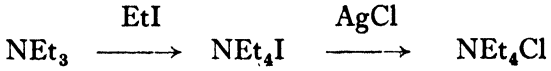
Properties. Edrophonium chloride is a white crystalline powder with a melting-point of 162° to 163° (dec.) and is freely soluble in water. A 1 per cent aqueous solution is acidic with pH 4·0 to 5·0. It is also soluble in ethanol. The corresponding bromide melts at 151° to 152° (dec.) and the iodide at 113° to 115°.

Edrophonium chloride was introduced in 1950 as an antagonist of tubocurarine, its dimethyl ether, and gallamine.

AUTONOMIC BLOCKING AGENTS

Tetraethylammonium chloride. $C_8H_{20}ClN$. (XIII).

Preparation. Triethylamine is ethylated with ethyl iodide in acetone and the tetraethylammonium iodide so obtained is converted to the chloride by reaction with silver chloride.



XIII

Properties. Tetraethylammonium chloride is a hygroscopic white solid that forms a tetrahydrate of m.p. 37·5°. The picrate melts at 262°. The chloride forms the following solutions at 35° (per cent by weight): water (75·5), methanol (72), ethanol (60), acetone (0·4). A 50 per cent aqueous solution has pH 5·8 to 6·5. Tetraethylammonium chloride forms complexes with many substances including ethanol, acids, halogens and many metallic salts.

It was studied by many workers in the early years of this century, but it was not until the work of Acheson and Moe in 1946 led to the clinical trials of Lyons in 1947 that it came into general use as the first synthetic hypotensive. Its effect is reversed by neostigmine.

Hexamethonium salts.

Preparation. Although 1 : 6-diiodohexane may be reacted with dimethylamine to yield bis-dimethylaminohexane (XIV) or with trimethylamine to yield hexamethonium iodide, it is more convenient in the preparation of hexamethonium compounds to use as the starting material, 1 : 6-diaminohexane. This is methylated by the Eschweiler reductive alkylation technique used by Clarke (23) to bis-dimethylaminohexane (XIV), a liquid of b.p. 112° at 25 mm. which on reaction with the appropriate alkyl halide yields hexamethonium iodide (XV) or chloride (XVII) or bromide (XVI). Alternately exhaustive methylation of hexanediamine with methyl iodide in methanol in the presence of caustic soda leads to hexamethonium iodide (24).

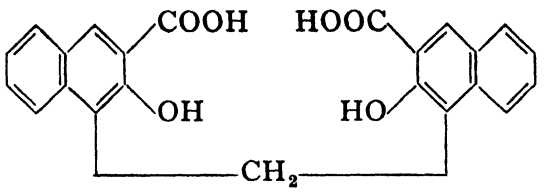
$$H_2N(CH_2)_6NH_2 \xrightarrow[HCOOH]{HCHO} Me_2N(CH_2)_6NMe_2$$

XIV

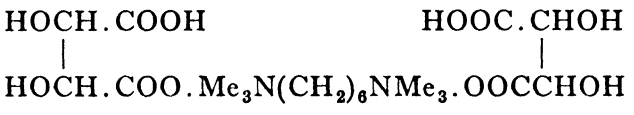
$$\xrightarrow{MeX} XMe_3N(CH_2)_6NMe_3X$$

XV X=I
XVI X=Br
XVII X=Cl

Hexamethonium tartrate is made from the corresponding methosulphate by the use of hexamethonium embonate. This method was introduced by Barber (25). A hot aqueous solution of hexamethonium methosulphate (26) is added to a boiling aqueous solution of sodium embonate. Embonic acid (XVIII) is the trivial name for 2 : 2-dihydroxy-1 : 1-dinaphthylmethane-3 : 3-dicarboxylic acid. The sparingly soluble hexamethonium embonate crystallises and is filtered. It is dissolved in a large volume of water and tartaric acid is added. Embonic acid deposits from the cooled aqueous solution. It is filtered and the solution is evaporated to yield crude hexamethonium tartrate (XIX) which is recrystallised from methanol.



XVIII



XIX

Properties. **Hexamethonium chloride**, $C_{12}H_{30}Cl_2N_2$, is a colourless, odourless, crystalline powder of m.p. 289° (dec.). It is hygroscopic and forms a dihydrate. The picrate melts at 238° to 240° and the picrolonate at 241° to 242°. Hexamethonium chloride is soluble in water (20°) 1 g in 0·65 ml and at 100° 1 g in 0·3 ml. A 1 per cent solution has pH 6·0 and a 10 per cent solution pH 3·6. In ethanol at 20° its solubility is 1 g in 3·2 ml, and at 78·5° 1 g in 1·7 ml. In methanol at 20° the solubility is 1 g in 1·4 ml, and at 64·1° 1 g in 0·8 ml. It is insoluble in acetone, benzene, chloroform and ether.

Hexamethonium bromide, $C_{12}H_{30}Br_2N_2$, is a colourless, odourless, crystalline powder of m.p. 272° (dec.). It is slightly hygroscopic. 1 g dissolves in 1 ml of water at 21° and 5 g in 1 ml at 100°. A 1 per cent solution has pH 6·6 and 10 per cent solution pH 6·0. In ethanol at 20° its solubility is 1 g in 30 ml and at 78·5° 1 g in 3 ml. Methanol dissolves 1 g in 5 ml at 20° and 1 g in 1 ml at 64·1°.

Hexamethonium iodide, $C_{12}H_{30}I_2N_2$, is a colourless, odourless, crystalline powder of m.p. 278°. The picrate melts at 239°. It is soluble in water (22°) 1 g in 1·8 ml and at 100° 1 g in 0·3 ml. A 1 per cent solution has pH 6·37 and a 10 per cent solution pH 6·24. In ethanol at 20° 0·3 g dissolves in 1 litre and at 78·5° 1 g in 390 ml. Methanol at 22° dissolves 1 g in 260 ml and at 64·1° 1 g in 12 ml. It is insoluble in acetone, benzene, chloroform and ether.

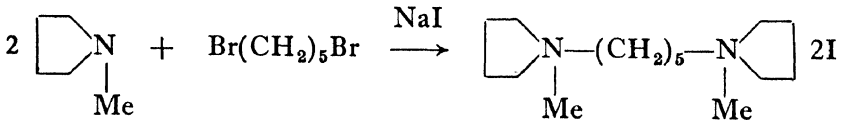
Hexamethonium tartrate, $C_{20}H_{40}N_2O_{12}$, is a white solid of m.p. 185° to 188° (dec.). It forms a monohydrate. It is soluble in water and methanol.

Hexamethonium compounds were made by Von Braun in 1910, but it was not until 1948 that the pharmacological studies of Barlow and Ing (8) and Paton and Zaimis (9, 10) brought them into prominence. They are used in the treatment of hypertension and for bloodless field surgery, a technique introduced by Enderby in 1950.

Pentolinium tartrate. Pentamethylene *bis*-(1-methylpyrrolidinium hydrogen tartrate). $C_{23}H_{38}N_2O_{12}$. (XXI).

Preparation. 1 : 5-Dibromopentane and N-methylpyrrolidine are reacted together in acetone in the presence of sodium iodide (27) to give pentolinium

iodide (XX). This is converted to the tartrate by the method described above under hexamethonium tartrate (28).



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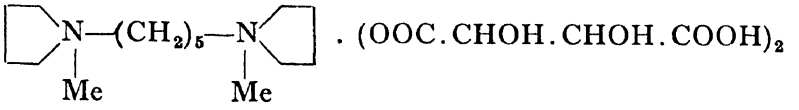

XXI

Properties. Pentolinium tartrate is a white, slightly hygroscopic powder with an acid taste. It is used for the treatment of hypertension.

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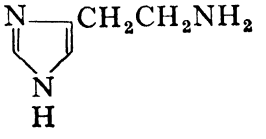
CHAPTER VIII

Antihistamines

INTRODUCTION. Histamine (I) is present in the cells of the body in a bound form as a histamine-protein complex.



I

It has been suggested that the symptoms of the acute condition termed anaphylactic shock and of the less severe but similar condition termed allergy are due to the release of free histamine in the body. In man, histamine causes the contraction of involuntary muscle, the dilatation of arteries and capillaries (hence causing a lowering of the blood pressure) and also stimulates the secretory cells of the gastric mucosa and salivary glands.

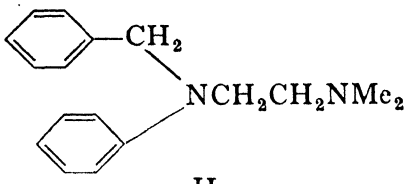
These effects of histamine could be antagonised by one of three different mechanisms: (*a*) chemical, (*b*) indirect or (*c*) substrate competition. Certain substances such as formaldehyde, carbon dioxide and presumably the enzyme histaminase inactivate histamine by chemical means. An indirect antagonism is shown by adrenaline which can initiate pharmacological responses in the body that are opposed to those of histamine. By definition (1) antihistamines are those drugs that diminish or prevent several of the effects due to histamine by a mechanism that does not involve the production of pharmacologically opposite responses. Probably antihistamines act as substrate competitors and prevent histamine from reaching the sensitive receptor surfaces of the tissues. The mode of action is complex, however, and not yet fully understood.

Many antihistaminic drugs have a sedative effect and anti-acetylcholine and local anaesthetic properties are common. These side actions lead to drowsiness, dizziness and dryness of the nasal and buccal mucosa. In general, however, the antihistamines have a high therapeutic index, since the acute toxicities are low and the effective dose small.

Antihistaminic drugs are used for combating rhinitis, urticaria, hay-fever and pruritus.

Research on these drugs began in France in 1937; it was discovered by Bovet and his colleagues (2) that certain derivatives of 2-aminoethanol that had been prepared for their adrenolytic activity were also antihistamines. These early ethers were too toxic for human therapy and, later, derivatives of ethylenediamine

were tested. The first antihistamine of this type was introduced in 1939 (3) and was followed in 1942 (4) by Antergan[P] (II).



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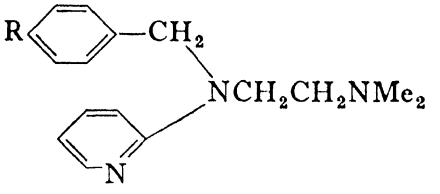

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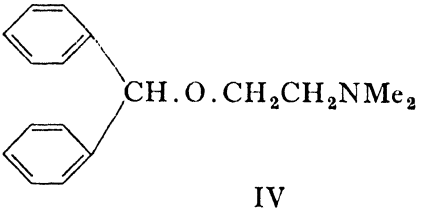


IV

This was the first antihistamine to be used successfully in the treatment of human allergic conditions, but it has now been superseded by less toxic compounds. The French workers in 1942 turned their attention to compounds of the Antergan type but containing heterocyclic substituents. During this period tripelennamine (III, R=H) and mepyramine (III, R=OMe) were prepared and tested (5, 6).

Research on similar lines was proceeding independently in the U.S.A. and in 1945 (7) the first useful ether was introduced, a compound now named diphenhydramine (IV). Tripelennamine (III, R=H) was prepared in the same year (8). From that time onwards many compounds with antihistaminic activity have been made and some of the most useful have been described in this chapter. They are classified on the basis of their chemical constitution according to the system used by Huttrer (9) as follows:

(*a*) Alkylenediamines, including straight or branched-chain diamines, cyclic diamines and aminocyclic diamines.
(*b*) Aminoalkyl ethers.
(*c*) Alkylamines.

All these compounds are related in that they are derived from a common structural pattern $R_4R_3XR_2NR_1R_1$. In the alkylenediamines X=N, in the ethers X=—OCH— and in the alkylamines X=—CH.

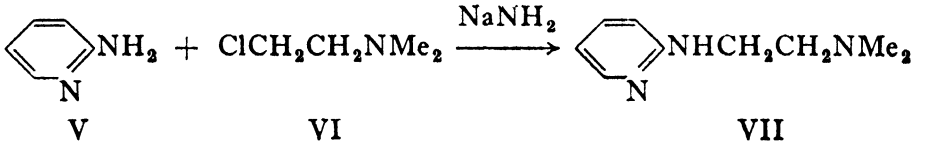
In addition antihistaminic substances have been found that belong to the following chemical groups, haloalkylamines, aminoketones, secondary amino-alcohols and aminoalkyl esters. None of these types are described in this chapter as they are not used in medicine.

The identification of antihistamines by colour reactions is complicated and tests for individual compounds are not given in the text. A useful table of these colour reactions is given by Idson (10).

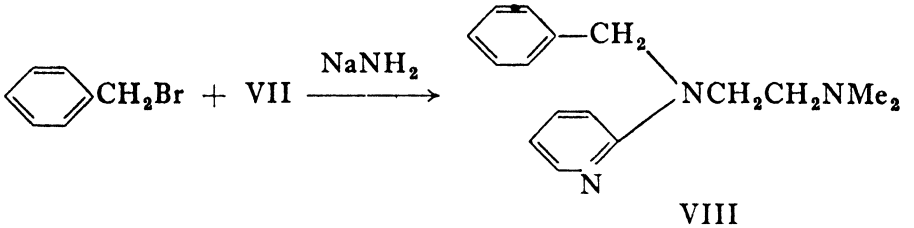
ALKYLENEDIAMINES

Tripelennamine. N-Benzyl-N-2-pyridyl-N'N'-dimethylethylenediamine. $C_{16}H_{21}N_3$. (VIII).

Preparation. 2-Aminopyridine (V) is alkylated with 1-chloro-2-dimethyl-aminoethane (VI) in toluene in the presence of sodamide or lithium amide; the 2-(2-dimethylaminoethyl)aminopyridine formed is purified by distillation. Further alkylation of this secondary amine (VII) with benzyl bromide in toluene in the presence of sodamide leads to the tertiary amine, tripelennamine.



V VI VII



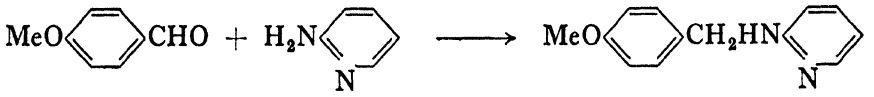
VIII

Properties. Tripelennamine is usually employed in the form of the monohydrochloride which is a white crystalline powder melting at 193°; it slowly darkens on exposure to light. It is very soluble in water, soluble in ethanol and chloroform, sparingly soluble in acetone and insoluble in benzene, ether and ethyl acetate. The citrate melts at 110° and the dipicrate at 185° to 190°.

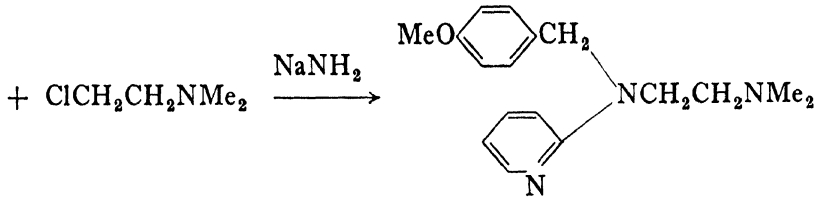
Mepyramine. Pyrilamine. N-*p*-Methoxybenzyl-N-2-pyridyl-N'N'-dimethyl-ethylenediamine. $C_{17}H_{23}ON_3$. (X).

Preparation. Mepyramine is closely related to tripelennamine and may be prepared by an analogous method, but a better yield is obtained by the use of an alternative approach (11, 12). *p*-Methoxybenzylaminopyridine (IX) is obtained by reacting 2-aminopyridine with anisaldehyde (13); a Schiff's base forms and becomes reduced to the required secondary amine. This compound is alkylated by 1-chloro-2-dimethylaminoethane in benzene in the presence of

sodium amide or lithium amide. Mepyramine (X) is produced and is purified by fractional distillation under reduced pressure.



IX

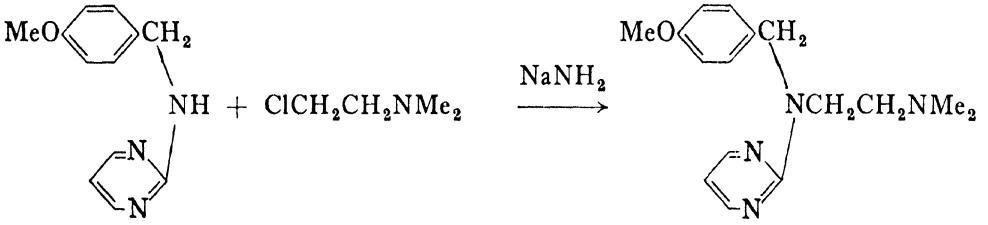


X

Properties. Mepyramine hydrogen maleate is a white powder, melting at 101° to 102°; it is soluble in water, chloroform and ethanol and sparingly soluble in ether or benzene. The hydrochloride melts at 135° and the dipicrate at about 163°. Many antihistamines are used in the form of their salts with organic acids because the hydrohalides are sometimes difficult to prepare or are hygroscopic (15); in addition the organic salts are often more active or less toxic than the hydrohalides (14).

Thonzylamine. N-4-Methoxybenzyl-N-2-pyrimidyl-N′N′-dimethylethylenediamine. $C_{16}H_{22}ON_4$. (XII).

Preparation. The method follows the usual course (16). 4-Methoxybenzylaminopyrimidine (XI) is converted to its sodio derivative by reaction with sodamide in toluene and 1-chloro-2-dimethylaminoethane is added to give thonzylamine. This is an oil of b.p. 185° to 187° at 2·2 mm which on addition to aqueous acetone containing hydrogen chloride forms the hydrochloride.

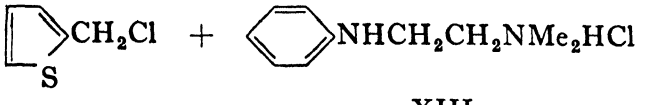


XI XII

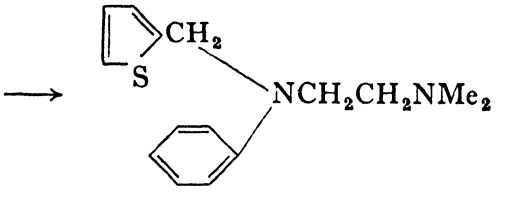
Properties. The hydrochloride is a white crystalline powder which melts at 173° to 176°; it is very soluble in water, ethanol or chloroform, but almost insoluble in ether; the dipicrate melts at 141° to 145°.

Methaphenilene. N-Phenyl-N-2-thenyl-N′N′-dimethylethylenediamine. $C_{15}H_{20}N_2S$. (XIV).

Preparation. A procedure has been described (17) whereby aniline may be reacted successively with 2-thenyl chloride and 1-chloro-2-dimethylaminoethane, but a better approach appears to be the use of N-phenyl-N'N'-dimethylethylenediamine which may be prepared (11) from aniline and 1-bromo-2-dimethylaminoethane. The secondary amine is first converted to the hydrochloride (XIII) to protect the alkylamino group and to minimise the production of quaternary compounds.



XIII



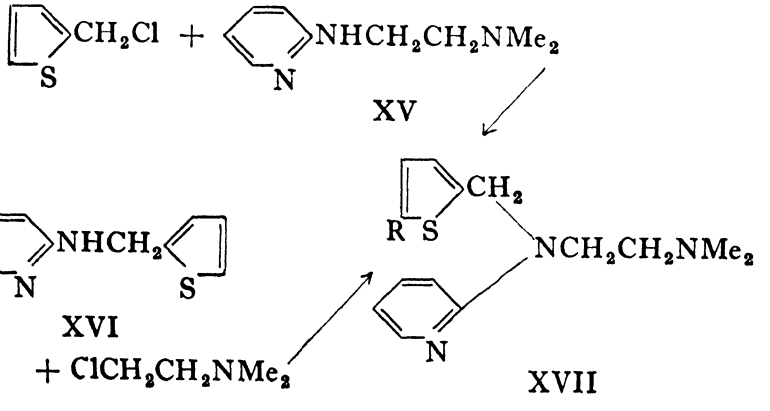
XIV

This amine hydrochloride is reacted in hot benzene with 2-thenyl chloride and, after basification and distillation at reduced pressure, methaphenilene is obtained as an oil, which is then converted to its hydrochloride (18).

Properties. Methaphenilene hydrochloride is a white crystalline powder, soluble in water and sparingly soluble in ethanol and chloroform; it melts at 186° to 189° and the dipicrate at 130° to 135°.

Methapyrilene. N-2-Pyridyl-N-2-thenyl-N'N'-dimethylethylenediamine. $C_{14}H_{19}N_3S$. (XVII, R=H).

Preparation. Methapyrilene is the thiophene analogue of tripelennamine. It may be prepared by reacting 2-thenyl chloride with N-2-pyridyl-N'N'-dimethylethylenediamine (XV). 2-Thenyl chloride is obtained by the chlormethylation of thiophene (20); it is an unstable compound and must be stored in a refrigerator.



Alternatively N-2-pyridyl-N-2-thenylamine (XVI) may be reacted with 1-chloro-2-dimethylaminoethane in boiling toluene in the presence of sodamide (21).

Properties. It sometimes happens that a phenyl group, if present in a physiologically active compound, may be replaced by 2-thenyl to give a substance with comparable activity (19). The phenyl group of tripelennamine is replaced in methapyrilene by 2-thenyl and the two compounds are equally active. Methapyrilene monohydrochloride is soluble in water, ethanol and chloroform, but almost insoluble in ether and benzene. It melts at 160° to 162°; the methiodide melts at 156° to 157°.

Chloropyrilene. N-(5-Chloro-2-thenyl)-N-2-pyridyl-N'N'-dimethylethylenediamine. $C_{14}H_{18}N_3SCl$. (XVII, R=Cl).

Preparation. Chloropyrilene differs from methapyrilene in having a chlorine atom in the 5- position of the thiophene group. The methods of preparation (22, 23) are similar to those described for methapyrilene. 5-Chloro-2-thenyl chloride is made (24) by chlormethylation of 5-chlorothiophene.

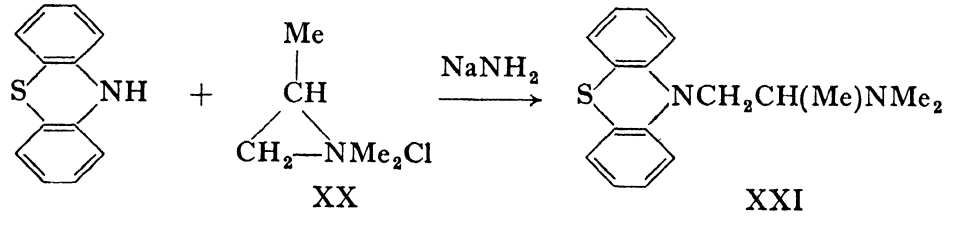
Properties. Chloropyrilene is an oil; the monohydrochloride melts at 106° to 108° and the picrate at 145° to 148°.

Promethazine. N-(2-Dimethylaminopropyl)phenothiazine. $C_{17}H_{20}N_2S$. (XXI).

Preparation. Phenothiazine in xylene is converted to its sodio derivative by reaction with sodamide and may then be reacted (25) with either 1-chloro-2-dimethylaminopropane (XVIII) or 2-chloro-1-dimethylaminopropane (XIX) to give promethazine (XXI).

$ClCH_2CH(Me)NMe_2$ XVIII $MeCHClCH_2NMe_2$ XIX

Probably the reaction with the chloramine passes through a common intermediate cyclic compound (XX) which splits to give a mixture of chloramines and thus a mixture of phenothiazine derivatives (26).



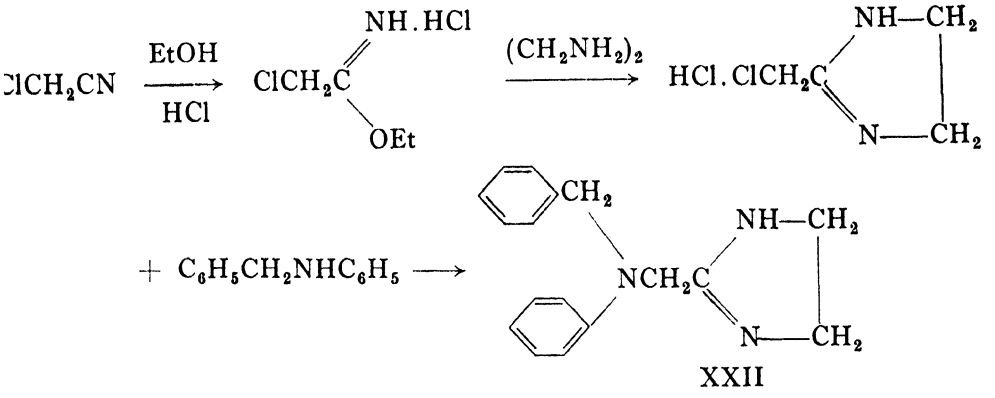
XX XXI

Properties. Promethazine hydrochloride is a white powder with a very bitter taste; it is soluble in water, ethanol or chloroform. The base boils at 190° to 192° at 3 mm pressure; the hydrochloride melts at 221° to 225° and the picrate at 160°.

Antazoline. 2-(N-Benzyl-N-phenylaminomethyl)iminazoline. $C_{17}H_{19}N_3$. (XXII).

Preparation. Antazoline may be prepared by the following series of reactions (27, 28, 29). Chloroacetonitrile is converted to the chloroiminoether which is cyclised with ethylenediamine to yield 2-chloromethyliminazoline hydrochloride. On condensation with N-benzylaniline antazoline is obtained. The hydrochloride

is formed by neutralisation with aqueous hydrochloric acid and evaporation to dryness followed by recrystallisation from ethanol. Alternative syntheses have been published (30, 31).

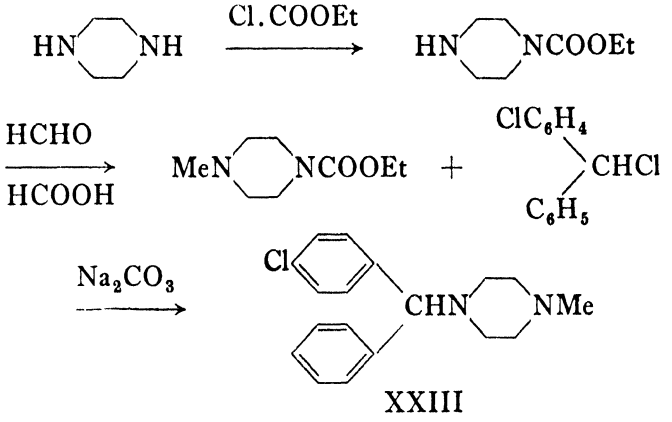


XXII

Properties. Antazoline is one of the earlier antihistamines and was introduced in Switzerland in 1946. It melts at 121° to 123°; the hydrochloride melts at 230° to 232°.

Chlorcyclizine. 1-Methyl-4-(*p*-chlorobenzhydryl)piperazine. $C_{18}H_{21}N_2Cl$. (XXIII).

Preparation. In the following method (32) one of the nitrogen atoms of piperazine is protected by reaction with ethyl chloroformate and the ethyl piperazine-1-carboxylate so formed is methylated by the Eschweiler method with



XXIII

formaldehyde and formic acid. Treatment with concentrated hydrochloric acid yields methylpiperazine; this reacts with *p*-chlorobenzhydryl chloride when refluxed in xylene in the presence of anhydrous sodium carbonate to give chlorcyclizine (XXIII). The *p*-chlorobenzhydryl chloride is obtained from the corresponding carbinol (XXIV) which is made by reacting together phenylmagnesium bromide and *p*-chlorobenzaldehyde (33).

$$C_6H_5MgBr + ClC_6H_4CHO \longrightarrow C_6H_5(ClC_6H_4)CHOH$$

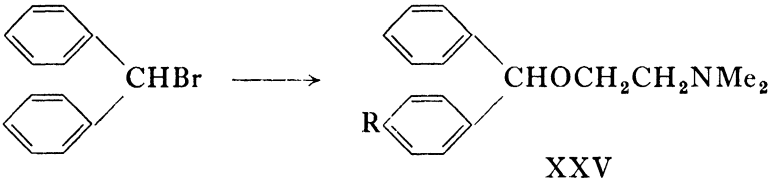
XXIV

Properties. Chlorcyclizine monohydrochloride melts at 223° to 224° and the dihydrochloride at 220° to 221°; these are formed by the addition of the calculated quantity of hydrogen chloride in *iso*propanol. The base is an oil boiling at 160° to 161° at 0·5 mm pressure.

AMINOALKYL ETHERS

Diphenhydramine. 2-(Benzhydryloxy)-NN-dimethylethylamine. $C_{17}H_{21}ON$. (XXV, R=H).

Preparation. Diphenylmethane is heated to 130° with stirring and bromine is added while the reaction mixture is illuminated by a strong electric lamp. The benzhydryl bromide so obtained is dissolved in benzene and may be used directly or distilled to give the pure product in good yield. Dimethylaminoethanol and anhydrous sodium carbonate are mixed and heated to 110° and the benzhydryl bromide is added slowly; diphenhydramine is formed and is purified by distillation *in vacuo* (34). Other synthetic approaches have been used (35).



XXV

Properties. Diphenhydramine is an oil, boiling at 150° to 165° at 2 mm pressure. The hydrochloride is used in therapy and melts at 166° to 168°; it is a white crystalline powder, very soluble in water, ethanol or chloroform.

Bromodiphenhydramine. 2-(4-Bromobenzhydryloxy)-NN-dimethylethylamine. $C_{17}H_{20}ONBr$. (XXV, R=Br).

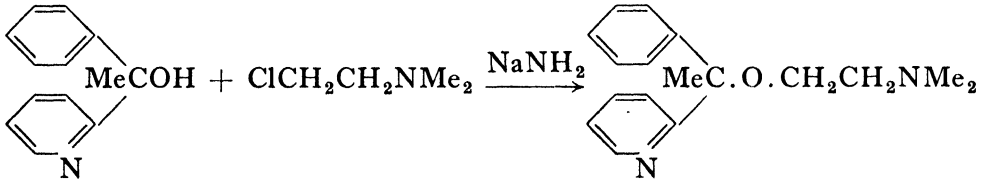
Preparation. Bromodiphenhydramine is a bromo derivative of diphenhydramine and is prepared (36) by a similar method.

Properties. Bromodiphenhydramine hydrochloride melts at 144° to 145°.

Dimenhydrinate is a compound of diphenhydramine and 8-chlorotheophylline; it is used to prevent travel sickness.

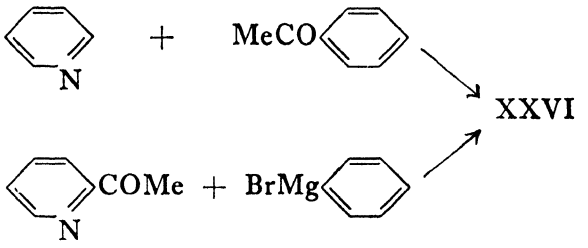
Doxylamine. Dimethylaminoethyl 1-(2-pyridyl)-1-phenylethyl ether. $C_{17}H_{22}ON_2$. (XXVII).

Preparation. Doxylamine is an ether formed by the reaction of methylphenyl-(2-pyridyl)methanol (XXVI) with 1-chloro-2-dimethylaminoethane in an inert solvent such as toluene. The carbinol may be converted to its reactive sodio derivative by means of sodium or sodamide.



XXVI XXVII

The carbinol (XXVI) has been prepared by the following methods.



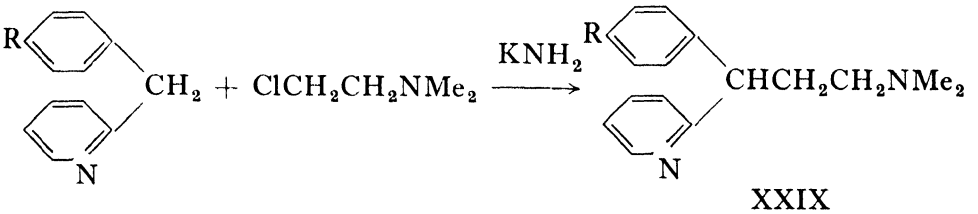
In method (*a*) (37) aluminium activated by mercury, mercuric chloride and a crystal of iodine is stirred at 100°, acetophenone and pyridine are added and refluxed. The reaction mixture, after cooling, is decomposed with caustic alkali, the carbinol is separated and purified by distillation *in vacuo*.

In method (*b*) (38) bromobenzene is converted to magnesium phenyl bromide in ether; to the solution of the Grignard reagent is added 2-acetylpyridine. The reaction mixture is boiled for several hours and decomposed with hydrochloric acid and ice; the aqueous acid layer is made alkaline and the carbinol so obtained is separated and distilled.

Properties. Doxylamine and similar compounds were prepared and tested because it was felt that, since the replacement of the phenyl group in Antergan led to tripelennamine, a similar substitution in diphenhydramine might be of interest. Doxylamine is an oil at ordinary temperatures, boiling at 145° at 0·8 mm pressure. The monohydrochloride melts at 169° to 170° and the succinate at 103° to 104°.

ALKYLAMINES

Prophenpyridamine. Phenitamine. 3-Phenyl-3-(2-pyridyl)-NN-dimethylpropylamine. $C_{16}H_{20}N_2$. (XXIX, R=H).



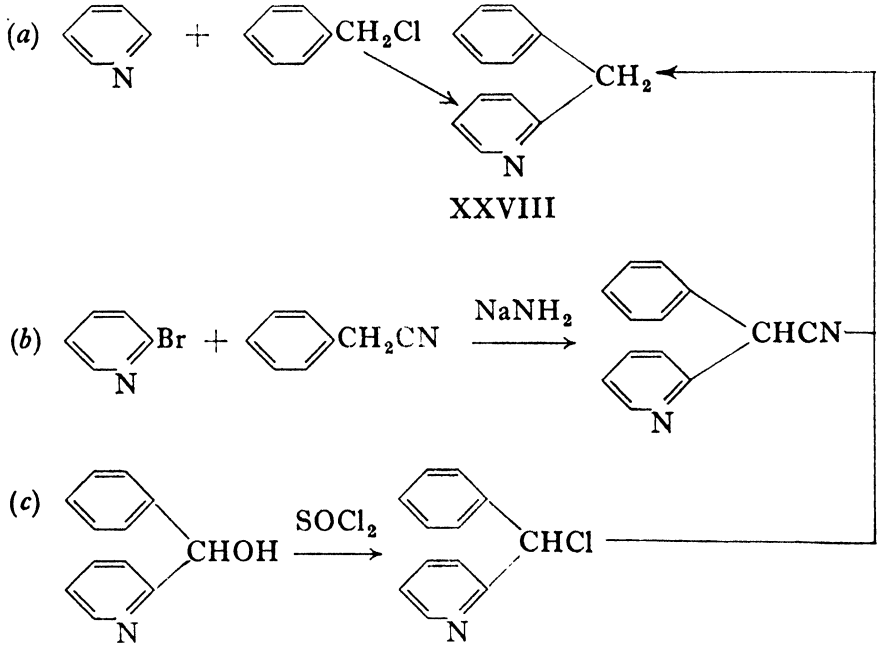
XXIX

Preparation. In one method which is similar to others in the antihistamine group benzyl-2-pyridine (XXVIII) is alkylated with 1-chloro-2-dimethylaminoethane in liquid ammonia in the presence of potassium amide (39). The benzyl-2-pyridine may be prepared by any of the methods shown on p. 104.

(*a*) Pyridine and benzyl chloride are reacted together in the presence of copper powder as catalyst (40); a mixture of isomers is formed and must be separated by fractional distillation (41).

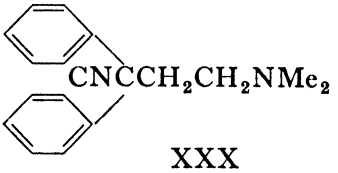
(*b*) 2-Bromopyridine may be combined with benzyl cyanide in the presence of sodamide; the disubstituted methyl cyanide so obtained is easily hydrolysed and decarboxylated (42) to benzyl-2-pyridine.

(*c*) Butyl-lithium (prepared from lithium and butyl chloride) is reacted with 2-bromopyridine forming 2-pyridyl-lithium; this with benzaldehyde at −30° forms phenyl-2-pyridyl carbinol; treatment with thionyl chloride replaces the hydroxyl group by chlorine and reduction with zinc and acetic acid yields benzyl-2-pyridine (43).



XXVIII

An alternative route for the preparation of prophenpyridamine is via 1-phenyl-1-(dimethylaminoethyl)-2-pyridylacetonitrile (XXX).



XXX

This compound is prepared by the alkylation of benzyl cyanide, first with 2-bromopyridine and then with 1-chloro-2-dimethylaminoethane; the compound formed is hydrolysed and decarboxylated to prophenpyridamine by hot 75 per cent sulphuric acid (39). Other methods of synthesis of prophenpyridamine have been explored (44).

Properties. The base is a liquid boiling at 127° to 129° at 1 mm pressure. Prophenpyridamine hydrogen maleate melts at 107° to 108°, the monohydrochloride at 117° to 119° and the dipicrate at 203° to 204°.

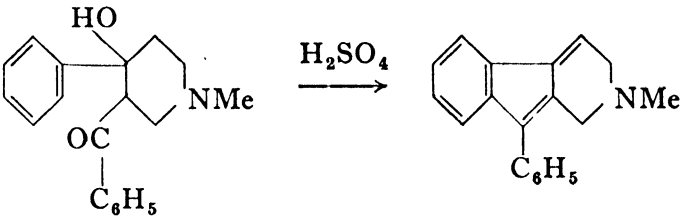
Chlorpheniramine. 3-(*p*-Chlorophenyl)-3-(2-pyridyl)-NN-dimethylpropylamine. $C_{16}H_{19}N_2Cl$. (XXIX, R=Cl).

Preparation. The methods are analogous to those used for prophenpyridamine.

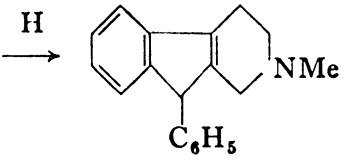
Properties. This antihistamine is a very active compound. It is used as its hydrogen maleate which is a white powder melting at 132·5° to 133°; the hydrogen oxalate melts at 137° to 139°. The base is a liquid at ordinary temperatures and boils at 141° to 143° at 1 mm pressure.

Phenindamine. 1 : 2 : 3: 4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene. $C_{19}H_{19}N$. (XXXIII).

Preparation. 3-Benzoyl-4-hydroxy-N-methyl-4-phenylpiperidine (XXXI) is treated with 65 per cent sulphuric acid and the dihydroazafluorene derivative (XXXII) so obtained (45) is catalytically reduced (46) to phenindamine.

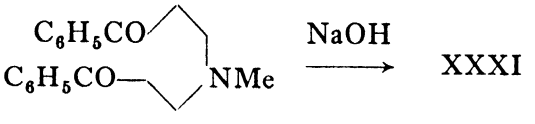


XXXI XXXII



XXXIII

Compound XXXI is prepared (47) by condensing together methylamine, formaldehyde and acetophenone to form bis(2-benzoylethyl)methylamine, which, on treatment with sodium hydroxide solution, gives XXXI by ring closure.



Properties. Phenindamine hydrogen tartrate is the salt used therapeutically; it is a white powder with a bitter taste, soluble in water and almost insoluble in ethanol, ether or chloroform; it melts at 158° to 160°. The hydrochloride melts at 151° to 154°.

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CHAPTER IX

Bactericides and Bacteriostats

A BACTERICIDE kills bacteria whereas a bacteriostat only prevents their growth. Both are included in the term antiseptic. The class of substances called antibiotics includes both bactericidal and bacteriostatic compounds but the term is usually confined to substances produced by living organisms such as penicillin. These are described in Chapter XVII.

Until the discovery of the sulphonamides the known antiseptics were all in differing degrees poisonous to the tissues and, for this reason, could not be introduced into the body. Their use was therefore confined to external application.

Formaldehyde. HCHO.

Preparation. Methanol is subjected to catalytic dehydrogenation. An air-methanol mixture containing approximately 40 per cent of methanol by volume is preheated to 250° and passed through a reactor containing a catalyst which can be silver or copper or a mixture of molybdenum, iron and vanadium oxides at a temperature of 500°, the time of contact being 0·01 seconds. The metallic oxide catalyst gives a very high conversion. The hot gases leaving the converter are cooled and pass to a scrubber. The resulting liquor is fractionated in a column when formaldehyde of about 40 per cent strength is removed from the bottom of the column and unconverted methanol is recovered at the top.

Properties. Formaldehyde is a colourless gas with an irritating odour. It melts at −118° and boils at −19°. It is soluble in water and ethanol but only slightly soluble in acetone, benzene, chloroform and ether. It forms explosive mixtures with air. Both in the gaseous state and in solution formaldehyde readily polymerises. It is commercially available as an aqueous solution containing 37 to 41 per cent of formaldehyde by weight; methanol is present in this solution as a stabiliser. Formaldehyde is a strong reducing agent; it restores the colour to Schiff's reagent and reduces ammoniacal silver nitrate solution to silver.

The two chief polymers of formaldehyde are paraformaldehyde, $HO(CH_2O)_nH$ (where n=8 to 50), and trioxymethylene, $(CH_2O)_3$. The former compound volatilises at 100° and is readily converted into formaldehyde when boiled with water. It has been used in lozenges as a throat antiseptic.

Hexamine. Hexamethylenetetramine. $C_6H_{12}N_4$.

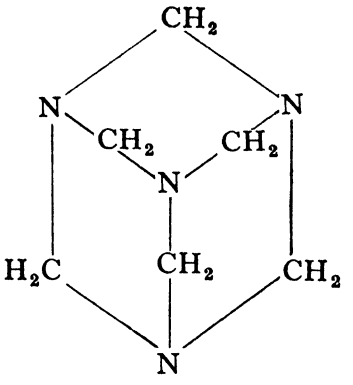
Preparation. Hexamine is formed in high yield when formaldehyde is condensed with ammonia:

$$6HCHO + 4NH_3 \longrightarrow (CH_2)_6N_4 + 6H_2O$$

Ammonia gas in slight excess is led under the surface of aqueous 37 per cent formaldehyde solution kept at 25°. The reaction mixture is then concentrated and crystallisation occurs. The damp crystals are centrifuged, washed with water

and dried. The technical product can be purified by recrystallisation from ethanol or by precipitation from aqueous solution with ammonia.

The structure of hexamine may be represented as:



Hexamine

Properties. Hexamine occurs as colourless crystals or as a white crystalline powder with a sweet taste; it does not melt but sublimes at 230° to 270° under vacuum. It is soluble in water (46·5 g in 100 g at 25° and 43·4 g in 100 g at 70°) and slightly soluble in ether and aromatic hydrocarbons. When it is heated with acids formaldehyde is liberated, while with alkalis ammonia is given off. It has been used as a urinary antiseptic.

PHENOLS AND DERIVATIVES

Phenol. Carbolic acid. C_6H_5OH.

Preparation. Runge discovered phenol in 1834 in the products of coal tar distillation. It is now either extracted from coal tar or prepared synthetically. The first synthetic method, known as the benzenesulphonate process, depended on the sulphonation of benzene with sulphuric acid; the sodium salt of the benzenesulphonic acid so formed was fused with sodium hydroxide to give sodium phenate, which, on acidification, yields phenol. This method is being replaced by the more economical modern processes. Chlorobenzene may be converted to sodium phenate by hydrolysis with sodium carbonate or sodium hydroxide under pressure; another process for the production of synthetic phenol depends on the oxidation of benzene, diphenyl being formed as a by-product.

$$3C_6H_6 + O_2 \longrightarrow C_6H_5OH + C_6H_5.C_6H_5 + H_2O$$

A process by which a great deal of synthetic phenol is made is the Raschig or regenerative process. Benzene is converted in two catalytic stages to phenol by

vapour-phase reactions. Benzene is mixed with air and hydrogen chloride and the mixture is passed at 220° over a supported catalyst formed of copper and iron chlorides. The chlorobenzene obtained in this manner is mixed with water and heated to 500°; phenol is formed by passage over a silica catalyst.

$$2C_6H_6 + 2HCl + O_2 \longrightarrow 2C_6H_5Cl + H_2O$$

$$C_6H_5Cl + H_2O \longrightarrow C_6H_5OH + HCl$$

A little diphenyl ether is obtained as a by-product. A new process recently introduced into Great Britain from the U.S.A. involves the reaction of benzene and propylene to yield cumene or *iso*propylbenzene which, on catalytic oxidation, gives phenol and acetone. This process has the advantage that the acetone obtained as a by-product can be sold.

The preparation from coal tar is effected by washing with dilute sodium hydroxide solution the fraction of the tar distilling between 170° and 230° (known as 'carbolic oil'). When phenol alone is required the tar is washed with sufficient alkali to extract the phenol alone. Some cresol is also extracted, but if the aqueous solution is shaken with another portion of 'carbolic oil' the cresol is replaced by phenol and an almost pure solution of sodium phenate is obtained. The sodium phenate solution is purified by blowing steam through it to remove naphthalene, pyridine and neutral oils. The phenol is then separated from solution by the addition of acid or by blowing in carbon dioxide. The crude phenol is fractionated and further purified by treatment with a small quantity of potassium dichromate and sulphuric acid, and redistilled.

Properties. Phenol forms white crystals which tend to become pink if impure and to absorb moisture from the air; it has a sharp burning taste and a characteristic odour. Pure phenol melts at 42·2°; the commercial product should not freeze below 39°. The boiling-point is 181·4° and the specific gravity is 1·071 at 25°. Phenol is soluble in water (8·2 g in 100 g at 15° and in all proportions above 65·3°); 100 g of phenol dissolve about 25 g of water at 15°; addition of more water causes separation into two layers. Phenol is also soluble in ethanol, ether and chloroform. It behaves as a weak acid and dissolves in alkalis. An aqueous solution gives a violet colour with ferric chloride and a pale yellow precipitate with bromine water of tribromophenol which melts at 93°.

Phenol is an antiseptic but has been superseded by more potent compounds. It is the starting-point in the manufacture of salicylic acid, phenacetin and many other compounds.

Cresol. Hydroxytoluene. $CH_3.C_6H_4.OH$.

Preparation. Commercial cresol or cresylic acid is a product of the coal-tar industry and is a mixture of the *o*-, *m*- and *p*- forms. The cresols are extracted from the 'creosote oil' fraction of coal tar by sodium hydroxide. The sodium salts are converted to the crude cresols by adding sulphuric acid and the separated product is fractionally distilled; the *o*- isomer can be obtained from the mixture by further fractionation but the *m*- and *p*- isomers are more difficult to separate.

Properties. The three isomers have the following properties:

o-Cresol is a white crystalline solid melting at 38° and boiling at 190·8°; it is soluble in ethanol, ether and chloroform and slightly soluble in water (2·5 g in 100 g at 20°).

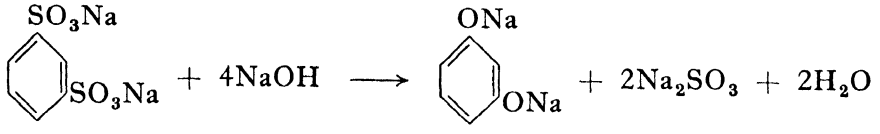
m-Cresol is a colourless liquid boiling at 202·8°; it melts at 10·9°.

p-Cresol is a white crystalline solid melting at 36° and boiling at 202°.

Purified cresol is largely used for the manufacture of Lysol which contains 50 per cent of cresol dissolved in a solution of soap. Many alkyl derivatives of cresol, of which 4-amyl-*m*-cresol is an example, have higher bactericidal values than cresol. For chlorocresol see p. 112.

Resorcinol. Resorcin. 1 : 3-Dihydroxybenzene. $C_6H_4(OH)_2$.

Preparation. The di-sodium salt of benzene-1 : 3-disulphonic acid is reacted with fused sodium hydroxide and the product is acidified.



The disulphonic acid is prepared by reacting fuming sulphuric acid with boiling benzene to give the monosubstituted compound and then heating the latter at 275° with fuming sulphuric acid which converts it to benzenedisulphonic acid.

Properties. Resorcinol occurs as white crystals with a faint characteristic odour. It melts at 110°. It dissolves readily in water, ethanol or ether. Resorcinol gives a red colour when warmed with nitric acid and a dark violet colour with ferric chloride solution. It reduces ammoniacal silver nitrate solution and Fehling's solution and gives a heavy precipitate of dibromoresorcinol (m.p. 112°) with bromine water. When fused with an equal weight of phthalic anhydride, dissolved in dilute sulphuric acid and poured into water a yellowish-green fluorescence, due to the formation of fluorescein, is produced.

Hexylresorcinol. 4-*n*-Hexylresorcinol. $C_{12}H_{18}O_2$. (II).

Preparation. Hexoic acid (caproic acid) is reacted at 140° with resorcinol in the presence of zinc chloride. Hexoylresorcinol (I) is thus obtained and is purified by distillation *in vacuo* and crystallisation from toluene and light petroleum. This intermediate is then reduced with aluminium amalgam in ethanolic hydrochloric acid to hexylresorcinol (II).

$(HO)_2C_6H_3CO(CH_2)_4CH_3$ I $\qquad$ $(HO)_2C_6H_3(CH_2)_5CH_3$ II

Properties. Hexylresorcinol forms colourless crystals that melt at 67·5° to 69°. It has been used as a urinary antiseptic and as an anthelmintic.

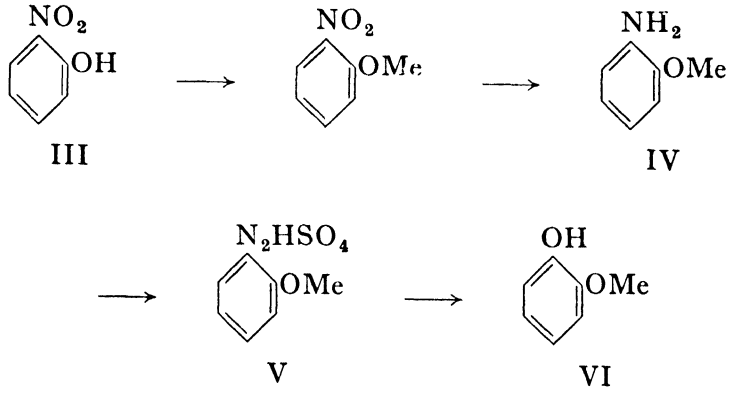
Creosote. The creosote used in medicine is obtained by the fractional distillation of beechwood tar. It contains a mixture of phenolic compounds of which the chief are guaiacol (q.v.) and creosol which is 4-hydroxy-3-methoxy-

1-methylbenzene. Methyl ethers of trihydroxyphenols, for example the dimethyl ether of pyrogallol, are also present in creosote.

Properties. Creosote is a nearly colourless liquid with a strong characteristic odour. The specific gravity is 1·070 to 1·087 and it distils between 200° and 230°. It is optically inactive.

Guaiacol. The monomethyl ether of 1 : 2-dihydroxybenzene. $C_7H_8O_2$. (VI).

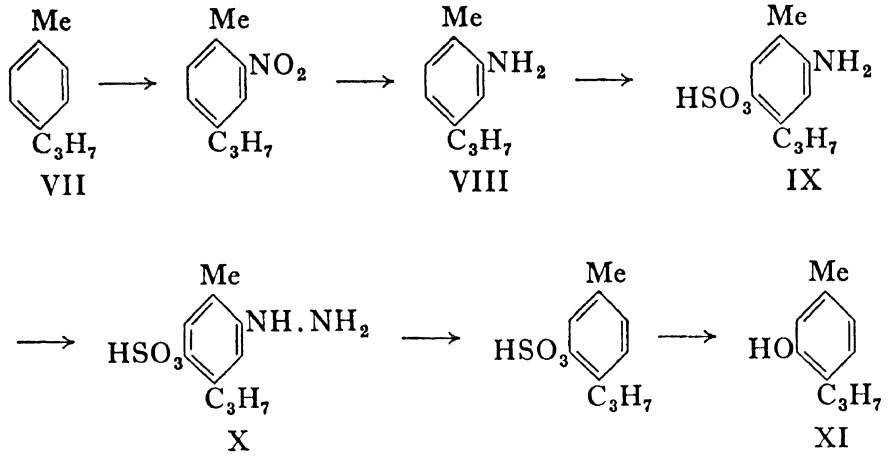
Preparation. Guaiacol may be obtained directly from wood tar produced by the destructive distillation of hardwood or by the fractionation of creosote. It may also be prepared synthetically by the methylation of catechol in an alkaline medium with methyl sulphate or by the following process. *o*-Nitrophenol (III) is methylated with methyl sulphate in the presence of sodium hydroxide; the *o*-nitroanisole so obtained is reduced with iron and hydrochloric acid to *o*-aminoanisole (IV) which is purified by distillation *in vacuo*. It is diazotised with sodium nitrite and sulphuric acid and the diazo compound (V) is converted to guaiacol (VI) by steam distillation.



Properties. Synthetic guaiacol forms colourless crystals melting at 28·5° and boiling at 203°. The product from creosote is liquid at ordinary temperatures. It is slightly soluble in water and readily soluble in most organic solvents. An ethanolic solution gives a blue colour with ferric chloride solution.

Thymol. 6-*iso*Propyl-*m*-cresol. $C_{10}H_{14}O$. (XI).

Preparation. Thymol is present in volatile oils of thyme and of ajowan seeds from which it may be extracted with sodium hydroxide, liberated from the sodium compound with acid and purified by crystallisation. Many synthetic routes to thymol begin with *p*-cymene (VII) which is a by-product of the sulphite treatment of wood pulp. The following method has been patented (1). *p*-Cymene is nitrated in the 2-position and the nitro compound is reduced to 2-amino-*p*-cymene (VIII) which is converted to the 2-amino-5-sulphonic acid (IX); this is diazotised and reduced to 2-hydrazino-*p*-cymene-5-sulphonic acid (X). The $NH.NH_2$ group is removed with copper sulphate and the sulphonate group is converted to a phenolic hydroxyl group with potassium hydroxide. Thymol may also be obtained by a Friedel-Craft reaction on *m*-cresol (2).



VII VIII IX X XI

Properties. Thymol occurs as colourless crystals with an odour of thyme. It melts at 51° and boils at 232° at 752 mm. The phenylurethane melts at 107° and the nitroso compound at 161°. Thymol dissolves in alkalis, and on addition of chloroform a violet colour is produced.

CHLOROPHENOLS

Chlorocresol. 6-Chloro-3-hydroxytoluene. $CH_3(C_6H_3)OH.Cl$ (1 : 3 : 6).

Preparation and properties. Chlorocresol is prepared by the chlorination of *m*-cresol. It melts at 65° and is only slightly soluble in water (1 in 250) but is readily soluble in organic solvents. Aqueous solutions are strongly bactericidal; it is mainly used for the preservation of injection solutions.

Chloroxylenol. 2-Chloro-5-hydroxy-1 : 3-dimethylbenzene.

$(CH_3)_2C_6H_2(Cl)OH$.

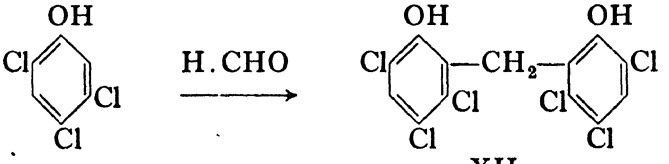
Preparation and properties. Chloroxylenol is prepared by the action of sulphuryl chloride on xylen-5-ol. It melts at 115·5° to 116° and is only slightly soluble in water (1 in 3000), more soluble in boiling water (1 in 200), in soap solutions and in organic solvents.

Chloroxylenol is a powerful and non-irritant bactericide and is used as a constituent of antiseptic solutions.

Hexachlorophane. 2 : 2′-Methylenebis(3 : 4 : 6-trichlorophenol).

$C_{13}H_6Cl_6O_2$. (XII).

Preparation. Trichlorophenol is condensed with formaldehyde in methanol at 0° to 5° and the crude reaction product is recrystallised from benzene or ethylene dichloride (3).



XII

Properties. Hexachlorophane occurs as a white odourless crystalline powder that is readily soluble in acetone, ethanol and ether but insoluble in water; it melts at 162°. Hexachlorophane was introduced in 1944 and is incorporated into soaps, lotions and creams for cleansing and disinfecting the skin.

MERCURY COMPOUNDS

Soon after the introduction of phenol as a disinfectant for wounds mercuric chloride was used for the same purpose but, on account of its irritating properties, it can only be used in high dilution; it is more useful as a skin disinfectant. In order to overcome these drawbacks many organic mercury compounds have been introduced. While some of these are powerful antiseptics their efficacy is often considerably reduced in the presence of blood serum. The antibacterial power is stated to depend on the $C_6H_5Hg^+$ cation.

Phenylmercury nitrate. $C_6H_5HgNO_3$.

Preparation. Pure phenylmercury nitrate is obtained when mercuric nitrate reacts with excess of benzene in the presence of mercuric oxide and calcium sulphate; these two compounds prevent the secondary effects of the nitric acid and water formed in the reaction (4). The mercuration of benzene is preferably carried out in an atmosphere of carbon dioxide with high-speed stirring.

Older methods for the preparation of phenylmercury nitrate (5, 6) lead to a mixture of the nitrate and the hydroxide.

Properties. Phenylmercury nitrate melts at 131° to 131·5° (corr.). It is soluble in benzene, ethanediol and diethyleneglycol monoethyl ether (Carbitol), but insoluble in water. When treated with potassium iodide a solution of phenylmercury nitrate in acetone gives crystals of phenylmercury iodide, m.p. 264·5° to 266° (corr.).

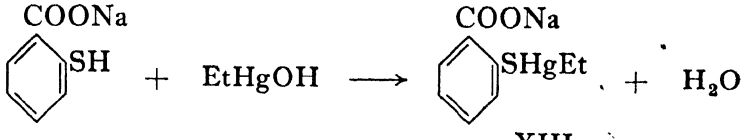
Phenylmercury acetate. $C_6H_5HgOOC.CH_3$.

Preparation. Mercuric acetate is heated for two or three hours at 95° with benzene in the presence of glacial acetic acid (7).

Thiomersal. Thimerosal. Sodium ethylmercurythiosalicylate.

$C_9H_9O_2SHgNa$. (XIII).

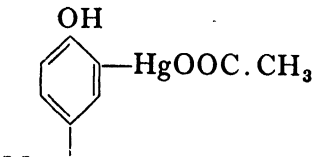
Preparation. Mercuric chloride is reacted with ethylmagnesium bromide and the ethylmercury chloride obtained is converted to the hydroxide by sodium hydroxide. Sodium thiosalicylate and ethylmercury hydroxide are then reacted together to give thiomersal (8). The free acid melts at 110°.



XIII

Acetomeroctol. 2-Acetoxymercury-4-(1 : 1 : 3 : 3-tetramethylbutyl)-phenol. $C_{16}H_{24}O_3Hg$. (XIV).

Preparation. The parent phenol is reacted with the calculated quantity of mercuric acetate in aqueous ethanol containing glacial acetic acid. The crude product is crystallised from the same solvent mixture (9).

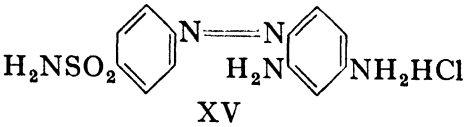


XIV

Properties. Acetomeroctol is a white solid melting at 158°. It is soluble in ethanol, ether and chloroform, sparingly soluble in benzene and insoluble in water. It is used in an acetone - ethanol solution as a topical antiseptic.

SULPHONAMIDES

4-Aminobenzenesulphonamide, now known as sulphanilamide, was first synthesised in 1908 (10), but the therapeutic value of this type of compound was not appreciated until in 1935 Domagk (11) showed that a new azo dyestuff, 4-sulphamido-2′ : 4′-diaminoazobenzene possessed highly protective properties when injected in cases of experimental streptococcal infections in mice. The new compound, called Prontosil rubrum (XV) had been made in 1932 by Mietzsch and Klarer and its preparation was patented in 1935 (12).



XV

In 1935 workers at the Pasteur Institute in Paris (13) showed that Prontosil rubrum is broken down in the body to 4-aminobenzenesulphonamide which had the therapeutic properties of the parent compound. In the following year British workers, Colebrook and Kenny (14) and Buttle and his colleagues (15) published clinical results on the use of Prontosil and sulphanilamide in blood infections. Their success was remarkable since, up to that time, no drug was known that could be absorbed into the bloodstream and combat infections without damage to the blood cells. Since 1936 research has been directed towards the preparation of more active and less toxic sulphonamide compounds.

Modern theories of the mode of action of these drugs are based on observations made by Woods and Fildes (16) in 1940. They suggested that, by virtue of its structural similarity to 4-aminobenzoic acid, sulphanilamide could replace it in certain enzyme systems. Bell and Roblin in 1942 (17) linked ionisation and therapeutic activity and showed that the bacteriostatic power of a sulphonamide of the type $R.NH.SO_2.C_6H_4.NH_2$ was proportional to the negative charge on the SO_2 group.

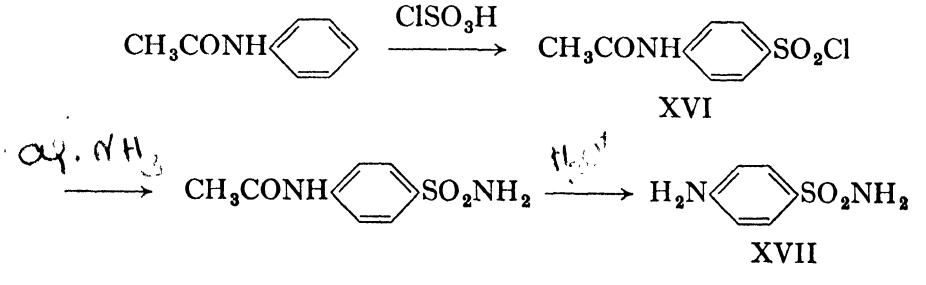
Sulphonamide drugs in use today are all substituted amides. Sulphanilamide itself has fallen out of use except as a dusting powder because of its liability to cause toxic side-effects. Even with the more modern derivatives mild toxic effects are not uncommon. The comparative solubilities of the sulphonamides are shown in the following table:

Drug	Solubility in water g per 100 ml	
	16–17°	37°
Sulphanilamide	0·44	1·48
Sulphacetamide	0·46	1·10
Sulphapyridine	0·017	0·054
Sulphathiazole	0·036	0·096
Sulphadiazine	0·008	0·012
Sulphadimidine	—	0·062
Sulphamerazine	—	0·032
Sulphaguanidine	—	0·220
Succinylsulphathiazole	—	0·070

The solubility generally increases in alkaline solution. The sodium compounds of sulphapyridine, sulphadiazine, sulphacetamide and sulphathiazole are used where increased solubility is required. In addition radicals attached to the 4-amino group have been used to confer increased solubility on the molecule and for this purpose the aldehyde bisulphite, the formaldehyde sulphoxylate and the hexose derivatives have been used.

Sulphanilamide. 4-Aminobenzenesulphonamide. $C_6H_8N_2O_2S$. (XVII).

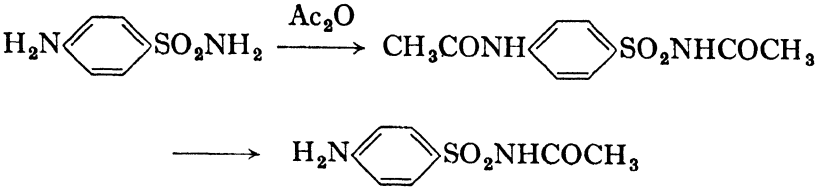
Preparation. 4-Acetylaminobenzenesulphonyl chloride (XVI) is made by the sulphonation of acetanilide with chlorosulphonic acid (18) and is reacted with aqueous ammonia to yield the corresponding amide. The acetyl group is then hydrolysed and sulphanilamide is obtained (19).



Properties. Sulphanilamide is a white crystalline powder that is slightly soluble in water, more soluble in solutions of alkali hydroxides, sparingly soluble in ethanol and insoluble in ether and chloroform. It melts at 164·5° to 166·5°.

Sulphacetamide. 4-Aminobenzenesulphonacetamide. $C_8H_{10}N_2O_3S$. (XVIII).

Preparation. Sulphacetamide was first prepared by Dohrn and Diedrich (20) in 1938 and independently by Northey (21). When sulphanilamide is acetylated by acetic anhydride a diacetyl derivative is obtained; the acetyl group attached to the amino nitrogen can be removed by careful hydrolysis (22) and sulphacetamide is obtained.

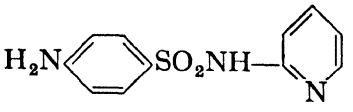


XVIII

Properties. Sulphacetamide is slightly soluble in water, more soluble in ethanol or acetone, mineral acids and solutions of alkali carbonates; it is insoluble in ether. It melts at 181° to 184°. The sodium compound is used in local infections of the eye.

Sulphapyridine. 2-(4-Aminobenzenesulphonamido)pyridine. $C_{11}H_{11}N_3O_2S$. (XIX).

Preparation. Sulphapyridine was first made by Ewins and Phillips (23) and was synthesised independently by workers in the U.S.A. (24) and in the U.S.S.R. (25). It was the first heterocyclic sulphonamide to be introduced for therapeutic use. 2-Aminopyridine is condensed with 4-acetylaminobenzenesulphonyl chloride and the acetyl group is removed by hydrolysis.

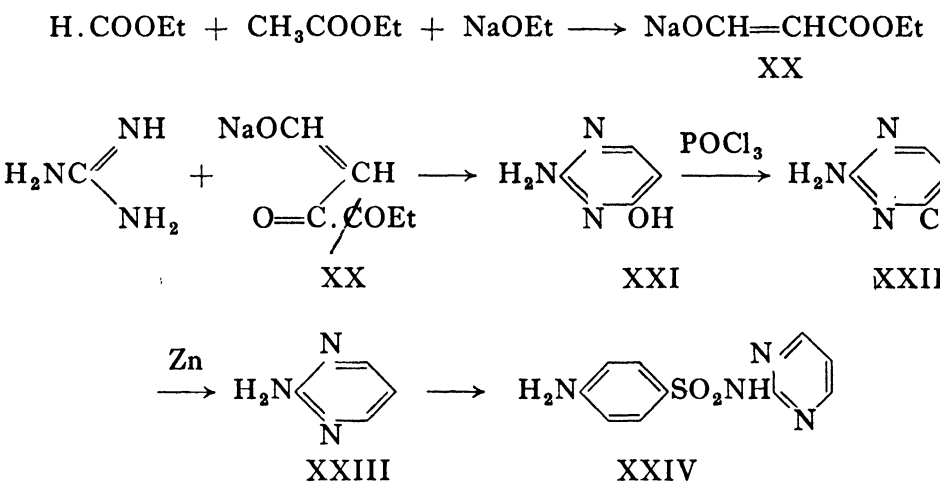


XIX

Properties. Sulphapyridine is a white crystalline powder, very sparingly soluble in water but more soluble in hot water; it dissolves in ethanol, acetone and mineral acids and in aqueous alkali hydroxides. It melts at 191° to 193°.

Sulphadiazine. 2-(4-Aminobenzenesulphonamido)pyrimidine. $C_{10}H_{10}N_4O_2S$. (XXIV).

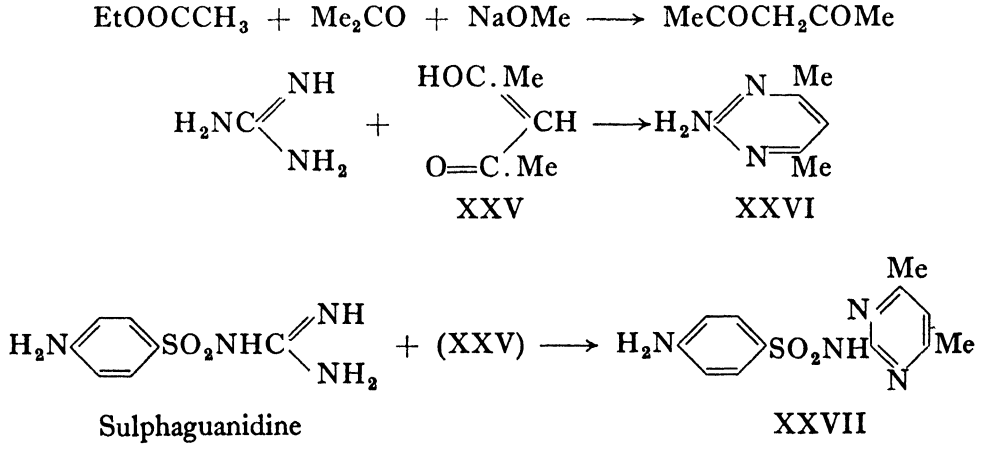
Preparation. This compound was prepared by Roblin in 1940 (26) and is made by the usual method from 2-aminopyrimidine (27). 2-Aminopyrimidine is made commercially (28) by the reaction of ethyl formate and ethyl acetate in the presence of sodium ethoxide to give sodium formylacetic ester (XX); this is condensed with guanidine and the *iso*cytosine obtained (XXI) is reacted with phosphorus oxychloride and chlorosulphonic acid to give 2-amino-4-chloropyrimidine (XXII); this is dechlorinated with zinc dust in the presence of ammonia and sodium bicarbonate forming 2-aminopyrimidine (XXIII).



Properties. Sulphadiazine melts at 252° to 256°. It is a white powder that darkens on exposure to light. It is soluble in hot water, in mineral acids and in alkali hydroxide solutions. It is sparingly soluble in ethanol and acetone and insoluble in ether or chloroform.

Sulphadimidine. 2-(4-Aminobenzenesulphonamido)-4 : 6-dimethylpyrimidine. $C_{12}H_{14}N_4O_2S$. (XXVII).

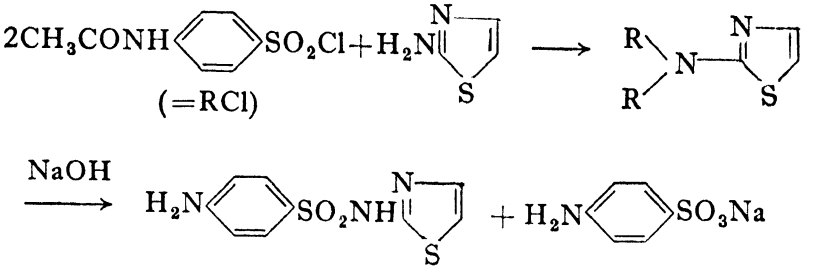
Preparation. 2-Amino-4 : 6-dimethylpyrimidine (XXVI) is converted to sulphadimidine by the same process as is used for the preparation of sulphapyridine (29, 30, 31). The 2-amino-4 : 6-dimethylpyrimidine is obtained by the condensation of acetylacetone (XXV) (made from ethyl acetate and acetone) with a guanidine salt. In an alternative synthesis (32) of sulphadimidine acetylacetone is condensed with sulphaguanidine.



Properties. Sulphadimidine melts at 196° to 199°. It is a white powder, soluble in acetone, slightly soluble in ethanol or water and freely soluble in mineral acids or aqueous solutions of alkali hydroxides.

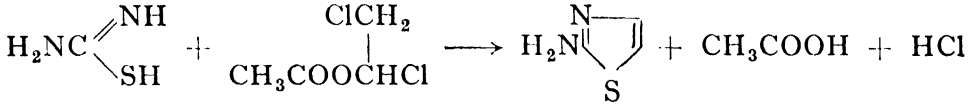
Sulphathiazole. 2-(4-Aminobenzenesulphonamido)thiazole. $C_9H_9N_3O_2S_2$. (XXVIII).

Preparation. Sulphathiazole was introduced by two groups of workers at about the same time (33, 34). In Great Britain and the U.S.A. the usual manufacturing method has been based on the reaction of dry 4-acetylaminobenzenesulphonyl chloride in dry pyridine with 2-aminothiazole and the hydrolysis of the resulting acetylsulphathiazole. This involves drying the acid chloride and aminothiazole and recovering the pyridine. In German practice the moist raw materials and no pyridine are used (35). Under these conditions a disulphonyl derivative of aminothiazole forms and one benzenesulphonyl group is wasted on hydrolysis.



XXVIII

The 2-aminothiazole required for the manufacture of sulphathiazole was formerly obtained by the reaction of thiourea with 1 : 2-dichloroethyl ether, but now most 2-aminothiazole is manufactured from vinyl acetate, which is chlorinated at −5° to form 1 : 2-dichloroethyl acetate (XXIX) and this is condensed with thiourea with the formation of 2-aminothiazole (36).

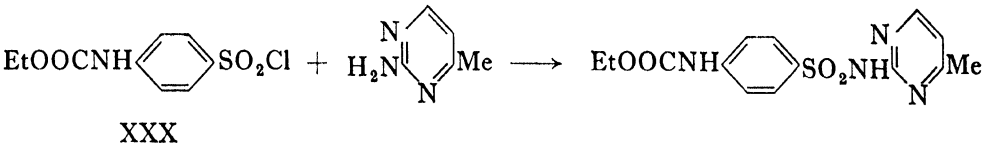


XXIX

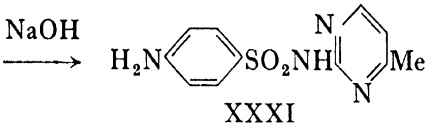
Properties. Sulphathiazole is a white powder melting at 200° to 203°; it is almost insoluble in water, slightly soluble in ethanol and soluble in mineral acids and in aqueous solutions of alkali hydroxides and carbonates.

Sulphamerazine. 2-(4-Aminobenzenesulphonamido)-4-methylpyrimidine. $C_{11}H_{12}N_4O_2S$. (XXXI).

Preparation. 2-Amino-4-methylpyrimidine is converted by the same procedures as are used for the preparation of sulphapyridine (26, 37). Instead of 4-acetylaminobenzenesulphonyl chloride, carbethoxyaminobenzenesulphonyl chloride (XXX) has been used (38). The 2-amino-4-methylpyrimidine may be obtained by condensing ethyl acetoacetate with guanidine carbonate and then following the procedure described under sulphadiazine for the preparation of 2-aminopyrimidine (39). Other routes have also been used (40).



XXX

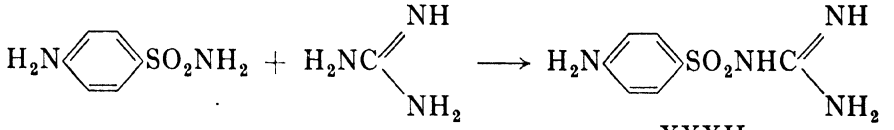


XXXI

Properties. Sulphamerazine melts at 235° to 239° (dec.). It is a white powder but may darken on exposure to light. It is almost insoluble in water, ether or chloroform and sparingly soluble in ethanol; it dissolves in mineral acids or in solutions of alkalis.

Sulphaguanidine. 4-Aminobenzenesulphonylguanidine hydrate. $C_7H_{10}N_4O_2S.H_2O$. (XXXII).

Preparation. 4-Acetylaminobenzenesulphonyl chloride may be condensed with guanidine nitrate in the presence of sodium hydroxide and the acetyl group removed by acid hydrolysis (41). Alternatively the acetylated compound is obtained on fusing 4-acetylaminobenzene sulphonamide and dicyanodiamide at 205° (42). A more direct method is that by which equimolecular quantities of sulphanilamide and guanidine carbonate are heated in an autoclave at 200° and the crude reaction product is then purified (43).

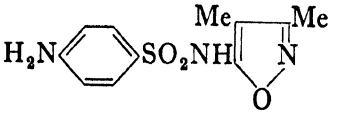


XXXII

Properties. Sulphaguanidine is a white crystalline powder which melts at 190° to 192·5°. It is soluble in hot water and sparingly soluble in cold water, ethanol or acetone; it dissolves in mineral acids but is insoluble in alkalis.

Sulphafurazole. Sulfisoxazole. 5-(4-Aminobenzenesulphonamido)-3 : 4-dimethylisoxazole. $C_{11}H_{13}N_3O_3S$. (XXXIII).

Preparation. The usual method may be used (44) in which 4-acetylaminobenzenesulphonyl chloride is reacted with 3 : 4-dimethyl-5-aminoisoxazole in pyridine and the acetylated compound obtained is hydrolysed to form sulphafurazole.



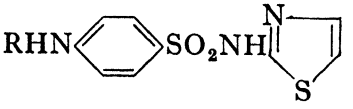
XXXIII

Properties. Sulphafurazole is a white powder melting at 192° to 195°. It is soluble in water and has a high solubility in urine and is useful in combating urinary infections.

Succinylsulphathiazole. 2-(4-Succinylaminobenzenesulphonamido)thiazole monohydrate. $C_{13}H_{13}N_3O_5S_2.H_2O$. (XXXIV).

Preparation. First prepared by Moore and Miller in 1942 (45) by the reaction of sulphathiazole with succinic acid or succinic anhydride, succinylsulphathiazole can also be obtained by reacting 4-succinylaminobenzenesulphonyl chloride with 2-aminothiazole (46).

Properties. Succinylsulphathiazole is a white powder that darkens on exposure to light; it melts at 188° to 195° (dec.). It is soluble in aqueous alkalis and sparingly soluble in ethanol and acetone but almost insoluble in water. It is absorbed only to a very small extent in the alimentary tract and is used for the treatment of bacillary dysentery.



XXXIV R=HOOC.$(CH_2)_2$CO—
XXXV R=HOOC.C_6H_4.CO—

Phthalylsulphathiazole. 2-(4-Phthalylaminobenzenesulphonamido)thiazole. $C_{17}H_{13}N_3O_5S_2$. (XXXV).

Preparation. The method is similar to that for succinylsulphathiazole (45, 46).

Properties. Phthalylsulphathiazole does not melt normally but chars at about 260°. It is a white powder, insoluble in water and chloroform and slightly soluble in ethanol. It resembles succinylsulphathiazole in its action but its bacteriostatic activity is about twice as great.

CATIONIC ANTISEPTICS

This group of therapeutic agents includes some quaternary ammonium compounds, the basic dyes and the acridine antiseptics.

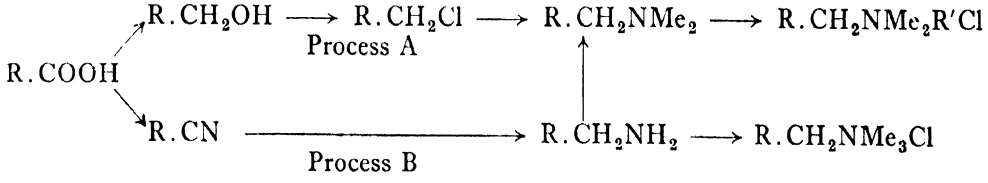
Quaternary Ammonium Compounds

The antibacterial properties of quaternary compounds was first observed in the late nineteenth century when the carbonium dyestuffs such as auramin, methyl violet and malachite green were found to be active. In 1916 Jacobs and later Browning investigated some quaternary compounds for therapeutic use, but it was the work of Domagk in 1935 (47) that really stimulated research into these compounds. He showed that a quaternary ammonium salt containing a long aliphatic group had very useful germicidal properties. Nowadays this group of compounds is commercially important and many are available for use (48).

The general formula for the quaternary ammonium compounds is $(R_1R_2R_3R_4N)^+.X^-$, where the nitrogen atom is positively charged and X is an anionic group such as chloride or bromide. The complex cation is responsible for the antibacterial activity resident in the molecule and the anion may be changed without affecting this activity. The positively charged cation confers

detergent properties on the molecule and it is this combination of detergency and antibacterial activity that makes these compounds valuable. They are used for the cleansing of wounds as well as for the sterilisation of dairy and domestic utensils. Since the activity is due to the free cation any factor suppressing ionisation lowers activity as, for instance, soaps, anionic detergents and acids.

The methods of preparation of these compounds usually follow a standard pattern. An amine is alkylated with an alkyl halide and the product purified. The two major industrial routes starting from a long-chain fatty acid R.COOH are shown below. In process A the acid is converted to an ester and thence by reduction to the alcohol. Reaction with hydrochloric acid furnishes the alkyl halide which is reacted, first with a secondary amine and then with an aralkyl halide. In process B the acid is reacted with ammonia to give the nitrile which on reduction yields the primary amine and this may be alkylated to form the final product. Process A may be linked to process B by the alkylation of the primary amine $R.CH_2NH_2$ to the tertiary amine $R.CH_2NR_2$. This step is carried out by the Eschweiler reductive alkylation method by the use of formic acid and formaldehyde as reagents when a dimethylated amine is required.



A review of quaternary ammonium germicides has been published by De Benneville (49).

Benzalkonium chloride. Alkylbenzyldimethylammonium chloride. $(C_6H_5CH_2NMe_2R)Cl$ where R is between C_8H_{17} and $C_{18}H_{37}$.

Preparation. Process A above is used. The corresponding sulphonate has also been used (50).

Properties. This compound is not a single chemical entity because the alkyl chloride used is impure. Benzalkonium chloride is a white amorphous powder with a bitter taste. It is very soluble in water and foams in solution; it is also soluble in ethanol or acetone and slightly soluble in benzene.

Cetrimide. Hexadecyltrimethylammonium bromide. $C_{19}H_{42}BrN$. (XXXVI).

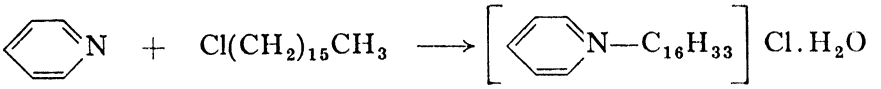
Preparation. Hexadecylamine is reductively methylated to dimethylhexadecylamine which, when reacted with methyl bromide under pressure (51, 52), yields cetrimide.

$$C_{16}H_{33}NMe_2 \xrightarrow{MeBr} C_{16}H_{33}NMe_3Br$$

Properties. Cetrimide is a white non-hydroscopic powder melting at 235° to 237°. It is very soluble in water; the solubility curve has been determined (53, 54). The chloride is known as *cetrimonium chloride* and melts at 228° (dec.); the nitrate melts at about 195°.

Cetylpyridinium chloride. $C_{21}H_{40}ClNO$. (XXXVII).

Preparation. Pyridine is alkylated with hexadecyl chloride (55).



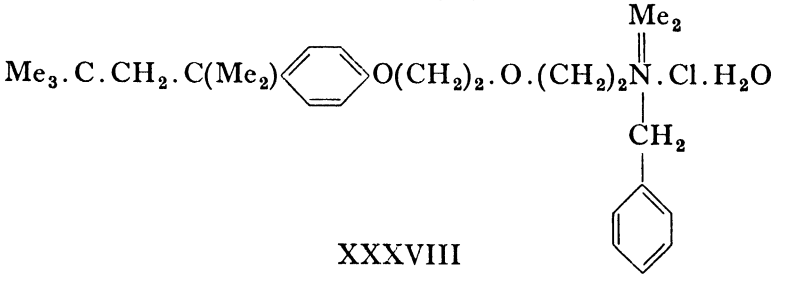
XXXVII

Properties. It is a white powder, soluble in water, ethanol and chloroform. The monohydrate melts at 80° to 83°.

Benzethonium chloride. Benzyldimethyl { 2-[2-(*p*-1 : 1 : 3 : 3-tetramethylbutylphenoxy) ethoxy] ethyl } ammonium chloride monohydrate.

$C_{27}H_{42}NO_2Cl.H_2O$. (XXXVIII).

Preparation. Phenol with the appropriate paraffin chain in the 4-position is reacted with dichloroethyl ether. The product obtained is reacted first with dimethylamine, then with benzyl chloride (56).



XXXVIII

The product is a white water-soluble powder with a bitter taste.

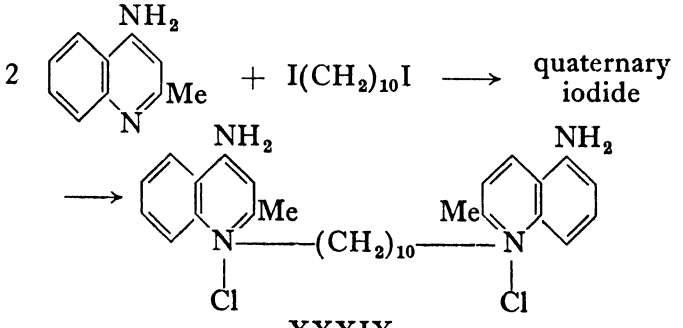
Domiphen bromide. Phenoxyethyldimethyldodecylammonium bromide. $C_{22}H_{40}BrNO$.

Preparation. Phenoxyethyldimethylamine is reacted with dodecyl bromide for 2 hours on a water-bath (57).

Properties. Domiphen bromide is a white powder melting at 112°; it has a bitter taste. At 20° 1 part dissolves in less than 2 parts of water or ethanol and in 30 parts of acetone. The aqueous solution is neutral in reaction and is stable towards acids and alkalis. The chloride melts at 129° to 130° (58).

Dequalinium chloride. Decamethylene-1 : 10-bis(4-aminoquinaldinium) dichloride. $C_{30}H_{40}Cl_2N_4$. (XXXIX).

Preparation. 4-Aminoquinaldine is quaternised by 1 : 10-diiododecane and the resultant quaternary iodide is converted to the chloride by reaction with silver chloride in methanol (59).

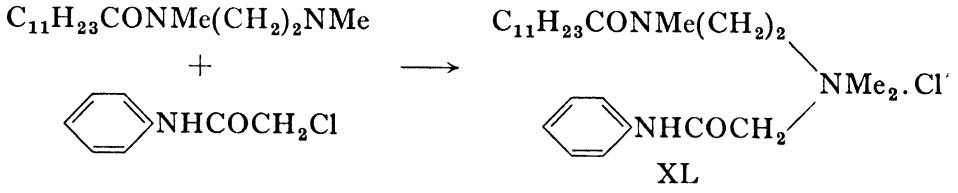


XXXIX

Properties. The compound is a white powder with a bitter taste melting at 320° (dec.) and is slightly soluble in water (0·5 g. per 100 g.) at room temperature. The iodide melts at 306° (dec.) and the nitrate at 299° to 301° (dec.). This antimicrobial agent was introduced in 1956.

Dimethyl(2 - N - methyldodecanamidoethyl)phenylcarbamoylmethyl chloride. $C_{25}H_{44}ClN_3O_2$. (XL).

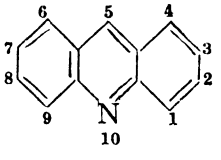
Preparation. The appropriate tertiary amine is reacted with phenylcarbamoylmethyl chloride (60) in boiling ethyl acetate. The product may be recrystallised from acetone and then melts at 124°.



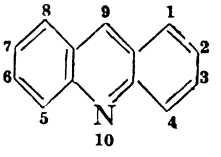
XL

ACRIDINE DERIVATIVES

A number of aminoacridines are in use as antiseptics, the most important being acriflavine, proflavine, 2 : 7-diaminoacridine and aminacrine. The numbering of the acridine ring is likely to cause confusion. The system usual in this country is A, but in the U.S.A. system B is used.



A



B

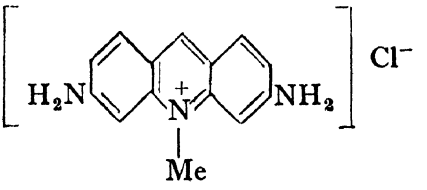
A thorough investigation of the aminoacridines by Albert, Linnell and others has revealed that there are certain relations between their chemical constitution and pharmacological action (61). In this series is found a classic example of a positive correlation between ionisation and biological activity. Chemical structure in the series is unimportant except in so far as it renders a compound more or less basic, i.e. more or less able to form the acridinium cation.

The discovery of the antibacterial properties of acridines arose accidentally from Ehrlich's search for trypanocides; the trypanocidal properties of tryparosan (a fuchsin-type dye) were found to be dependent on the presence of a small amount of acridines as impurities. All the available acridine dyes were tested and acriflavine was synthesised. This work was done in 1912 (62). The outbreak of war in 1914 led to an increased demand for antibacterials and Browning (63) introduced proflavine and acriflavine. The war of 1939–45 led to the introduction of aminacrine (64).

Acriflavine. 2 : 8-Diamino-10-methylacridinium chloride. $C_{14}H_{14}N_3Cl$. (XLI).

Preparation. This substance was first made by Benda in 1912 (62) by

methylating diacetylated 2 : 8-diaminoacridine with methyl *p*-toluenesulphonate and hydrolysing the acetyl groups with hydrochloric acid. In a second method dimethyl sulphate is used as alkylating agent (65). A modern approach avoids the acetylation and hydrolysis. Proflavine base is methylated with methyl sulphate in nitrobenzene; addition of hydrochloric acid to the product gives the dihydrochloride which is converted to free acriflavine base by the addition of sodium carbonate (66).

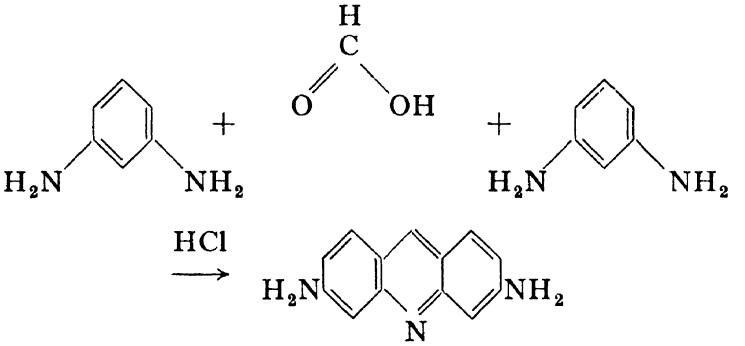


XLI

Properties. The name has often been applied also to the monohydrochloride. The commercial product is a mixture of the hydrochlorides of 2 : 8-diamino-10-methylacridinium chloride and 2 : 8-diaminoacridine and contains approximately one-third of its weight of 2 : 8-diaminoacridine dihydrochloride. It therefore has no definite melting-point. Proflavine hemisulphate is now more often used.

Proflavine. 2 : 8-Diaminoacridine. $C_{13}H_{11}N_3$. (XLII).

Preparation. Proflavine is most easily prepared by the one-stage reaction between *m*-phenylenediamine, formic acid, glycerin and concentrated hydrochloric acid (66, 67). Oxalic acid may be used instead of formic acid and is converted to the latter compound *in situ*. The overall reaction is catalysed by hydrogen ions.



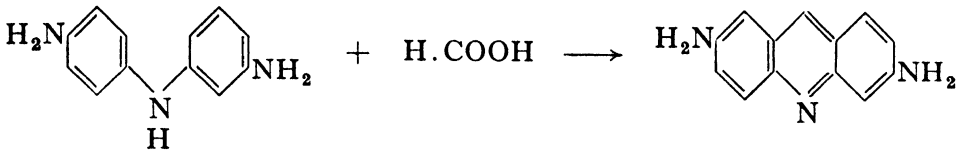
XLII

Properties. Proflavine base melts at 276° (sealed tube). The *hemisulphate*, $B_2H_2SO_4H_2O$, is the salt usually used; this is an orange crystalline powder, soluble in water (1 in 150), in boiling water (1 in 1) and in glycerin (1 in 32). A dilute aqueous solution shows a green fluorescence.

2 : 7-Diaminoacridine. $C_{13}H_{11}N_3$. (XLIII).

Preparation. This compound is made by a method similar to that used for the

2 : 8- isomer. 3 : 4-Diaminodiphenylamine, glycerin, formic acid and concentrated hydrochloric acid are heated together (68).

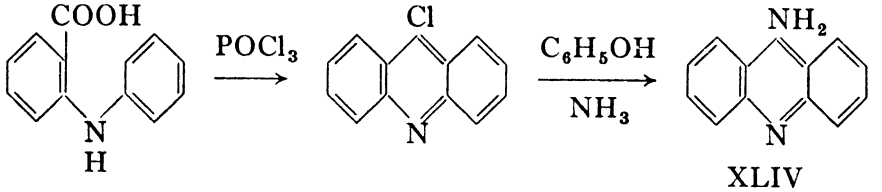


XLIII

The base forms orange-yellow crystals melting at 355°.

Aminacrine. 5-Aminoacridine. $C_{13}H_{10}N_2$. (XLIV).

Preparation. N-Phenylanthranilic acid is ring-closed by means of phosphorus oxychloride to yield 5-chloroacridine; this is dissolved in phenol forming 5-phenoxyacridine which, on treatment with gaseous ammonia, gives 5-aminoacridine hydrochloride which can be purified by crystallisation from water (69, 70).



XLIV

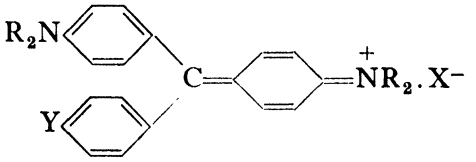
Properties. The base melts at 235°. The *hydrochloride*, $C_{13}H_{10}N_2.HCl.H_2O$, is used as a local antiseptic; it is soluble in water (1 in 300 at 20°), less soluble in normal saline solution (1 in 2000). The solution is highly fluorescent.

Antiseptic Dyestuffs

Brilliant green and crystal violet are triphenylmethane dyes. Since high antiseptic potency is linked in this series with basicity it appears that, as in the case of the acridines, the antibacterial action is dependent on the cation.

Brilliant green. The hydrogen sulphate of di(*p*-diethylamino)-triphenylcarbinol anhydride. $C_{27}H_{34}N_2O_4S$. (XLV).

Preparation. Diethylaniline is condensed with benzaldehyde, the product is oxidised and converted to the hydrogen sulphate (71).



XLV. Y=H, R=Et, X=HSO_4
XLVI. Y=NMe_2, R=Me, X=Cl

Properties. Brilliant green forms glistening golden crystals; it is soluble in water (1 in 5) and in ethanol. It has been used in the treatment of infected wounds and burns.

Crystal violet. Methylrosaniline chloride. Medicinal Gentian violet. Hexamethyl-*p*-rosaniline chloride. $C_{25}H_{30}N_3Cl$. (XLVI).

Preparation. First prepared by Caro in 1884 it is now made by the reaction of phosgene with dimethylaniline in the presence of zinc chloride.

Properties. Crystal violet forms greenish-bronze crystals, soluble in water (1 in 150) and in ethanol (1 in 20). It is used as a skin antiseptic and, since 1930, as an anthelmintic.

Methylene blue. Tetramethylthionine chloride. $C_{16}H_{18}N_3ClS.3H_2O$.

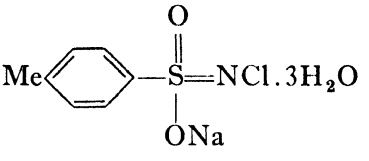
Preparation. NN-Dimethyl-*p*-phenylenediamine is oxidised by sodium dichromate in the presence of dimethylaniline, sodium thiosulphate and zinc chloride.

Properties. Methylene blue forms dark green lustrous crystals, soluble in water, ethanol or chloroform. It is a weak antiseptic.

CHLORINE COMPOUNDS

Chloramine. Chloramine T. Sodium *p*-toluenesulphonchlorpamide. $C_7H_7ClNNaO_2S.3H_2O$. (XLVII).

Preparation. Toluene is converted to toluene-4-sulphonyl chloride which is treated with ammonia to yield the amide. Reaction with sodium hypochlorite gives chloramine (72).



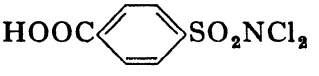
XLVII

Properties. Chloramine is a white crystalline powder with a bitter taste and a faint chlorine-like odour; it slowly decomposes when exposed to air, moisture and light. The water of crystallisation is lost at 100°. Chloramine is soluble at 20° in 7 parts of water and at 100° in 2 parts. An aqueous solution is alkaline to phenolphthalein. It dissolves in 12 parts of ethanol at 20° and is insoluble in ether, chloroform and benzene.

Chloramine was originally prepared by Chattaway in 1905 and was extensively used as a wound disinfectant in World War I.

Halazone. 4-Carboxybenzenesulphondichloroamide. 4-(Dichlorosulphamyl)-benzoic acid. $C_7H_5Cl_2NO_4S$. (XLVIII).

Preparation. Toluene-4-sulphonamide may be prepared as described above under Chloramine, the methyl group being oxidised to carboxyl (73, 74). Alternatively 4-carboxybenzenesulphonamide can be prepared and reacted with sodium hypochlorite (75).

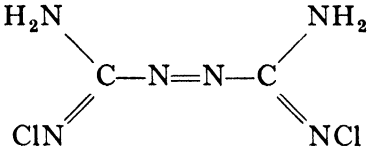


XLVIII

Properties. Halazone was introduced by Dakin in 1918 and is used in tablets for the sterilisation of drinking water. It is a white crystalline powder that has a chlorine-like odour. It melts at 213°. It is soluble in glacial acetic acid and in alkali hydroxide solutions, but is sparingly soluble in water or chloroform.

Chloroazodin. 1 : 1′-Azo-bis(chloroformamidine). $C_2H_4Cl_2N_6$. (XLIX).

Preparation. Guanidine or one of its salts is chlorinated with sodium hypochlorite at 0° (76, 77).

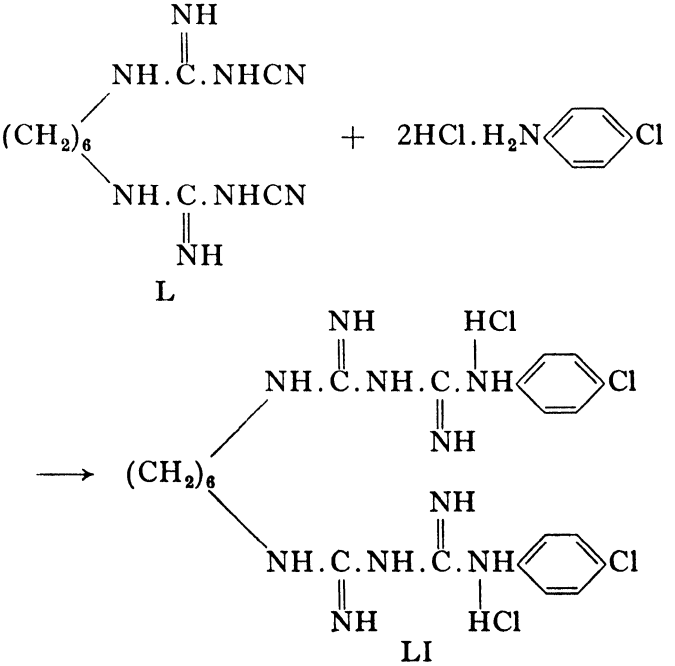


XLIX

Properties. Chloroazodin was introduced in 1934 as a wound antiseptic for which it is used as a solution in glyceryl triacetate. It forms yellow crystals that have a faint odour of chlorine. It explodes at 155° and is decomposed by light or on contact with metals. It is almost insoluble in water and sparingly soluble in ethanol, glycerin and chloroform.

Chlorhexidine dihydrochloride. bis(*p*-Chlorophenyldiguanido)hexane hydrochloride. $C_{22}H_{20}Cl_2N_{10}.2HCl$. (LI).

Preparation. 1 : 6-Hexanediamine is first reacted with two molecular proportions of sodium dicyanimide in boiling butanol yielding hexamethylene bis-(dicyandiamide) (L). This is heated with the hydrochloride of 4-chloroaniline in 2-ethoxyethanol yielding crude chlorhexidine dihydrochloride which is filtered and recrystallised from 50 per cent aqueous acetic aid (78, 79).



L

LI

Properties. Chlorohexidine is a colourless strongly basic solid, melting at 134°. The dihydrochloride melts at 260° to 262° (dec.). It is slightly soluble in water at 20° (0·06 g in 100 ml). The diacetate melts at 154° (corr.) and is soluble in water at 20° (1·9 g in 100 ml). Chlorhexidine salts were introduced as antiseptics in 1954 (80).

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CHAPTER X

Tuberculostats and Anti-Leprotic Drugs

TUBERCULOSTATS

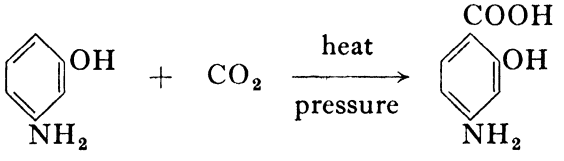
THE micro-organism which causes tuberculosis is known as *Mycobacterium tuberculosis*. It is difficult to kill, and rapidly becomes resistant to chemotherapeutic agents. In addition, once the bacterium has entered the body, it soon becomes encased in a nodule of tissue, and it can then only be reached with difficulty by drugs. Many chemical compounds have been found to be active *in vitro*, but very few are active *in vivo*. Even those that are active must be used with discretion, since drug resistance is an ever present danger.

The tuberculostats now in use include 4-aminosalicylic acid, thiacetazone, isoniazid and streptomycin. The last substance is an antibiotic, and its preparation and properties are described in Part II, Chapter XVII.

An account of the search for new synthetic tuberculostats indicates the large part played by chance in their discovery.

4-Aminosalicylic acid. $C_7H_7NO_3$. (I). This compound was introduced by Lehmann (1) in 1946. He knew that benzoates and salicylates caused increased respiration in pathogenic mycobacteria, and on the assumption that these compounds were essential metabolites, he searched for a competitive inhibitor of their action. 4-Aminosalicylic acid was the most active of fifty benzoic acid derivatives tested. It now appears, however, that 4-aminosalicylic acid competes not with salicylic acid but with 4-aminobenzoic acid.

Preparation. The Kolbe-Schmitt carboxylation of 3-aminophenol is used:



I

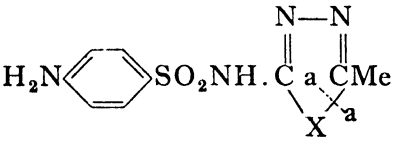
The reaction may be carried out in the presence of aqueous alkaline bicarbonates (2, 3, 4) or with dry potassium carbonate (5). The crude acid is purified by conversion to its sodium salt and reprecipitation with mineral acid (6).

Properties. 4-Aminosalicylic acid is a white powder of m.p. 135° to 140° (dec.). It is soluble in ethanol at 25° (1 part in 21) and sparingly soluble in water (1 part in 500). It dissolves in aqueous sodium bicarbonate solution.

Sodium aminosalicylate is now widely used in conjunction with streptomycin to prevent the emergence of bacteria resistant to the antibiotic.

Thiosemicarbazones. In 1944, Peak *et al.* (7) noticed that a sulphonamide

was active against *Mycobacterium tuberculosis in vitro.* It was 2-sulphanilamido-5-methyl-1 : 3 : 4-oxadiazole (II, X=O). Later, 2-sulphanilamido-5-methyl-1 : 3 : 4-thiadiazole (II, X=S) was also found to be active. These compounds, their homologues and derivatives were inactive *in vivo.*



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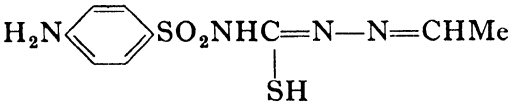

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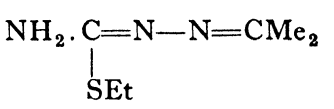
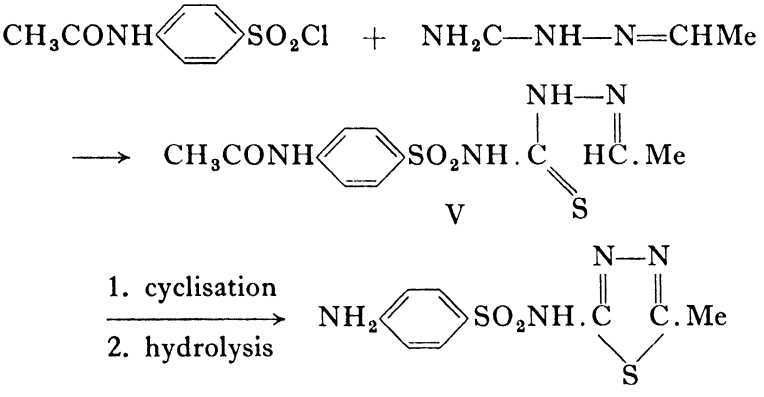


IV

Modifications of the structure were sought and uncyclised forms of the thiadiazole, in which fission may be regarded to have occurred at aa in (II), were investigated. The open chain compound corresponding to (II) is 4-sulphanilyl-3-methyl*iso*thiosemicarbazone (III). Such compounds containing the sulphanilyl group were inactive, but the simple 3-alkyl*iso*thiosemicarbazones such as acetone-3-ethyl*iso*thiosemicarbazone (IV) possessed activity *in vitro* but not *in vivo.*

During the same period, Domagk and his chemical colleagues in Germany were working along similar lines to the British team. Domagk, too, found the thiadiazole structure (II, X=S) to be active. This compound has been prepared from the corresponding acetylated thiosemicarbazone (V) by the following process (8):



4-Acetylaminobenzenesulphonyl chloride when reacted with acetaldehyde thiosemicarbazone yields the sulphanilyl thiosemicarbazone (V) which on cyclisation and hydrolysis gives the thiadiazole. When supplied by the chemist Behnisch with the intermediate (V) Domagk found it to be active *in vivo.* Therefore, thiosemicarbazones were investigated and 4-acetylaminobenzaldehyde thiosemicarbazone (thiacetazone) has gained a place in therapy.

It is of interest that notwithstanding the apparent logic of the approach, the activities of the thiadiazoles and of the thiosemicarbazones are in fact entirely unrelated. In addition, the fact that the *iso*thiosemicarbazones are more closely related structurally to the thiadiazoles than are the thiosemicarbazones is apparently without significance.

Thiacetazone. Amithiozone. 4-Acetylaminobenzaldehyde thiosemicarbazone. $C_{10}H_{12}N_4OS$. (VII).

Preparation. Thiacetazone may be prepared by the direct reaction between 4-acetylaminobenzaldehyde and thiosemicarbazide, $NH_2.NH.CS.NH_2$ (9), but thiosemicarbazide is expensive and cheaper methods have been investigated. Potassium thiocyanate, for example, may be reacted with hydrazine sulphate and the resultant aqueous solution of hydrazine thiocyanate (VI) may be reacted (10) with 4-acetylaminobenzaldehyde in acetic acid to yield thiacetazone (VII).

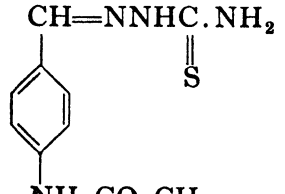
$$2KCNS + (NH_2NH_2)_2H_2SO_4 \longrightarrow \underset{\text{VI}}{NH_2NH_2.HCNS}$$

$$\xrightarrow{CH_3CONH.C_6H_4CHO} \underset{\text{VII}}{CH_3CONH\langle\bigcirc\rangle CH{=}NNHCSNH_2}$$

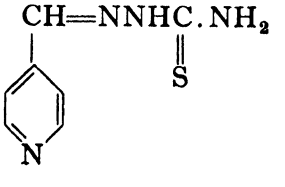
In a variation of this approach (11) 4-acetylaminobenzaldehyde was reacted with hydrazine to give the hydrazone $RCH{=}NNH_2$ which was reacted in aqueous hydrochloric acid with ammonium thiocyanate to give thiacetazone. Other methods have been employed (12).

Properties. Thiacetazone is a white crystalline powder possessing a bitter taste. It melts at 226° to 227° (dec.). It is insoluble in water, sparingly soluble in cold ethanol but soluble in hot ethanol, soluble at 20° in 100 parts of ethylene glycol. It is almost insoluble in chloroform or ether. Thiacetazone was introduced in 1946 (13), but has not been used widely in Britain or the U.S.A.

Isoniazid. *iso*Nicotinic acid hydrazide. *iso*Nicotinoyl hydrazine. $C_6H_7N_3O$. (X). First prepared in 1912 (14) the antitubercular properties of this compound were unknown until 1952 when independent announcements were made by three groups of workers, two in the U.S.A. (15, 16) and one in Germany (17). Fox (18) has described how the discovery occurred in his laboratory. Thiacetazone (VII) had been known since 1946 to possess antitubercular powers and it was a logical step to attempt the preparation of *iso*nicotinaldehyde thiosemicarbazone (VIII) where the 4-amino group of thiacetazone has been replaced by the pyridyl nitrogen.



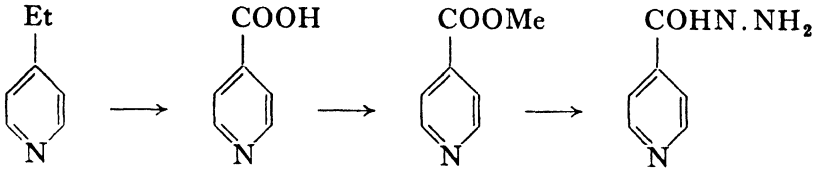
VII



VIII

*iso*Nicotinaldehyde proved difficult to prepare, however, and so a synthesis of *iso*nicotinaldehyde thiosemicarbazone was devised, which went through *iso*-nicotinic acid hydrazide as an intermediate. The thiosemicarbazone was active but when the hydrazide was tested, it too was found to be active.

Preparation. 4-Ethylpyridine (IX), prepared from pyridine and acetic anhydride (19), is oxidised (20, 21, 22) to *iso*nicotinic acid which is converted to its methyl (23, 24) or ethyl ester (21, 25, 26). The ester is reacted with 95 per cent hydrazine in boiling ethanol and on cooling isoniazid (X) is obtained and may be recrystallised from ethanol (27, 28).



IX X

Properties. Isoniazid is a white crystalline powder of m.p. 173°. It is soluble at 20° in 8 parts of water, 100 parts of ethanol and 1000 parts of chloroform. It is insoluble in ether. *Mycobacterium tuberculosis* rapidly becomes resistant to isoniazid and the drug is often used in conjunction with streptomycin or 4-amino-salicylic acid.

ANTI-LEPROTIC DRUGS

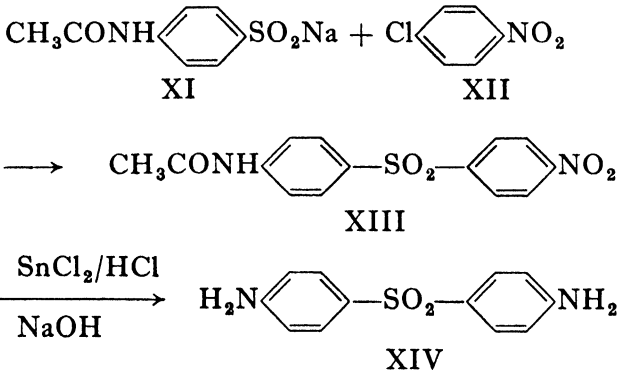
Leprosy is caused by *Mycobacterium leprae.* This micro-organism has never been cultivated, nor has it given a progressive disease in animals. Drugs to combat leprosy must therefore all be given clinical trial. Even this is not conclusive, for even in the absence of treatment the disease waxes and wanes, and may die out completely. Owing to these circumstances, the activity of a drug under trial is difficult to assess.

The sulphones are the drugs of choice, but they are far from ideal, for although clinical arrest of the disease is fairly easily achieved, it may take three to five years to eradicate the micro-organisms from the body. Dapsone (XIV) is widely used and is the basis for the synthesis of many similar compounds that are claimed to be less toxic and more active. However, these derivatives of dapsone are expensive and the present tendency is to use small doses of dapsone in place of larger doses of the less toxic derivatives.

Dapsone. 4 : 4′-Diaminodiphenylsulphone. 4 : 4′-Sulphonyl-bisaniline. $C_{12}H_{12}N_2O_2S$. (XIV).

Preparation. 4-Acetylaminobenzenesulphinic acid (29, 30) is first converted to its sodium salt (XI) which is then reacted in a mixture of ethylene glycol and ethoxyethanol with 1-chloro-4-nitrobenzene (XII). The 4-nitro-4′-acetyl-aminodiphenylsulphone (XIII) so obtained is filtered and dried. The nitro group is then reduced with stannous chloride in hydrochloric acid and the

acetyl group is simultaneously hydrolysed. Addition of caustic soda precipitates the required diamine. It can be recrystallised from 95 per cent ethanol (31).

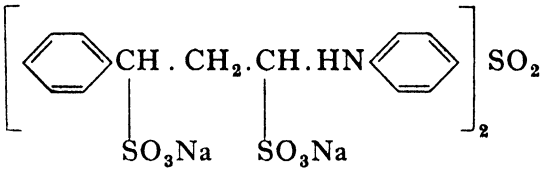


Properties. Dapsone is a white crystalline powder that exists in two forms, melting at 178·5° and 180·5°. The normal melting-point range is 176° to 181°. It is soluble in ethanol, acetone and excess of dilute hydrochloric acid, but it is insoluble in water. When diazotised and the solution heated, di-4-hydroxydiphenylsulphone m.p. 146° is obtained.

Solapsone. This substance consists mainly of the hydrated tetrasodium salt of 4 : 4′-di(3-phenyl-1 : 3-disulphopropylamino)diphenylsulphone.

$C_{30}H_{28}N_2O_{14}S_5Na_4$. (XV).

Preparation. Dapsone is treated with cinnamic aldehyde and 4 : 4′-dicinnamylideneamino diphenylsulphone is obtained. This is digested with aqueous sodium hydrogen sulphite (32, 33) to yield solapsone (XV).



Properties. Solapsone consists of a major component which comprises 94 per cent of the total, and 6 per cent of a minor component (34). It is insoluble in organic solvents and very soluble in water.

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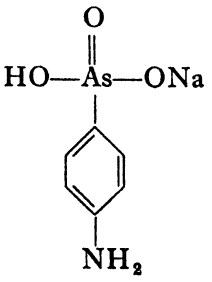
CHAPTER XI

Trypanocides

TRYPANOSOMIASIS or sleeping sickness is a disease of men and cattle in tropical Africa. The therapy of human trypanosomiasis is sufficiently effective for the disease to be kept under control, and the immediate problem in Africa is the control of sleeping sickness in cattle. Trypanosomes, the causal organisms, are flagellated protozoa that are transmitted by the bite of the tsetse fly. An early stage and a later stage of the disease are recognised. In the latter, the trypanosomes have entered the central nervous system; hence a successful trypanocide must be capable of penetrating the blood brain barrier.

All the trypanocides in common use are synthetic compounds and they may be divided (1) into the arsenicals, suramin, the amidines, the phenanthridinium compounds and quinapyramine. The arsenicals were introduced as antisyphilitics, but have been superseded for this purpose by the antibiotics.

Arsenicals. Arsenic trioxide has been regarded as a tonic for a considerable time and Livingstone, the African explorer, used it to treat cattle suffering from sleeping sickness. What beneficial properties it possessed were due to its trypanocidal action, however, and not to its tonic effects. The first aromatic arsenical was prepared in 1860 by Béchamp (2) and it was later (3) shown to be 4-aminobenzenearsonic acid. Atoxyl (I), the sodium salt of this acid, was shown by Thomas in 1904 (4) to have trypanocidal properties. Ehrlich was prompted by this discovery to investigate approximately one thousand arsenicals for trypanocidal and antisyphilitic action. Two compounds were found to be particularly active and they have the arsenoxide (II) and arsphenamine (III) structures:



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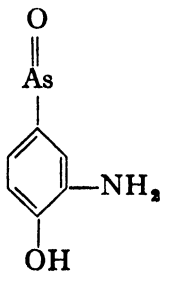

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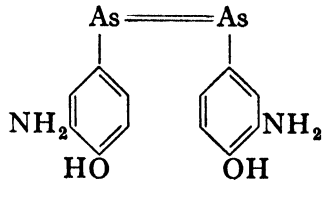
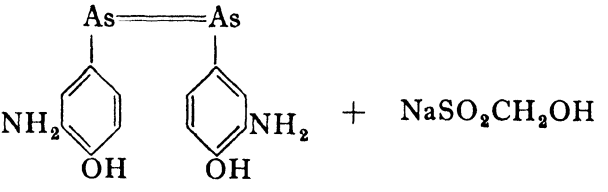


III

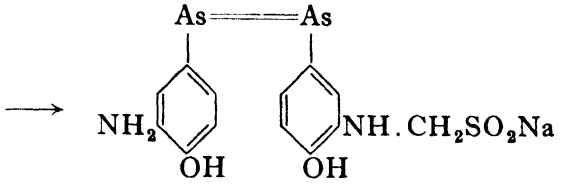
Compound III is Ehrlich's famous '606' or Salvarsan. It was later replaced in chemotherapy by the less toxic neoarsphenamine.

Neoarsphenamine. Sodium 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene-methylenesulphoxylate. $C_{13}H_{13}As_2N_2O_4SNa$. (V).

Preparation. Arsphenamine (III) is dissolved in water and an aqueous solution of sodium formaldehyde sulphoxylate (IV) is added, together with sodium carbonate. Hydrochloric acid precipitates the free sulphinic acid and this is suspended in water and converted to neoarsphenamine (V) by the addition of dilute caustic soda solution. When the aqueous solution is poured into ethanol neoarsphenamine is precipitated (5).



III IV



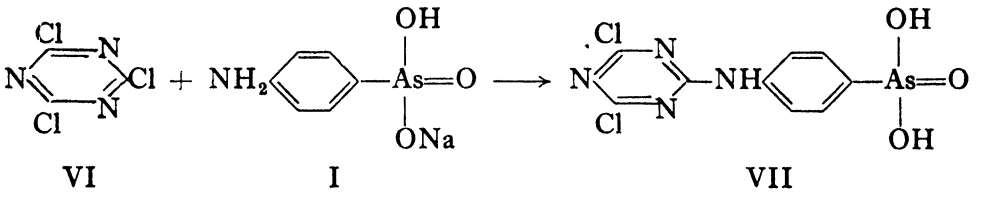
V

Properties. Neoarsphenamine is a yellow powder soluble in water, yielding a yellow neutral solution. When a 10 per cent solution is heated for 5 minutes with an equal volume of a 0·01 per cent solution of indigo carmine, the colour is destroyed. Uncombined formaldehyde sulphoxylate and inorganic salts may be present as impurities, and although the percentage of As present should be 32·2, it is often much lower than this.

Melarsoprol. This is a compound of 2 : 3-dimercaptopropanol (dimercaprol) with 2 : 4-diamino-6-*p*-arsenoanilino-*s*-triazine. $C_{11}H_{15}AsN_6OS_2$. (X).

Preparation. Atoxyl (I) is reacted with cyanuric chloride (VI) at pH 7·2 with ice cooling and the mixture is acidified, converted to the sodium salt and reprecipitated with acid to give *p*-(2 : 4-dichloro-*s*-triazinyl)aminophenylarsonic acid (VII). Reaction with ammonium hydroxide under pressure converts this to the diamino compound which is reduced with sulphur dioxide (6) to 2 : 4-diamino-6-*p*-arsenoanilino-*s*-triazine (VIII). This compound has been

called Melarsen oxide. On reaction with dimercaprol (IX) it yields melarsoprol (7).



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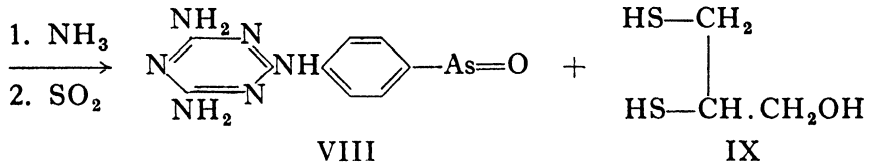

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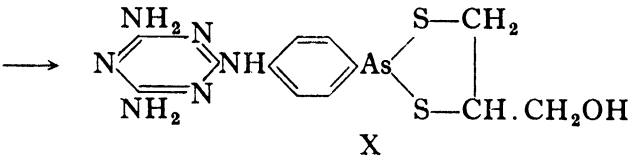


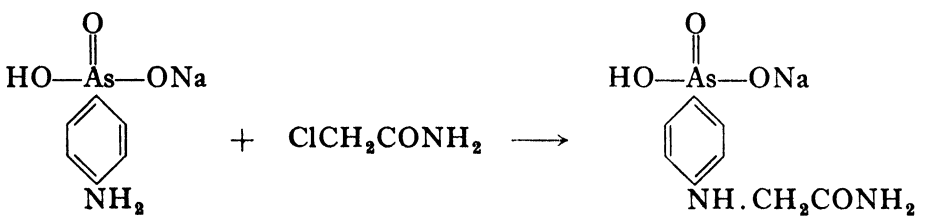
X

Properties. Melarsoprol is insoluble in water and cold methanol and ethanol, but it is soluble in propylene glycol. Of the melamine arsenicals introduced by Friedheim, melarsoprol appears to have promising properties (8). It is of interest that dimercaprol (B.A.L.) which forms part of the melarsoprol molecule has been used as an antidote for arsenical poisoning.

Tryparsamide. Sodium *p*-arsono-N-phenylglycinamide.

$C_8H_{10}AsN_2O_4Na \cdot \frac{1}{2}H_2O$. (XI).

Preparation. Atoxyl (I), which may be prepared by reacting aniline with arsenic acid, H_3AsO_4 (9) is condensed with chloroacetamide in alkaline solution. Hydrochloric acid is added to precipitate *p*-arsonophenylglycinamide and this is converted to its sodium salt (10).

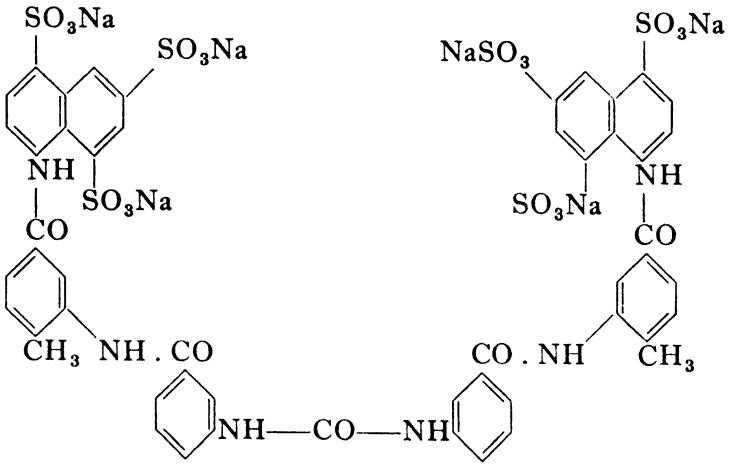


I XI

Properties. Tryparsamide is very soluble in water and almost insoluble in organic solvents. It was introduced in 1919 and is still the most useful drug for the late stage of sleeping sickness. The pentavalency of the arsenic atom gives the molecule the capacity to pass the blood brain barrier. When in the central nervous system, the arsenic is converted to the active trivalent form.

Suramin. Symmetrical urea of sodium 8-(3-benzamido-4-methylbenzamido)naphthalene-1 : 3 : 5-trisulphonate. $C_{51}H_{34}N_6O_{23}S_6Na_6$. (XII).

Preparation. 8-Aminonaphthalene-1 : 3 : 5-trisulphonic acid is condensed with 4-methyl-3-nitrobenzoyl chloride. The nitro group is then reduced to an amino group and this is linked with 3-nitrobenzoyl chloride. The nitro group is again reduced and two molecules of the complex amine so obtained are linked by reaction with phosgene (11).

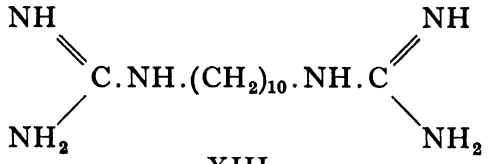


XII

Properties. Suramin is very soluble in water and almost insoluble in organic solvents. It was introduced by German workers in 1921 under the name of Bayer 205, but the formula was not disclosed. Fourneau and his colleagues synthesised it in 1924. It is a remarkable compound, for in spite of its large molecular size trivial changes in structure, such as removal of the methyl groups, destroy the activity. It is effective as a prophylactic.

Amidines

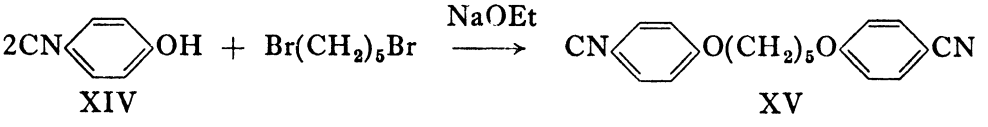
Synthalin, decamethylenediguanidine (XIII), was shown by Jancso in 1935 (12) to be trypanocidal, and it was suggested that its activity lay in its ability to reduce the blood sugar concentration, thus depriving the parasites of food. Lourie and Yorke (13) showed that the compound was directly toxic for trypanosomes and as a result of these observations many chemical compounds similar in structure to synthalin were prepared and tested. Of these, pentamidine (XVI) is a useful drug in trypanosomiasis.



XIII

Pentamidine. 4 : 4′-Pentamethylenedioxydibenzamidine. 1 : 5-Di(4-amidinophenoxy)pentane. $C_{19}H_{24}N_4O_2$. (XVI).

Preparation. 4-Aminophenol is converted by the Sandmeyer reaction, i.e. diazonium salt and cuprous cyanide, to 4-hydroxybenzonitrile (XIV). This is treated with sodium ethoxide to convert it to the corresponding sodium compound and 1 : 5-dibromopentane is added. The mixture is stirred at refluxing temperature. The product (XV) is filtered and washed free of sodium bromide. On treatment of XV with ethanolic hydrogen chloride at 0° to 5°, the nitrile groups are converted to the iminoether groups R.C(NH)OEt.HCl. Reaction with excess of alcoholic ammonia gives pentamidine hydrochloride (14, 15). Addition of aqueous sodium hydroxide liberates pentamidine (XVI).



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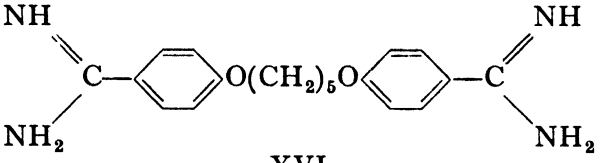


XVI

Other methods of preparation of pentamidine have been patented (16).

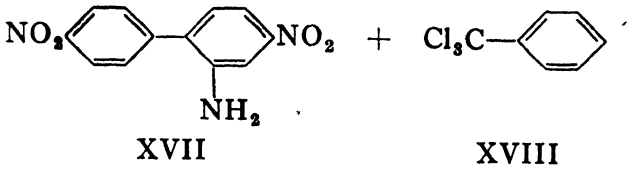
The salt of pentamidine most commonly used is the isethionate, i.e. the bishydroxyethane sulphonate, $B.2(CH_2OH.CH_2SO_3H)$ and it is prepared by the reaction between pentamidine and hydroxyethanesulphonic acid (17). Other methods have been used (18, 19).

Properties. Pentamidine isethionate is a white hygroscopic powder possessing a bitter taste. It is soluble in water and in glycerin, slightly soluble in ethanol and insoluble in ether, chloroform and liquid paraffin. It melts at 190° (dec.). The dihydrochloride dihydrate melts at 236° (dec.).

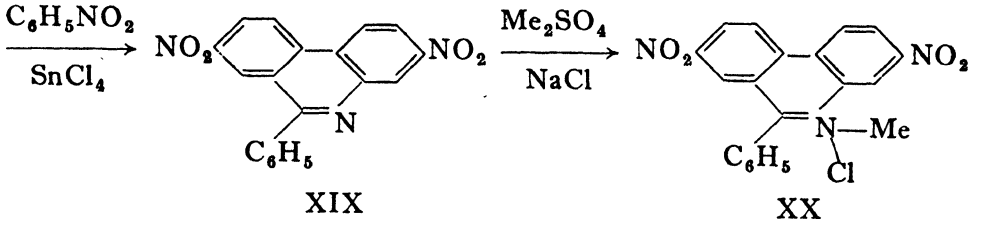
Dimidium bromide. 2 : 7-Diamino-9-phenyl-10-methylphenanthridinium bromide. 3 : 8-Diamino-5-methyl-6-phenylphenanthridinium bromide.

$C_{20}H_{18}BrN_3.H_2O$. (XXII).

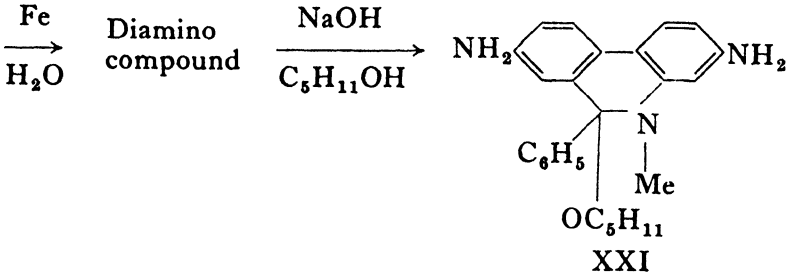
Preparation. Dimidium bromide was first prepared by Walls (20). An improved method has been published by Barber (21, 22). The reaction scheme is as follows:



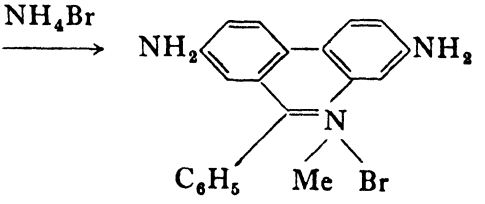
XVII XVIII



XIX XX



XXI



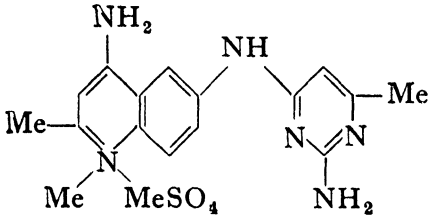
XXII

4 : 4′-Dinitro-2-aminodiphenyl (XVII) is reacted with benzotrichloride (XVIII) in nitrobenzene at 200° in the presence of a catalytic quantity of stannic chloride. Some solvent and catalyst are then distilled, dimethyl sulphate is added to the phenanthridine compound (XIX) left as residue, and the mixture is heated at 180°. It is sucked over into water, the nitrobenzene is steam-distilled and sodium chloride is added to the residual liquor to give 2 : 7-dinitro-9-phenyl-phenanthridine-10-methochloride (XX). This is reduced to the 4 : 4′-diamino compound by means of iron in boiling water; then, in a very interesting step, the normal quaternary hydroxide of XX is obtained by addition of caustic soda and is converted by reaction with pentanol to the quaternary pentoxide, which rearranges to the pseudo base (XXI). This is a crystalline material that can be isolated. It is suspended in an aqueous solution of ammonium bromide and water and pentanol are distilled. The solution is cooled to give dimidium bromide (XXII). It forms purple-black crystals that melt at 241° to 243° (dec.),

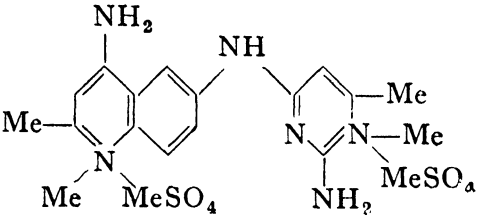
when anhydrous. It has been claimed that the ethobromide, called *ethidium bromide*, has properties that make it superior to dimidium bromide (23).

Quinapyramine sulphate. 4-Amino-6-(2′-amino-6′-methyl-4′-pyrimidylamino)-2-methylquinoline-1′-dimetho(methyl sulphate). $C_{17}H_{22}N_6.2MeSO_4$. (XXIV).

Preparation. Quinapyramine was investigated by Curd, Davey and their colleagues, i.e. the same team that discovered the antimalarial proguanil. It was known that some compounds based upon 4 : 6-diaminoquinaldine were trypanocidal and since pyrimidine compounds had been intensively studied during the work leading to proguanil, it was decided to prepare compounds of 4 : 6-diaminoquinaldine linked with pyrimidine. In the early stages of the investigation the monoquaternary compound (XXIII) was prepared, and thought to be active. In fact, the activity was due to the presence of a trace of quinapyramine present, and when this was recognised, quinapyramine (XXIV), the diquaternary compound, was prepared and investigated.

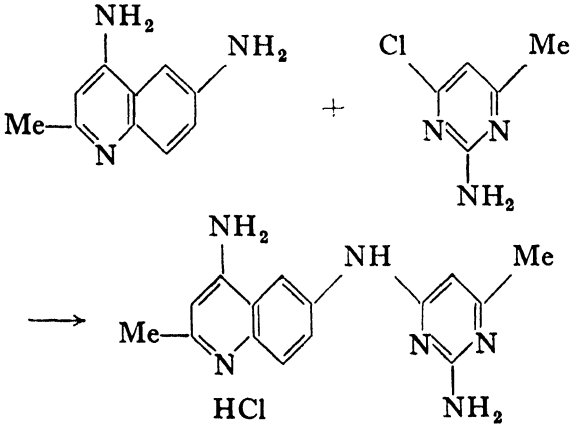


XXIII



XXIV

It is prepared by reacting together 4 : 6-diaminoquinaldine and 2-amino-4-chloro-6-methylpyrimidine in boiling dilute hydrochloric acid (24, 25). The reaction mixture is cooled and neutralised with ammonia to give 4-amino-6-(2′-amino-6′-methylpyrimidyl-4′-amino)quinaldine hydrochloride (XXV) which is salted out. It is converted to the tertiary base by treatment with caustic soda.



XXV

The base is then converted to the diquaternary salt by reaction with dimethyl sulphate in nitrobenzene at 110°. The dimetho(methyl sulphate) so obtained may be converted into the methochloride or methobromide by reaction with sodium chloride or sodium bromide in aqueous solution.

Properties. Quinapyramine sulphate was introduced in 1949 (26, 27). It melts at 259° to 266° and is a white powder with a bitter taste. It is very soluble in water, and almost insoluble in organic solvents. The chloride melts at 317° (dec.), the bromide at 316° (dec.) and the iodide at 313° (dec.). Quinapyramine is used to combat bovine trypanosomiasis. The sulphate is rapidly absorbed and the chloride more slowly and so a mixture of the two (called 'pro-salt') is often employed.

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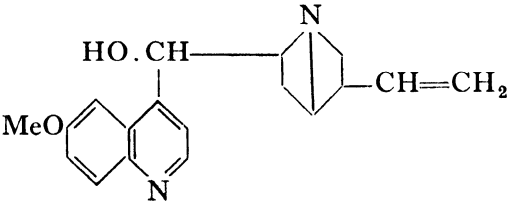
CHAPTER XII

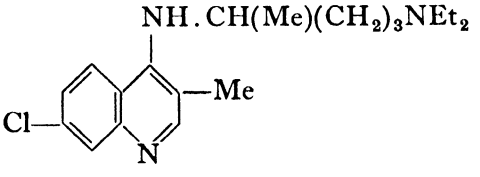
Antimalarials

MALARIA is a disease of great importance. It has been stated (1) that one-third of the world's population suffers from it at some time during their lives. Before World War II, three antimalarials were in general use. They were quinine (I), pamaquin (VIII) and mepacrine (XXXV).



I

During the war, Java and its cinchona tree plantations were captured by the Japanese, and so quinine became unobtainable. Mepacrine was chosen as a synthetic substitute and it was manufactured on a large scale for the use of the Allied Armed Forces. In addition, a programme of research designed for the discovery of new antimalarials was begun in the U.S.A. and in Great Britain. Pentaquine (XV) was discovered by American workers engaged in this project. Chloroquine (XXVI) has a rather different history. When Allied troops occupied Tunis in 1943, they found there supplies of a German antimalarial drug called Sontoquin[P] (II).



II

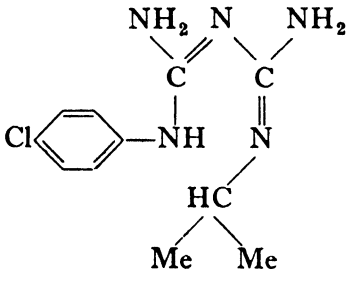
It was investigated and found to have the formula given above. Many similar compounds were prepared, and finally chloroquine was selected for use. Chloroquine had been prepared by the German inventors (2) of Sontoquin, but had been rejected after pharmacological testing as being inferior to the latter drug.

Proguanil (III) was discovered in 1944 by a team of British workers led by Curd and Rose. They decided to attempt the preparation of antimalarials containing the pyrimidine nucleus, because pyrimidine compounds are normally present in the body and because they had prior experience with such compounds. Active pyrimidine compounds were obtained and then for theoretical

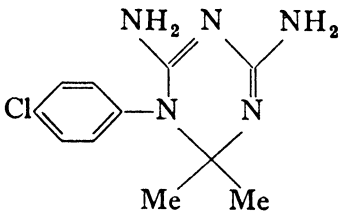
reasons connected with the tautomeric possibilities of the molecule diaguanides were investigated (3) and finally proguanil was chosen for trial.

In 1953 (4) proguanil, which was known to be inactive *in vitro*, was shown to be metabolised in the body to the active compound 4 : 6-diamino-1-(4-chlorophenyl)-1 : 2-dihydro-2 : 3-dimethyl-1 : 3 : 5-triazine (IV). Its preparation has been patented (5) and it may lead to an entirely new group of antimalarial drugs.

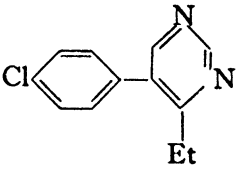
Pyrimethamine (V), which is a pyrimidine antimalarial, was the result of work begun by Hitchings *et al.* in 1948 (6). The resemblance between the structures of the tautomeric form of proguanil (III), its metabolite (IV) and pyrimethamine (V) is shown below:



III



IV

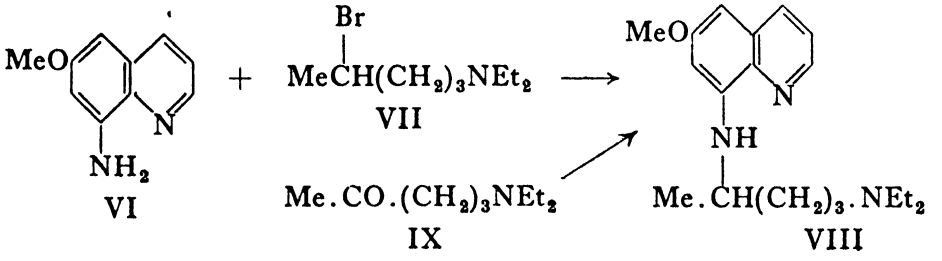


V

Pamaquin. 8-(4-Diethylamino-1-methylbutylamino)-6-methoxyquinoline. $C_{19}H_{29}N_3O$. (VIII).

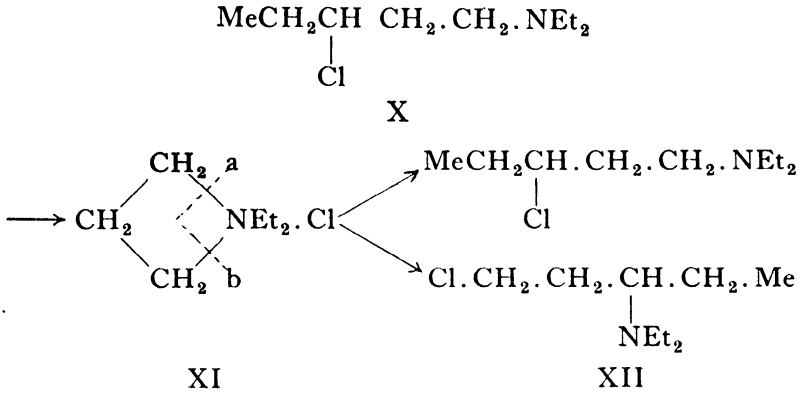
Preparation. Pure pamaquin may be made (7) by condensing 6-methoxy-8-aminoquinoline (VI) with 1-diethylamino-4-bromopentane (VII). Alternatively, the substituted quinoline can be reacted (8, 9) by reductive amination with 1-diethylamino-4-pentanone (IX).

Many other syntheses of pamaquin have been reported upon (10, 11, 12, 13). In the original German method (14) 1-diethylamino-4-chloropentane was condensed with 6-methoxy-8-aminoquinoline. The chloroamine was made by the



VI VII IX VIII

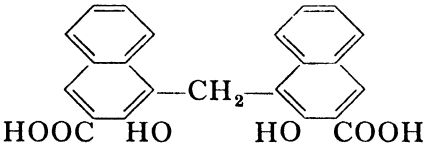
action of concentrated hydrochloric acid upon the corresponding alcohol. This method leads to 1-diethylamino-4-chloropentane contaminated with 1-diethylamino-3-chloropentane (X). The latter substance gives rise to a further isomer (XII) for in solution it forms the intermediate cyclic quaternary compound (XI) which, according to whether it breaks at bond (a) or bond (b), gives rise to 1-diethylamino-3-chloropentane (X) or 1-chloro-3-diethylaminopentane (XII). Thus commercial pamaquin prepared by the above method will contain (15) normal pamaquin and the two isomeric compounds from (X) and (XII).



X

XI XII

Properties. Pamaquin base is an oil of b.p. 175° to 180° at 0·3 mm. The citrate has a m.p. of 125° to 127°. Pamaquin is used in the form of its salt with 2 : 2′-dihydroxy-1 : 1-dinaphthylmethane-3 : 3′-dicarboxylic acid (XIII).



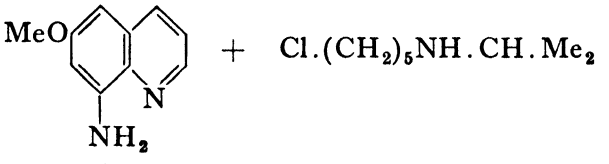
XIII

This salt of pamaquin is an orange-yellow powder possessing a bitter taste. It is insoluble in water, but is soluble at 20° in 20 parts of ethanol and in 10 parts of 95 per cent acetone.

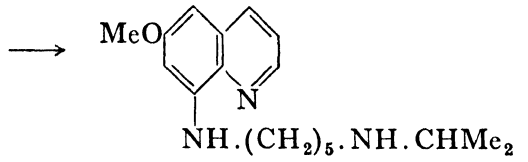
Pamaquin has been used in combination with quinine to prevent relapses in benign tertian malaria.

Pentaquine. 8-(5-*iso*Propylaminopentylamino)-6-methoxyquinoline. $C_{18}H_{27}N_3O$. (XV).

Preparation. Pentaquine was first prepared by Drake and his colleagues (16) by the following procedure:



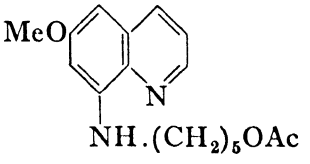
VI XIV



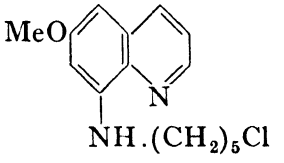
XV

Two molecular proportions of 8-amino-6-methoxyquinoline (VI) and one of 1-chloro-5-*iso*propylaminopentane (XIV) hydrochloride were reacted together in hot aqueous solution for 24 hours. Unreacted VI was removed, and from the reaction mixture pentaquine monohydrochloride was isolated. It was converted to pentaquine base by addition of sodium hydroxide, and to a solution of the base in ethanol was added phosphoric acid and pentaquine monophosphate was obtained.

In a variation of this process (17), 8-amino-6-methoxyquinoline may be reacted with 1-chloro-5-acetoxypentane to give XVI which, on hydrolysis and reaction with thionyl chloride, yields XVII. This compound may be condensed with *iso*propylamine to yield pentaquine monohydrochloride, and the series of steps described above converts the monohydrochloride to the monophosphate.



XVI



XVII

The preparation of 8-amino-6-methoxyquinoline (VI) has been described (18).

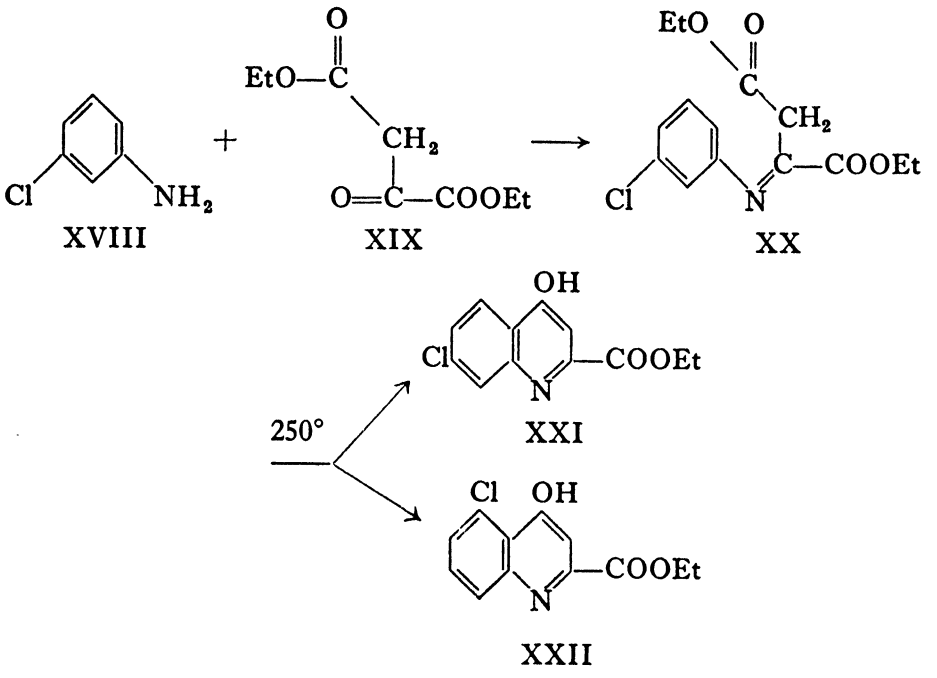
Properties. Pentaquine base is an oil of b.p. 165° to 170° at 0·05 mm. The dipicrate melts at 164·5° to 165·5°; the dihydrochloride at 218° to 219° (dec.) and the monohydrochloride at 152° to 153°. The monophosphate which is the pentaquine salt used in therapy is a yellow crystalline material with a bitter taste. It has a m.p. of 190·5°. 1 g dissolves in 25 ml of water, but it is almost insoluble in ethanol, chloroform or ether.

Pentaquine is used as a less toxic substitute for pamaquin in the treatment, in combination with quinine, of benign tertian malaria.

Chloroquine. 7-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline. $C_{18}H_{26}ClN_3$. (XXVI).

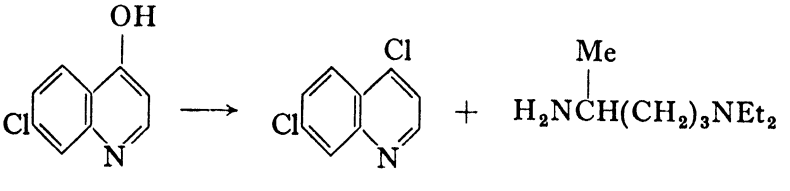
Preparation. Chloroquine was first made by German workers (2) and was later prepared by a team of chemists in the U.S.A. (19). A modification of the method used by the latter group was used for the large-scale manufacture of chloroquine during World War II (20). 3-Chloroaniline (XVIII) is condensed with ethyl ethoxalylacetate (XIX) in glacial acetic acid at 45° and, after removal of unchanged starting materials, the Schiff's base (XX) is cyclised

in a high-boiling solvent such as diphenyl ether at 250°, with elimination of ethanol.

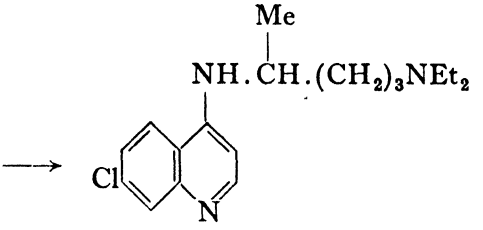


XVIII XIX XX XXI XXII

There are two free ortho hydrogen atoms in compound XX and cyclisation leads to a mixture of the two isomers XXI and XXII. The mixture of isomers is crystallised from pyridine containing ethanol and the required ethyl-7-chloro-4-hydroxyquinoline-2-carboxylate (XXI) is obtained. Hydrolysis of the 2-carboxylate group and addition of hydrochloric acid gives the 2-carboxylic acid, and heating in diphenyl ether at 240° causes the compound to decarboxylate. 7-Chloro-4-hydroxyquinoline (XXIII) is so obtained, and on reaction with phosphorus oxychloride, it yields 4 : 7-dichloroquinoline (XXIV). This compound is dissolved in phenol, and condensed with 4-diethylamino-1-methylbutylamine (XX) at 135° (21) to give chloroquine base (XXVI). The base was dissolved in methanol containing phosphoric acid to yield chloroquine diphosphate.



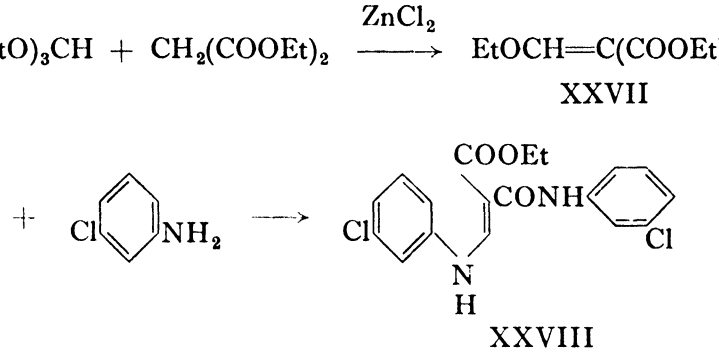
XXIII XXIV XXV



XXVI

The preparation of 4-diethylamino-1-methylbutylamine is described under mepacrine below, for chloroquine and mepacrine have the same side-chain.

By the use of diethyl ethoxymethylenemalonate (XXVII) (prepared from ethyl orthoformate and diethyl malonate) in place of ethyl ethoxalylacetate (XIX) in the above preparation of 7-chloro-4-hydroxyquinoline the proportion of unwanted isomer in the mixture is greatly decreased (22, 23, 24).



XXVIII

3-Chloroaniline is condensed with diethyl ethoxymethylenemalonate (XXVII) and the resulting compound (XXVIII) is cyclised, decarboxylated and chlorinated as before to give 4 : 7-dichloroquinoline (XXIV). Other methods for the preparation of chloroquine and its intermediates have been published (25, 26, 27).

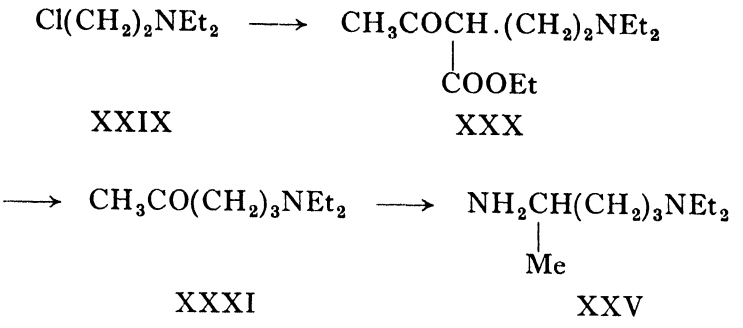
Properties. Chloroquine base is an oil of b.p. 212° to 214° at 0·2 mm. The diphosphate $B(H_3PO_4)_2$ is a white crystalline material with a bitter taste. It is soluble in water and almost insoluble in ethanol, chloroform and ether. It exists in two forms which melt at 193° to 195° and 215° to 218°.

Chloroquine cures tertian malaria but relapses occur after its use in benign tertian malaria.

Mepacrine. Quinacrine. 2-Chloro-7-methoxy-5-(4-diethylamino-1-methylbutylamino)acridine. 2-Methoxy-6-chloro-9-(4-diethylamino-1-methylbutylamino)-acridine. $C_{23}H_{30}ClN_3O$. (XXXV).

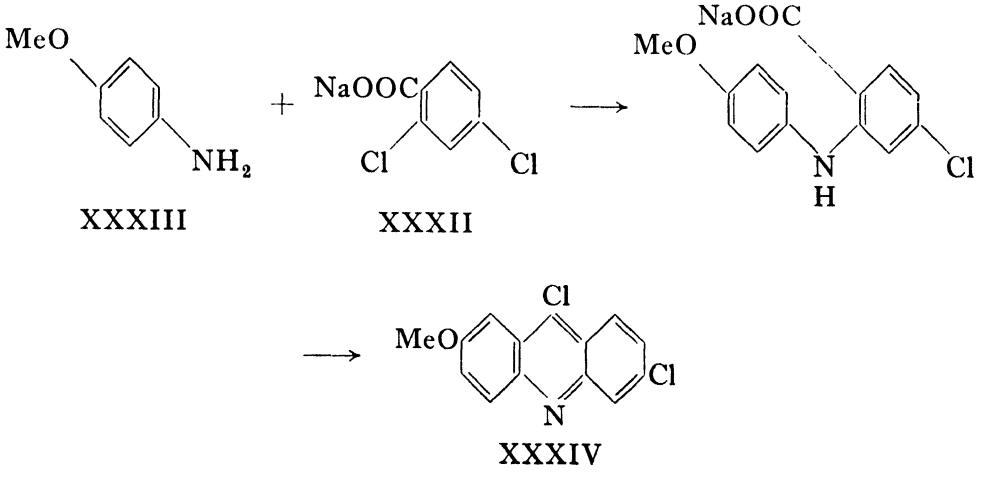
Preparation. 4-Diethylamino-1-methylbutylamine (XXV) has been made by the following method (28, 29, 30, 31). Ethylene oxide is reacted with diethylamine to yield diethylaminoethanol which is treated with thionyl chloride to give diethylaminoethyl chloride (XXIX). This is converted by means of a

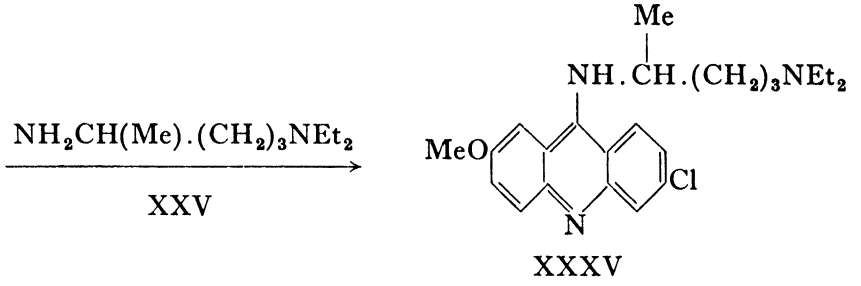
Claisen condensation with sodioacetoacetic ester to XXX which is simultaneously hydrolysed and decarboxylated by hot aqueous mineral acid to 5-diethylamino-2-pentanone (XXXI). It is then catalytically reduced by hydrogen over Raney nickel in methanol in the presence of ammonia and 4-diethylamino-1-methylbutylamine (XXV) is obtained (32).



Alternative routes for the preparation of the mepacrine side-chain have been explored (33, 34, 35, 36, 37).

The acridine moiety of the mepacrine molecule has been prepared by the following method (29, 30). 2 : 4-Dichlorobenzoic acid, obtained (38) from 2 : 4-dichlorotoluene, is converted to its sodium salt (XXXII) and then condensed with 4-anisidine (XXXIII) in water at 110°. Copper powder is used as a catalyst. This is an example of the Ullmann reaction. Ring-closure is then effected by the use of phosphorus oxychloride in chlorobenzene. 2 : 5-Dichlor-7-methoxyacridine (XXXIV) is thus obtained and is condensed with the side-chain 4-diethylamino-1-methylbutylamine (XXV) in phenol as a solvent (39). The phenolic reaction mixture is drowned in a vessel containing xylene and caustic soda solution. Acetic acid is added to the mepacrine solution in xylene and the mepacrine acetate obtained by this step is converted to the base (XXXV) and then to the dihydrochloride.

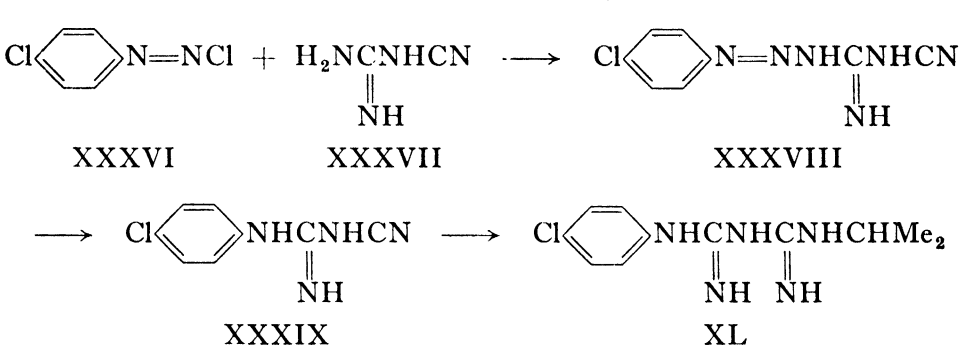




Properties. Mepacrine monohydrate base melts at 82·4° to 83·8° and the dihydrochloride at 253° to 256° (corr.). The latter salt is soluble in water to the extent of 4·2 g in 100 ml of water at 25°. The dimethanesulphonate or dimusonate as it has been called, melts at 136° to 138° and 100 ml of water dissolves 59·3 g of this compound. Many other salts have been prepared (40).

Proguanil. Chlorguanide. 1-(4-Chlorophenyl)-5-*iso*propyldiguanide. $C_{11}H_{16}ClN_5$. (XL).

Preparation. The original synthesis (41) of proguanil is as follows:



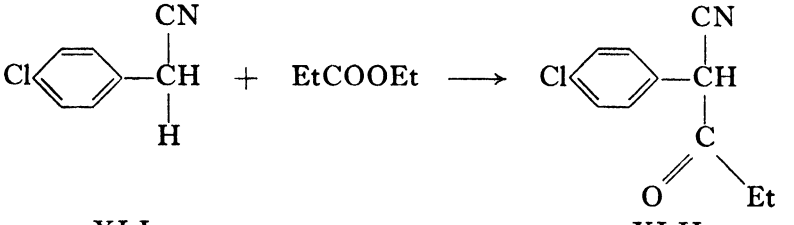
A suspension of 4-chloroaniline hydrochloride in hydrochloric acid is diazotised by the addition of sodium nitrite and the diazonium salt (XXXVI) is then coupled with dicyandiamide (XXXVII) in aqueous solution to give 4-chlorobenzeneazodicyanodiamide (XXXVIII). This compound, which is explosive when dry, is then added as a wet paste to a mixture of concentrated hydrochloric acid and ethoxyethanol. Nitrogen is evolved and 4-chlorophenyldicyandiamide (XXXIX) separates. It is reacted with *iso*propylamine in aqueous ethanol in the presence of copper sulphate. The diguanide is obtained as the copper complex which may be decomposed by hydrogen sulphide in acid solution. Addition of caustic soda liberates proguanil (XL).

Many other methods for the preparation of proguanil have been published (42, 43).

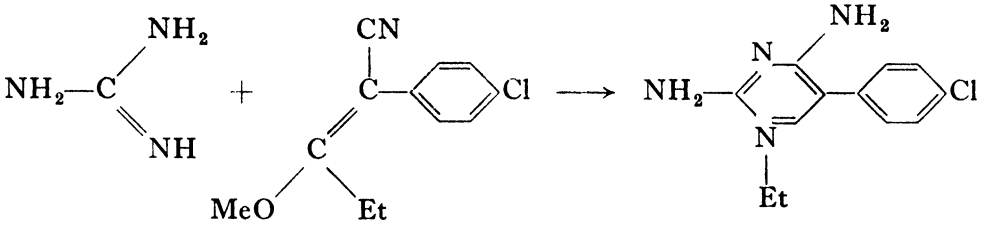
Properties. Proguanil base melts at 129°, the acetate at 184° and the hydrochloride, which is used in therapy, at 248° to 250°. The latter compound has a bitter taste. It is soluble in water (1 g in 110 ml) and in ethanol (1 g in 40 ml), but it is insoluble in chloroform and ether. Proguanil is used for the treatment of malignant and benign tertian malaria.

Pyrimethamine. 2 : 4-Diamino-5-(4-chlorophenyl)-6-ethylpyrimidine. $C_{12}H_{13}ClN_4$. (XLIV).

Preparation. Pyrimethamine may be obtained by the following reaction sequence (44, 45). 4-Chlorobenzyl chloride is reacted with potassium cyanide to yield the corresponding 4-chlorobenzyl cyanide (XLI). This compound is condensed with ethyl propionate in ethanol in the presence of sodium ethoxide to give propionyl-4-chlorophenylacetonitrile (XLII). This compound has to be reacted in its enol form with diazomethane to give the methyl enol ether (XLIII) which is then combined with guanidine in ethanolic sodium ethoxide and pyrimethamine (XLIV) is obtained.



XLI XLII



XLIII XLIV

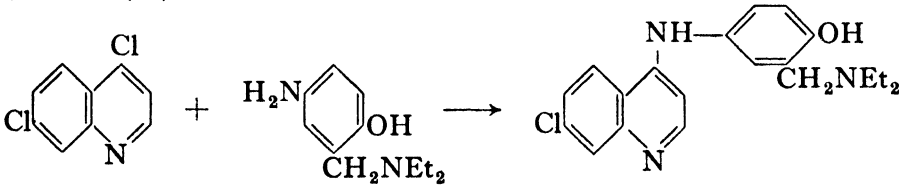
Alternative methods for the preparation of pyrimethamine have been published (46, 47).

Properties. Pyrimethamine is a white crystalline tasteless powder of m.p. 239° to 242°. It is sparingly soluble in water, but soluble in warm dilute sulphuric acid. It is sparingly soluble in most organic solvents.

Amodiaquine hydrochloride. 7-Chloro-4-(3′-diethylaminomethyl-4′-hydroxyanilino)quinoline dihydrochloride dihydrate.

$C_{20}H_{22}ClN_3O.2HCl.2H_2O$. (XLVII).

Preparation. In the original method (48) 4 : 7-dichloroquinoline (XLV) was condensed with 4-amino-2-diethylaminomethylphenol (XLVI), but in a later method (49) the alkylamino group was added as a last step. The procedure has been patented (50).

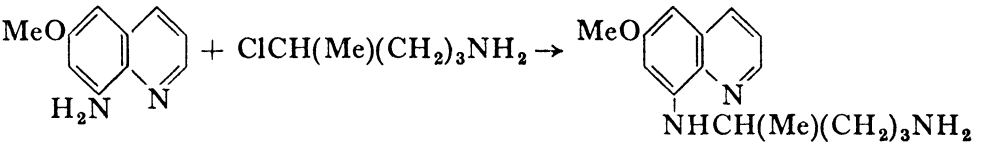


XLV XLVI XLVII

Properties. Amodiaquine hydrochloride is used as a suppressive agent in areas of endemic malaria. It is a yellow crystalline solid melting at 160°. The dihydrochloride hemihydrate melts at 243° and the dihydrochloride monohydrate at 183°. Amodiaquine hydrochloride is soluble in water, sparingly soluble in ethanol and very slightly soluble in benzene, chloroform and ether.

Primaquine phosphate. 8-(4-Amino-1-methylbutylamino)-6-methoxyquinoline diphosphate. $C_{15}H_{21}N_3O.2H_3PO_4$. (XLVIII).

Preparation. 6-Methoxy-8-aminoquinoline is coupled with 2-chloropentylamine yielding primaquine (51, 52).



Properties. Primaquine boils at 175° to 177° at 0·2 mm. The monohydrochloride melts at 106·7°.

Primaquine is used clinically for the treatment of relapsing vivax (benign tertian) malaria.

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CHAPTER XIII

Anthelmintics

PARASITIC worms inflict suffering upon man and animals in all parts of the world. In some areas, diseases caused by these parasites constitute a major health problem. Tapeworm infestation, for example, has been treated with extract of male fern, with pelletierine (a mixture of alkaloids from pomegranate bark), or with cusso, which consists of the dried panicles of *Brayera anthelmintica*. Chenopodium oil, extracted from the plant *Chenopodium ambrosioides*, and santonin, from various species of *Artemisia* have been used against hookworms.

Of the synthetic anthelmintics, carbon tetrachloride has been in general use since 1921 for the treatment of hookworm disease. Tetrachloroethylene has a similar use. Gentian violet, used against threadworms, and hexylresorcinol, which has a wide application against many worms, have both been described in Part I, Chapter IX. Diphenan, used since 1920 for the treatment of threadworms, is now declining in use, since piperazine has been found to serve the same purpose (1). Schistosomiasis (bilharzia) is caused by a parasitic fluke. The disease is very common and it has been estimated that there are 12 million infected persons in Egypt alone. Lucanthone and the antimony compounds have been used against this disease.

Tetrachloroethylene. $Cl_2C{=}CCl_2$.

Preparation. Acetylene and chlorine are reacted together at 300° in the presence of an inert gas (2). The product, after fractional distillation, is further purified before use (3).

Properties. Tetrachloroethylene is a colourless, mobile liquid with a weight per ml of 1·622 to 1·630 g at 20° and a b.p. of 121°. Thymol (0·01 per cent) may be present to inhibit decomposition. Tetrachloroethylene is soluble in organic solvents and insoluble in water. It is used for the expulsion of hookworms and in the treatment of ankylostomiasis.

Diphenan. 4-Benzylphenyl carbamate. $C_{14}H_{13}NO_2$. (II).

Preparation. 4-Benzylphenol is converted to the chloroformate (I) by reaction with phosgene (4) in the presence of dimethylaniline in benzene. The chloroformate with ammonia gives diphenan (II).

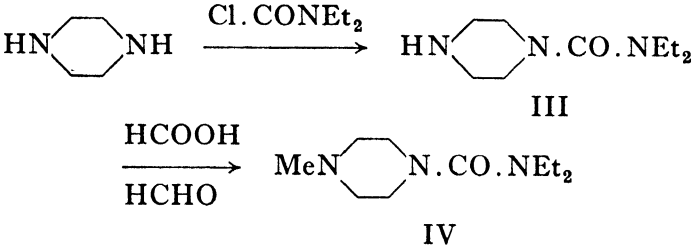
$$C_6H_5CH_2C_6H_5OH \xrightarrow{COCl_2} \underset{\text{I}}{C_6H_5CH_2C_6H_5OCOCl} \xrightarrow{NH_3} \underset{\text{II}}{C_6H_5CH_2C_6H_5OCONH_2}$$

Properties. Diphenan is a white tasteless crystalline powder with a m.p. of 147° to 150°. It is soluble in the usual organic solvents except light petroleum

and ethanol in which it is sparingly soluble. It is almost insoluble in water. Diphenan has been used for the expulsion of threadworms.

Diethylcarbamazine. 1-Diethylcarbamyl-4-methylpiperazine. NN-Diethyl-4-methyl-1-piperazinecarboxamide. $C_{10}H_{21}N_3O$. (IV).

Preparation. Diethylcarbamyl chloride is condensed with piperazine and the diethylcarbamyl piperazine (III) obtained is converted to the N-methyl compound, i.e. diethylcarbamazine (IV) by reductive methylation with formic acid and formaldehyde (5, 6).



In alternative syntheses, 4-methylpiperazine may be reacted with diethylcarbamyl chloride (7) or 4-methylpiperazine may be converted to the corresponding carbonyl chloride and this then reacted with diethylamine (8). Other methods of preparation have been published (9). The dihydrogen citrate which is the salt used for chemotherapy is prepared by reaction of the parent amine with citric acid in acetone (7).

Properties. Diethylcarbamazine has a m.p. of 48° and a b.p. of 108·5° to 111° at 3 mm. The hydrochloride melts at 157°. The dihydrogen citrate, $C_{16}H_{29}N_3O_8$, is a white crystalline powder that is soluble in water. It is sparingly soluble in cold ethanol and insoluble in acetone, ether and chloroform. It melts at 136° to 138°. Diethylcarbamazine citrate is used in the treatment of filarial infections and of the elephantiasis to which filariasis often gives rise.

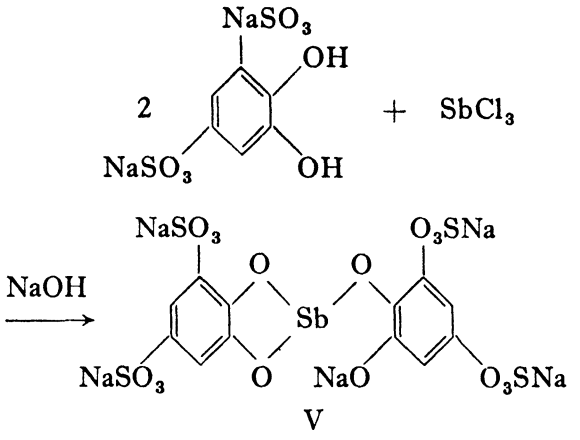
Antimony potassium tartrate. Tartar emetic. $C_4H_4KO_7Sb \cdot \frac{1}{2}H_2O$.

Preparation. Potassium hydrogen tartrate and antimony oxide, Sb_2O_3, are reacted together in hot water at pH 2·0. The solution is filtered free from insoluble matter and then concentrated to yield tartar emetic (10, 11).

Properties. Antimony potassium tartrate forms colourless crystals possessing a sweet taste. It is soluble at 15·5° in 17 parts of water and 20 parts of glycerin. It is soluble in 3 parts of boiling water, but insoluble in ethanol. Tartar emetic is used for the treatment of schistosomiasis.

Stibophen. Sodium antimony bispyrocatechol-3 : 5-sodium disulphonate. $C_{12}H_4Na_5O_{16}S_4Sb.7H_2O$. (V).

Preparation. Sodium pyrocatechol-3 : 5-disulphonate in aqueous solution is reacted with antimony trichloride in ethanol. The mixture is cooled and neutralised to pH 5·5 by means of aqueous sodium hydroxide. Ethanol is added to precipitate the product (12).



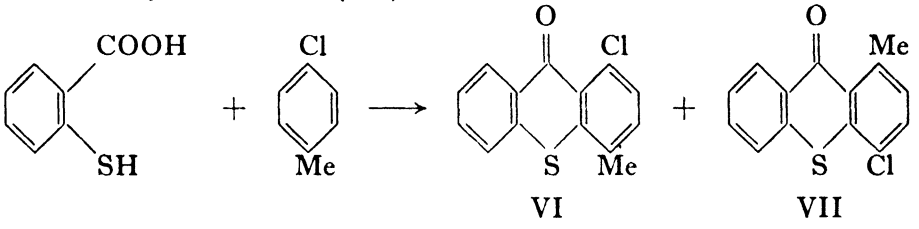
V

Properties. Stibophen dissolves in water to form a solution that becomes yellow on standing. When acidified and treated with a few drops of sodium sulphide a stibophen solution gives an orange precipitate of antimonious sulphide.

Lucanthone. 1-(2-Diethylaminoethylamino)-4-methylthiaxanthone.

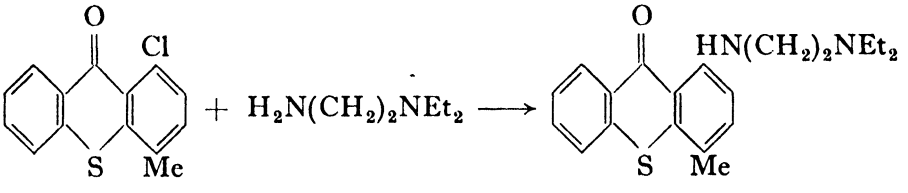
$C_{20}H_{24}N_2OS$. (VIII).

Preparation. In the original method (13, 14), thiosalicylic acid and 4-chlorotoluene were reacted to give a mixture of 1-chloro-4-methyl- (VI), and 4-chloro-1-methylthiaxanthone (VII).



VI VII

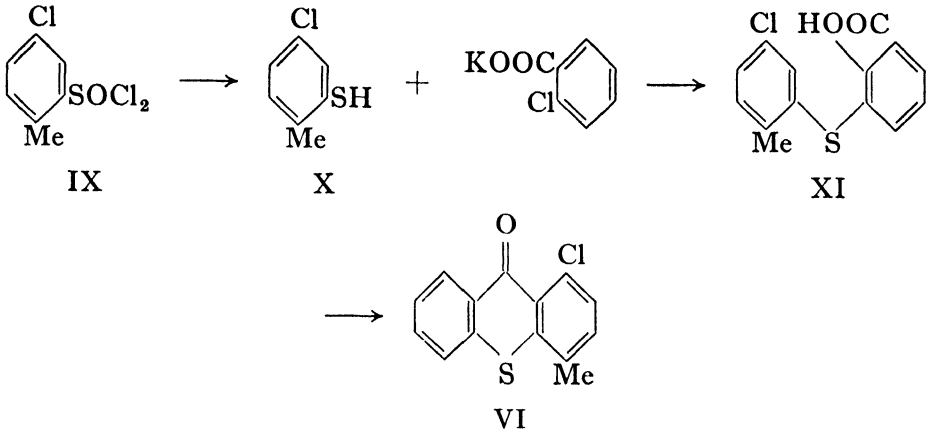
When this mixture of isomers was heated with 2-diethylaminoethylamine only the 1-chloro-4-methylthiaxanthone reacted and lucanthone (VIII) was obtained.



VI VIII

This method is wasteful and an improved process has been described (15, 16), by which it is claimed that pure 1-chloro-4-methylthiaxanthone is obtained. 4-Chlorotoluene is reacted with chlorosulphonic acid and yields 5-chloro-2-methylbenzenesulphonyl chloride (IX). This, on reduction with zinc and sulphuric acid, gives the thiol (X) which is condensed with potassium 2-chlorobenzoate. 2'-Carboxy-5-chloro-2-methyldiphenylsulphide (XI) is obtained and

on cyclisation with concentrated sulphuric acid, yields the required 1-chloro-4-methyl-thiaxanthone (VI). Other methods of synthesising lucanthone have been published (17).



Properties. Lucanthone melts at 64° to 65° and its methiodide at 237° (dec.). The hydrochloride, which is used orally in the treatment of schistosomiasis, melts at 195° to 198°. It forms yellow needles that are soluble in water (1 part in 110 of water at 20° and readily soluble at 60°). It is soluble in warm and sparingly soluble in cold ethanol.

Piperazine adipate. $C_{10}H_{20}N_2O_4$.

Preparation. Piperazine and adipic acid are reacted together in ethanol (18). The salt crystallises out and is filtered and dried.

Properties. Piperazine adipate is a colourless crystalline solid melting at 256° to 257°; it is soluble in water (5 in 100) and practically insoluble in the lower aliphatic alcohols (19). It is used in the treatment of filariasis.

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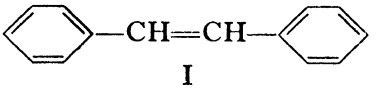
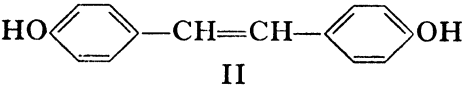
CHAPTER XIV

Synthetic Oestrogens

Introduction. When the work upon the isolation of the oestrogenic hormones was complete, it was found that a group of five steroid compounds possessed oestrogenic activity. It appeared, therefore, that this activity was not dependent upon a specific structure and Cook and Dodds and their collaborators began a study of chemically simpler compounds. All naturally occurring oestrogens contain the partially hydrogenated phenanthrene ring system and in 1933 certain derivatives of phenanthrene were found to possess slight activity (1). In 1936 it was found that compounds such as stilbene (I) and dihydroxystilbene (II), which contain only two rings, were active (2). Stilbene was of particular interest for it was the first synthetic oestrogen to be prepared that contained carbon and hydrogen only.

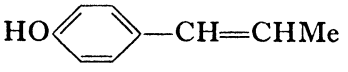


I

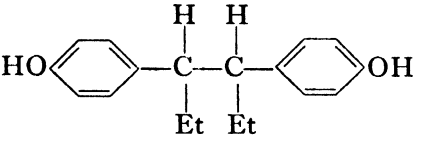


II

In an attempt to reduce the active molecule to still simpler proportions, anol (III) (4-propenylphenol) was prepared (3). It was at first thought to be active, but it was later shown (4) that the activity resided in the hexoestrol (IV) present as a by-product in the anol obtained.

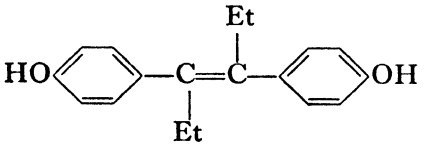


III

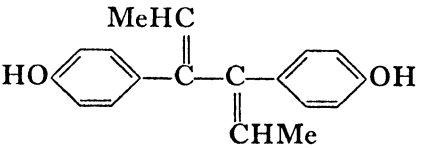


IV

At about the same time, Dodds and his co-workers prepared (5) stilboestrol (V) and dienoestrol (VI), both of which are highly active oestrogenic compounds.



V

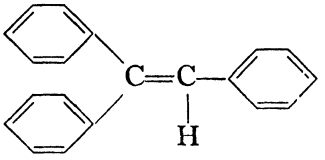


VI

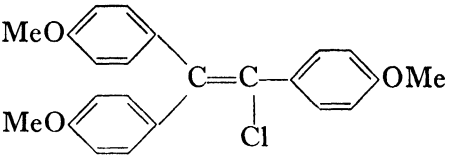
Many compounds related to stilboestrol have been prepared and some such as promethoestrol and benzestrol have been used in general practice.

Stilbene is diphenylethylene. The related compound, triphenylethylene (VII), possesses oestrogenic activity and some interest has been shown in

its derivatives. The earliest work in this series was carried out by Robson (6) and by Dodds (7). One compound that possesses considerable activity is chlorotrianisene (VIII).

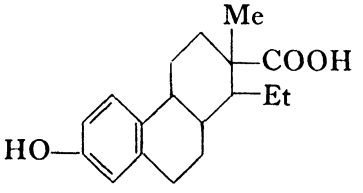


VII

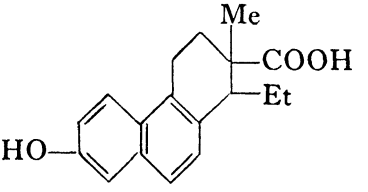


VIII

A further class of oestrogens is known as the doisynolic acids (8). In 1933 Doisy (9) found that by oxidation of oestradiol a degradation product could be obtained which possessed considerable oestrogenic activity. Miescher therefore prepared a number of chemical compounds corresponding to oestrone with the 5-membered ring opened. The following substances possess useful activity: doisynolic acid (IX), bis-dehydrodoisynolic acid (X) and its methyl ether.



IX



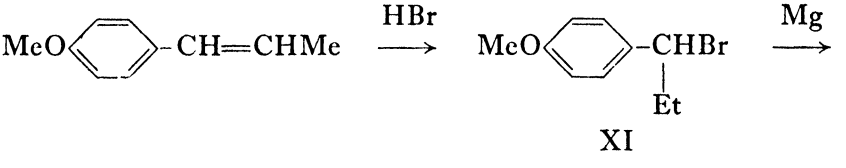
X

The chemistry of these compounds has been reviewed by Fieser (10) and the known chemistry of the synthetic oestrogens up to 1957 has been well reviewed by Grundy (11).

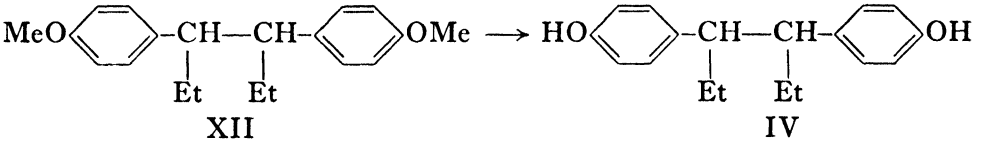
Hexoestrol. Hexestrol. *meso*-3 : 4-Bis-(4-hydroxyphenyl)-hexane.

$C_{18}H_{22}O_2$. (IV).

Preparation. The most useful method for the preparation of hexoestrol is that of Docken and Spielman (12). Anethole is reacted with hydrobromic acid to yield (XI), and two molecules of this compound are coupled in a Wurtz reaction with a metal such as magnesium to give 3 : 4-dianisylhexane (XII) which, on demethylation, yields hexoestrol (IV).



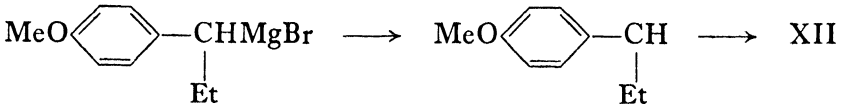
XI



XII IV

The method was reported independently by Peak and Short (13) and Bernstein and Wallis (14). Many variations and improvements upon the method

have been published (15 to 19). Hexoestrol can also be prepared by a method introduced by Kharasch and Kleiman (20). Anethole hydrobromide Grignard compound (XIII) is reduced by cobaltous chloride to a free radical which dimerizes in good yield to hexoestrol dimethyl ether (XII).



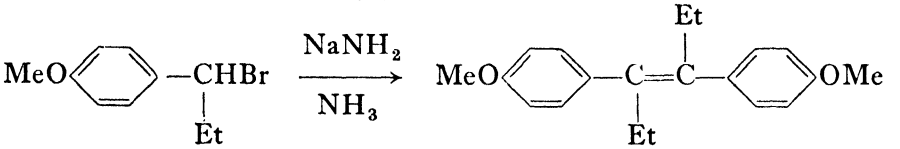
XIII

Many other methods for the synthesis of hexoestrol have been patented and published (21 to 26).

Properties. Hexoestrol is a *meso* compound. The racemate, named *iso*-hexoestrol, has been resolved (27). Hexoestrol, which is an odourless white crystalline powder, melts at 187° to 189°, whereas *iso*hexoestrol melts at 129°. Hexoestrol has the following solubilities (in g/100 ml of saturated solution at 15°): ether 29·1, acetone 10·2, 99 per cent ethanol 18·3, methanol 24·6, benzene 0·17, chloroform 0·19, water 0·007. It is soluble in dilute caustic alkalis.

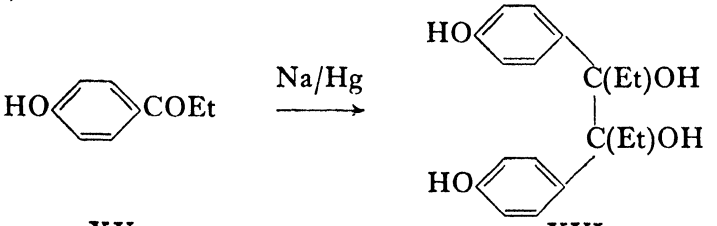
Stilboestrol. Diethylstilboestrol. *trans*-3 : 4-Di(4-hydroxyphenyl)hex-3-ene. $C_{18}H_{20}O_2$. (V).

Preparation. Numerous syntheses of stilboestrol have been published and those in the period up to 1957 have been reviewed by Grundy (11). Since that time, other methods have been described (28, 29, 30). Two routes seem worthy of special notice. In one, anethole hydrobromide, the compound used for the preparation of hexoestrol, is reacted with excess of sodamide in liquid ammonia to yield 4 : 4′-dimethoxy-3 : 4-diphenylhex-3-ene (XIV) which, on demethylation (31, 32), yields stilboestrol (V).

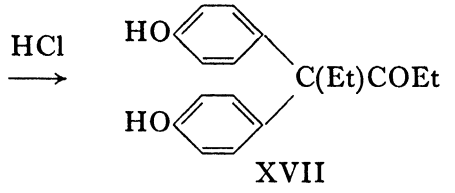


XIV

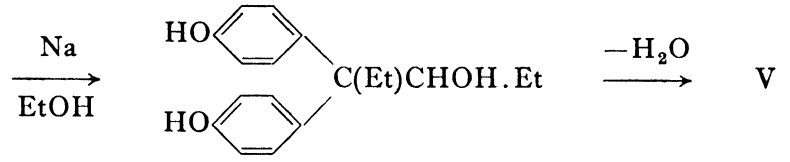
4-Hydroxypropiophenone (XV) is the starting-point for the second route (33, 34). It is reduced to the pinacol (XVI) which, on reaction with gaseous hydrogen chloride, gives the pinacolone (XVII), a compound also used in a synthesis due to Sisido (35). This pinacolone is reduced with sodium and ethanol to the pinacoline alcohol (XVIII) which, on dehydration, yields stilboestrol (V).



XV XVI



XVII



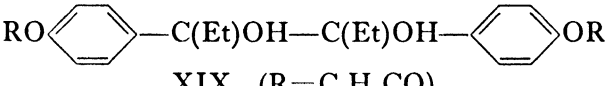
XVIII

Properties. Stilboestrol is the *trans* isomer (36). It is a colourless crystalline material with a m.p. of 170° to 171°. The solubility of stilboestrol in various solvents is as follows (g/100 ml of saturated solution at 15°): ether 32·0, acetone 18·4, ethanol 18·5, methanol 7·5, water 0·03. It is soluble in aqueous alkali hydroxides. The dipropionate melts at 106° to 107° (37).

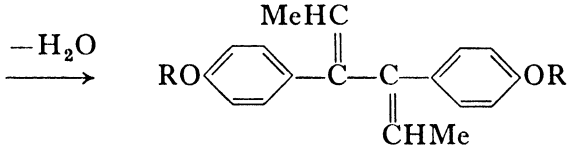
The *cis* isomer which has a m.p. of 110° is very unstable (38, 39). Its dipropionate melts at 79°.

Dienoestrol. Dienestrol. 3 : 4-Bis-(4-hydroxyphenyl)hexa-2 : 4-diene. $C_{18}H_{18}O_2$. (VI).

Preparation. Dienoestrol was first prepared by Dodds and his colleagues (5, 40) by a method involving the dehydration of the *meso* pinacol (XVI) used in the preparation of stilboestrol. This reaction has been studied by Hobday and Short (41, 42) and by Lane and Spialter (43). 4-Hydroxypropiophenone is reduced by sodium amalgam to the pinacol (XVI). This is benzoylated and the crude dibenzoate (XIX) is dehydrated by means of a mixture of acetyl chloride and acetic anhydride. The resulting dienoestrol dibenzoate (XX) is then hydrolysed by alcoholic potassium hydroxide to dienoestrol (VI).



XIX ($R=C_6H_5CO$)



XX ($R=C_6H_5CO$)

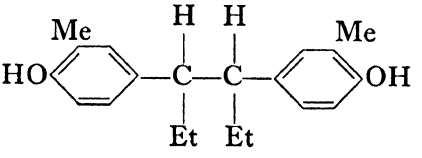
Other methods of synthesis have been patented (44).

Properties. Dienoestrol is the *trans-trans* compound. *Cis-cis* and *cis-trans* isomers also exist. It is a colourless crystalline solid of m.p. 232° to 234°, with the following solubilities in g/100 ml of saturated solution at 15°: ether 8·1, benzene 0·07, chloroform 0·14, acetone 11·6, methanol 13·6, 99 per cent ethanol

11·3, water 0·004. It is soluble in dilute aqueous caustic soda and unstable under mildly acid conditions. The diacetate melts at 119° to 120° and the dipropionate at 123° to 124°.

Promethoestrol. Dimethylhexoestrol. 3 : 4-Bis-(4-hydroxy-3-methyl-phenyl)-hexane. $C_{20}H_{26}O_2$. (XXI).

Preparation. Promethoestrol is made according to the same general method already described above for dienoestrol. In addition, the double bonds are hydrogenated as a final step (45). Another method has been described (46).

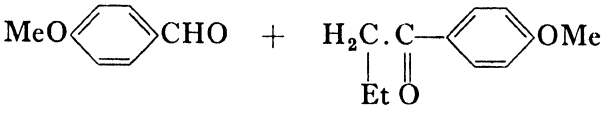


XXI

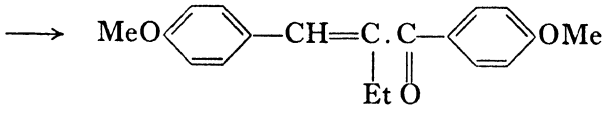
Properties. The dipropionate of m.p. 117° to 119° has been used clinically. It is freely soluble in benzene, ether, ethyl acetate and is slightly soluble in ethanol. It is almost insoluble in water.

Benzestrol. 2 : 4-Bis-(4-hydroxyphenyl)-3-ethylhexane. $C_{20}H_{26}O_2$.

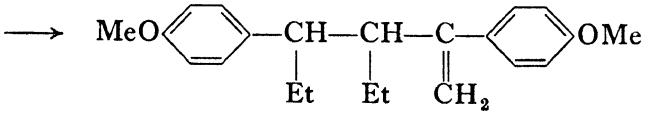
Preparation. This compound, which is a diphenylpropane derivative, was first described by Tallman in 1943 (47), and the synthesis was published in 1945 (48). The synthesis has also been patented (49). Anisaldehyde is condensed with 4-methoxybutyrophenone (XXII) and the compound (XXIII) is obtained. By a series of Grignard reactions the second ethyl group and a methylene group are introduced. Hydrogenation yields (XXIV) and demethylation of the ether leads to crude benzestrol (XXV).

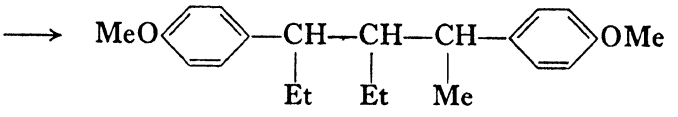


XXII

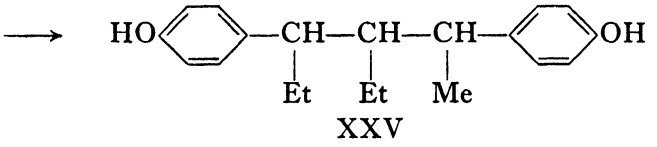


XXIII





XXIV



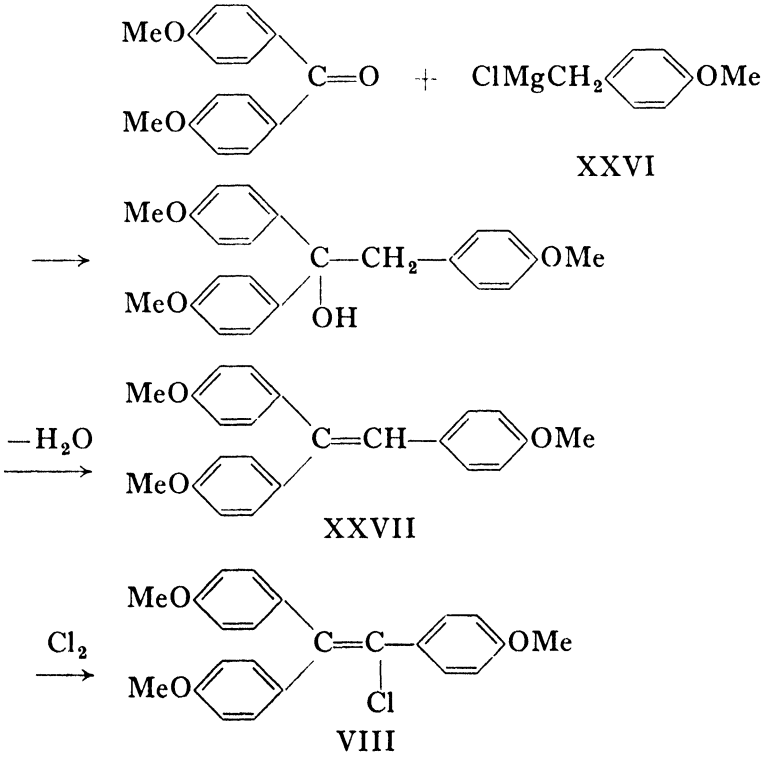
XXV

The reaction product is a mixture of four racemates, one of which is benzestrol. The required isomer is obtained by separation of the two racemic ketones formed as intermediates and further separation of the final product. Other methods for its preparation have been published (50).

Properties. Benzestrol melts at 162°. It is soluble in ether, acetone and ethanol and not very soluble in chloroform and benzene. It is insoluble in water.

Chlorotrianisene. 1 : 1 : 2-Tri-(4-anisyl)-2-chloroethylene. $C_{23}H_{21}ClO_3$. (VIII).

Preparation. Chlorotrianisene which is a triphenylethylene derivative was first described in 1945 (51). A synthesis was published in 1953 (52). It has also been protected by patent (53). 4 : 4′-Dimethoxybenzophenone is reacted in a mixture of ether and benzene with 4-methoxybenzyl-magnesium chloride (XXVI). A carbinol is obtained and is dehydrated by phosphoric acid to the triphenylethylene derivative (XXVII). Chlorination by chlorine in carbon tetrachloride leads to chlorotrianisene (VIII) which has a melting-point of 113° to 114°.



An alternative method of synthesis has been published (54).

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CHAPTER XV

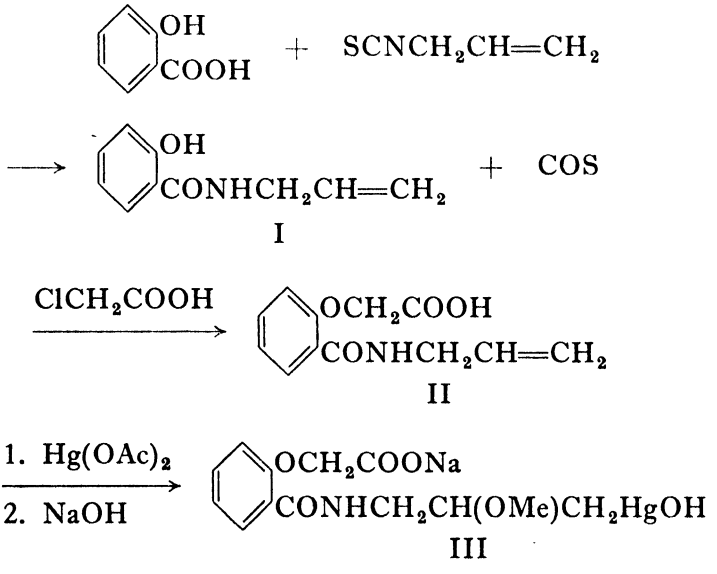
Diuretics

DIURETICS promote urinary secretion and so lead to a loss of body fluid. They are usually employed to stimulate the elimination of oedema fluid. The diuretics in common use are urea, simple salts such as sodium or ammonium chloride, the xanthines (caffeine, theobromine, theophylline and aminophylline), the mercurials and acetazoleamide.

All soluble mercurial compounds possess diuretic properties, and in the organic mercurials the degree of activity depends upon the amount of mercury present. Most of the therapeutic effect of these compounds is due to their affinity for proteins (1). All the mercurials described below, except for chlormerodrin and mercaptomerin, are used in combination with an equimolecular proportion of theophylline. This increases the diuretic effect and lowers the toxicity.

Mersalyl. Sodium salicyl-3-hydroxymercuri-2-methoxypropylamide-O-acetate. $C_{13}H_{16}HgNNaO_6$. (III).

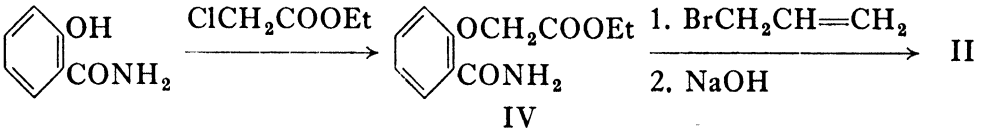
Preparation. The original method of preparation (2) is as follows:



Salicylic acid is heated with allyl *iso*thiocyanate at 140° for 20 hours (3, 4) to yield allylsalicylamide (I). Reaction with chloracetic acid gives a low yield of allylsalicylamide-O-acetic acid (II). Mercuric acetate converts this to mersalyl acid which is dissolved in caustic soda solution to give mersalyl (III).

In a variation of this approach (5) allylamine is first obtained by hydrolysis of allyl *iso*thiocyanate and then reacted with methyl salicylate to give the allylamide. The subsequent steps are the same as those in the original synthesis above.

An alternative approach has been announced (6, 7) in which the acetic acid grouping is fixed before the allyl group. Salicylamide is reacted with ethyl chloroacetate in ethanol in the presence of sodium ethoxide to yield the ethyl ester of salicylamide-O-acetic acid (IV). This is allylated by the use of allyl bromide and then saponified with caustic soda to yield allylsalicylamide-O-acetic acid (II). Mercuration then leads to mersalyl.

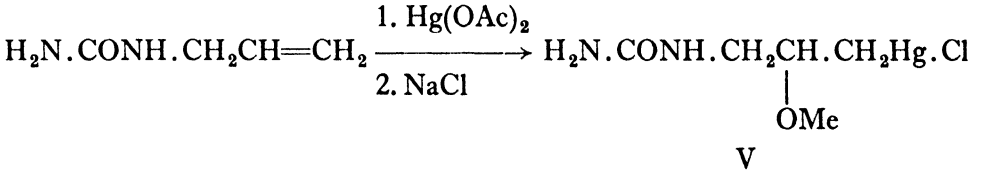


IV

Properties. Mersalyl is a white deliquescent powder with a bitter taste. It is soluble at 20° in 1 part of water, 3 of ethanol and 2 of methanol. It is insoluble in ether or chloroform.

Chlormerodrin. 3-Chloromercuri-2-methoxypropylurea. $C_5H_{11}ClHgN_2O_2$. (V).

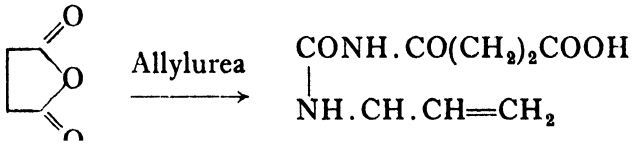
Preparation. Allylurea is reacted with mercuric acetate in methanol in the presence of acetic acid. The hydroxy compound obtained is converted to the chloride by reaction with aqueous sodium chloride solution (8, 9). The product is recrystallised from ethanol. It is a white powder of m.p. 152° to 153°. The above reaction of mercuric acetate with a diene such as allylurea is common in the preparation of organic mercurial diuretics.

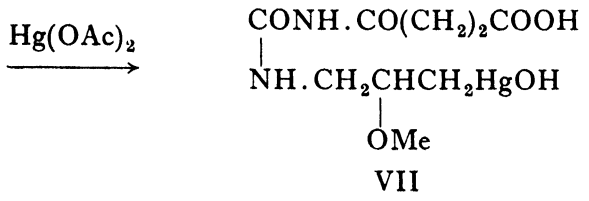


V

Meralluride. Methoxyhydroxymercuri-propylsuccinylurea. 1-(3-Hydroxymercuri-2-methoxypropyl)-3-succinylurea. $C_9H_{16}HgN_2O_6$. (VII).

Preparation. Allylurea and succinic anhydride are first reacted together to yield 2-carboxypropionylallylurea (VI). This is mercurated in methanol to meralluride (10, 11).



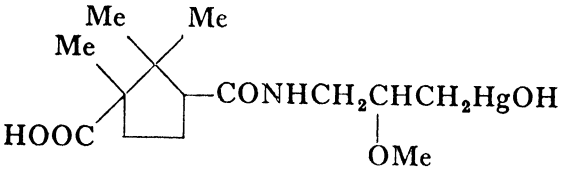


VII

Properties. Meralluride melts at 188·5° to 190·5° (dec.) and the corresponding bromide at 163° to 163·5°. This mercurial diuretic is converted to its sodium salt and combined with an equimolecular proportion of theophylline to give meralluride sodium with theophylline monohydrate.

Mercurophylline. 2-Methoxy-3-hydroxymercuripropylamide of trimethyl-*cyclo*pentanedicarboxylic acid. $C_{14}H_{25}HgNO_5$. (VIII).

Preparation. Mercurophylline is prepared by the action of mercuric acetate in methanol upon the corresponding allyl compound (12).

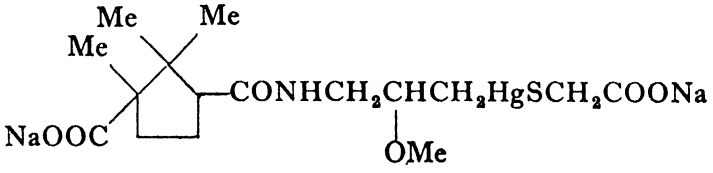


VIII

Properties. For use the mercurial compound above is converted to its sodium salt and then combined with theophylline. The complex so obtained is a white odourless powder that is hygroscopic and darkens in air. Its aqueous solutions are alkaline. 1 g dissolves in 5 ml of water. It is soluble in ethanol and insoluble in ether.

Mercaptomerin sodium. Disodium salt of N-(3-carboxymethylmercaptomercuri-2-methoxy)-propyl camphoramic acid. $C_{16}H_{25}HgNNa_2O_6S$. (IX).

Preparation. The compound (VIII) above is reacted with one equivalent proportion of the sodium salt of the thioglycollic acid, $NaOOC.CH_2SH$, in aqueous alkali (13). The solution is evaporated to give the disodium salt of mercaptomerin.

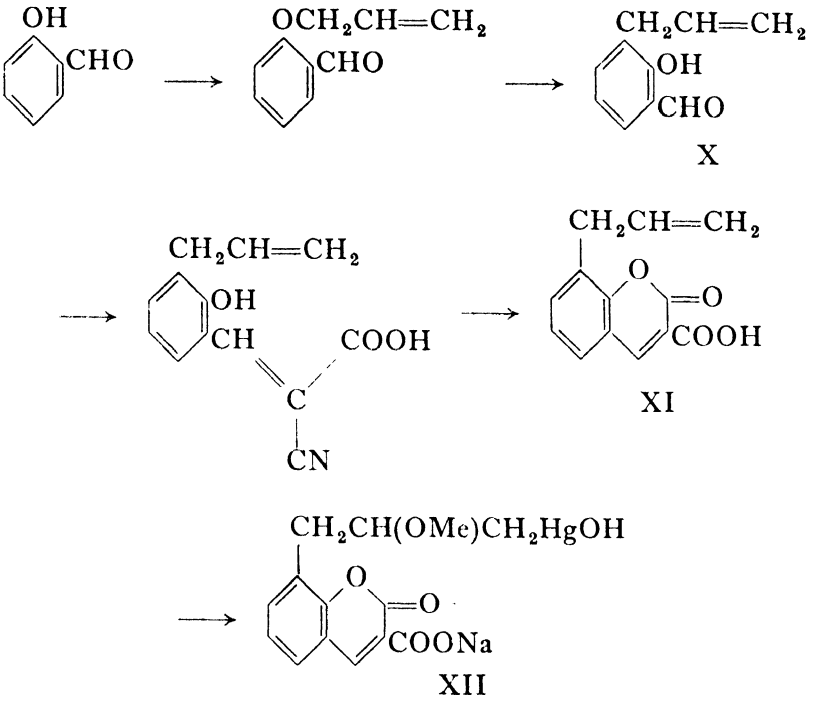


IX

Properties. Mercaptomerin sodium is a hygroscopic white solid that is soluble in water and in ethanol. It is almost insoluble in ether, benzene or chloroform.

Mercumatilin. Sodium salt of 8-(2-methoxy-3-hydroxymercuripropyl)-coumarin-3-carboxylic acid. $C_{14}H_{13}HgNaO_6$. (XII).

Preparation. Salicylaldehyde is reacted with allyl bromide in ethanol in the presence of potassium carbonate and the resulting allyl ether, on being heated to 225°, undergoes a curious rearrangement to give X. This is then reacted with cyanoacetic acid and the compound obtained, now containing a nitrile group, is hydrolysed, decarboxylated and ring-closed by hydrochloric acid. Thus 8-allylcoumarin-3-carboxylic acid (XI) is obtained. Addition of mercuric acetate in methanol as usual leads to the free acid corresponding to mercumatilin. Aqueous sodium bicarbonate is then added and mercumatilin is obtained. It is administered as the theophylline complex (14).

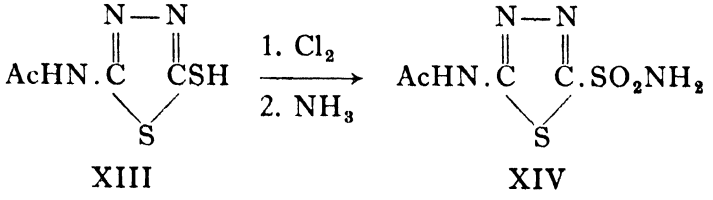


Properties. The free acid corresponding to mercumatilin melts at 155° to 160°.

Acetazolamide. 2-Acetylamino-1 : 3 : 4-thiadiazole-5-sulphonamide.

$C_4H_6N_4O_3S_2$. (XIV).

Preparation. 2-Acetylamino-1 : 3 : 4-thiadiazole-5-thiol (XIII) obtained from thiourea (15) is dissolved in dilute acetic acid, cooled and gaseous chlorine introduced (16). The sulphonyl chloride is obtained and is amidated by liquid ammonia to yield acetazolamide (XIV).

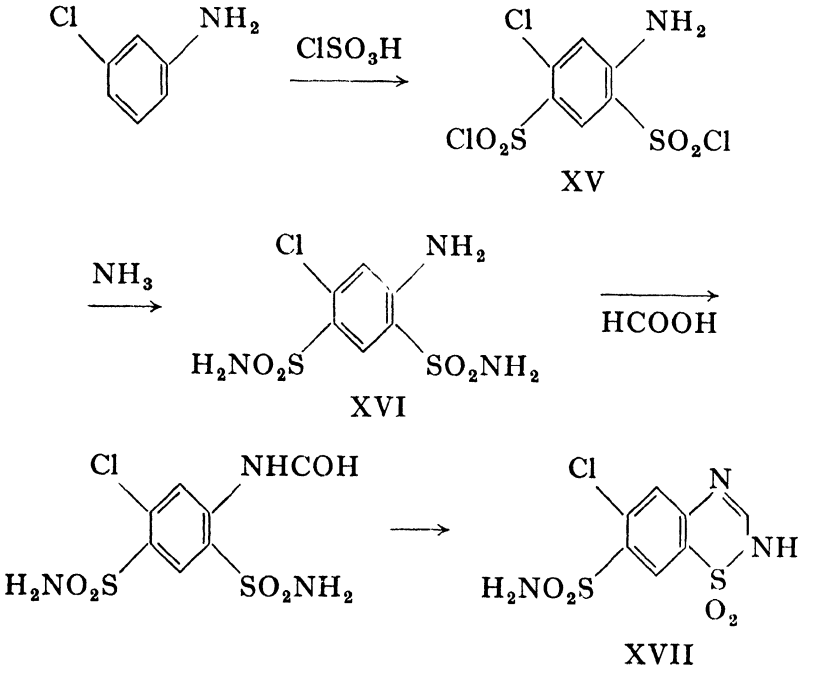


XIII XIV

Properties. Acetazolamide, which was introduced in 1952, is a new type of diuretic. It is a white solid of m.p. 258° to 259°.

Chlorothiazide. 6-Chloro-7-sulphamoylbenzo-1 : 2 : 4-thiadiazine-1 : 1-dioxide. $C_7H_6ClN_3O_4S_2$. (XVII).

Preparation. 3-Chloroaniline when reacted with chlorosulphonic acid in the presence of sodium chloride yielded the disulphonyl chloride (XV) which was converted to the disulphonamide (XVI). Formic acid gave the formyl compound which then ring closed to chlorothiazide (XVII). The disulphonamide and chlorothiazide both have diuretic properties (17, 18).



Properties. Chlorothiazide was introduced in 1957; it melts at 342·5° to 343° (dec.).

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CHAPTER XVI

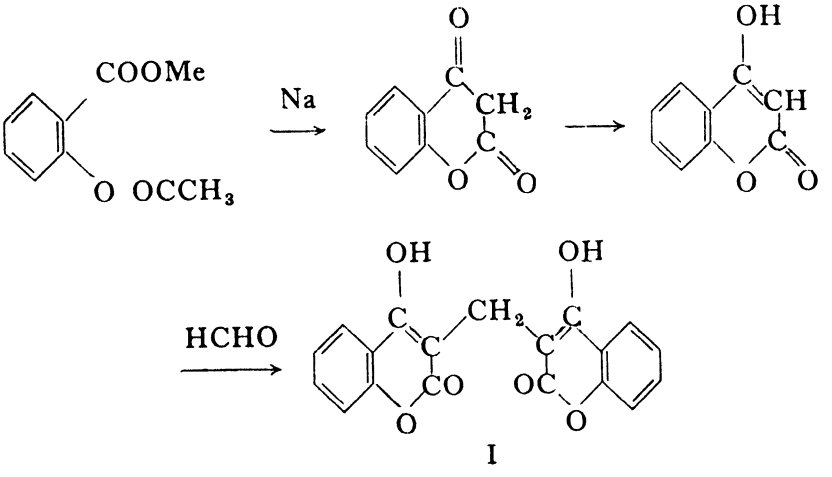
Anticoagulants

MANY cardiovascular difficulties involve the blood coagulation mechanism. Thrombosis, i.e. the clotting of blood within the blood vessels, is an ever present risk in all major surgical operations. The anticoagulant drugs are able to prevent this clotting by interference with the complicated biochemical mechanism that brings it about.

The main coagulants in use are heparin (see p. 367), dextran sulphate, the coumarin derivatives and phenindione. Heparin is the natural anticoagulant found in the body.

Dicoumarol. Bishydroxycoumarin. $C_{19}H_{12}O_6$. (I).

Preparation. Methyl salicylate is acetylated with acetic anhydride in the presence of a trace of concentrated sulphuric acid and methyl acetylsalicylate is obtained. When the latter compound is added to liquid paraffin at 245° containing molten sodium, the sodium compound of 4-hydroxycoumarin forms and is converted to the parent compound by addition of hydrochloric acid. Then by reaction of 4-hydroxycoumarin with aqueous formaldehyde, dicoumarol is precipitated (1).



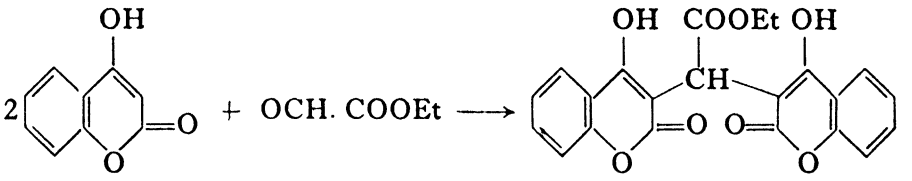
I

Properties. Dicoumarol was shown by Link and his associates (2) to be the active agent present in spoiled sweet clover that often caused a fatal haemorrhagic disease in cattle. It was in this way that its anticoagulant powers were discovered.

It is a white solid of m.p. 288° to 289° that is only slightly soluble in water but forms salts with strong alkalis and these compounds are water soluble at pH 8. It is active orally.

Ethyl biscoumacetate. $C_{22}H_{16}O_8$. (II).

Preparation. 4-Hydroxycoumarin is condensed with the ethyl ester of glyoxylic acid (3), ethyl dichloroacetate (4), ethyl diethoxyacetate (5) or the semiacetate HOCHOEt.COOEt (6).

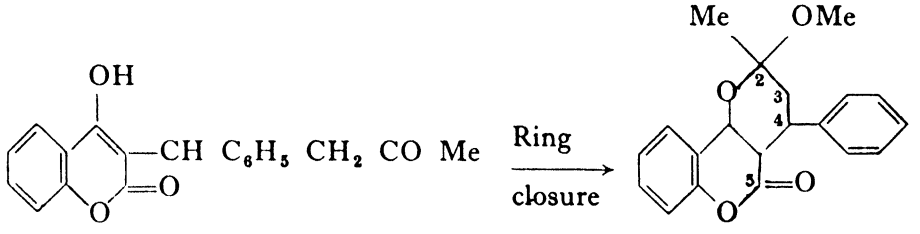


Ethyl glyoxylate II

Properties. Ethyl biscoumacetate is a white crystalline powder that exists in two forms having melting-points of 153° to 154° (from methanol) and 173° (from acetic acid). It is more prompt in action than dicoumarol.

Cyclocoumarol. 3 : 4-Dihydro-2-methoxy-2-methyl-4-phenyl-2H; 5H-pyrano-1-benzopyran-5-one. (IV).

Preparation. 3-(1-Phenyl-2-acetylethyl)-4-hydroxycoumarin (III) is reacted with methanolic hydrogen chloride at the b.p. (7). The preparation of III has been described (8).

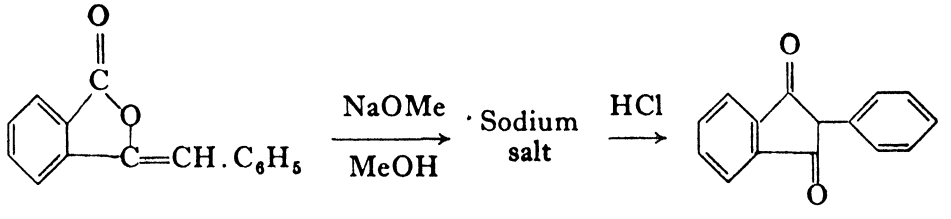


III IV

Properties. Cyclocoumarol has a m.p. of 166°. It is insoluble in water and slightly soluble in ethanol.

Phenindione. Phenylindanedione. $C_{15}H_{10}O_2$. (V).

Preparation. This compound was made by Nathanson (9) in 1893 by the following method:



Benzalphthalide V

Benzalphthalide which is obtained from phthalic anhydride and benzilic acid (10) is reacted with sodium methoxide in methanol. The sodium salt obtained is then acidified to give phenindione.

In an alternative method (11) phenindione is made by condensing phthalid with benzaldehyde.

Properties. Phenindione has a m.p. of 149°. It is soluble in the usual organic solvents and in caustic soda solution and ammonium hydroxide. It is insoluble in water.

Dextran sulphate.

Preparation. Dextran, which is a plasma substitute (12), is a polysaccharide composed entirely of glucose units, and is produced by the action of the non-pathogenic coccus *Leuconostoc mesenteroides* upon a substrate of sucrose and phosphate (13, 14). The sulphate is made by the reaction of dextran in pyridine with chlorosulphonic acid (15).

Properties. Only the lower polymers of molecule weight about 8,000 are sufficiently non-toxic for use as anticoagulants.

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CHAPTER XVII

Diagnostic Agents

THESE drugs are used to reveal anatomic evidences of disease, or to test the functional capacity of certain organs of the body. It is for the latter purpose that the X-ray contrast media are used.

Hypertension due to pheochromocytoma can be diagnosed by the use of certain drugs. In this condition a tumour is present in the body and characteristically gives rise to excessive adrenaline and noradrenaline in the blood stream. Adrenergic blocking agents counteract the pressor activity of these compounds and so cause a sharp fall in the blood pressure. Phentolamine, dibenzylaminoethyl chloride and piperoxane are used for this purpose. The first two compounds have been described under Adrenergic blocking agents (p. 74).

In the condition known as myasthenia gravis, the skeletal muscles are unable to function with their normal power, due to a low concentration of acetylcholine at the motor end-plates. Neostigmine or edrophonium, which are anticholinesterases, reduce the rate of destruction of acetylcholine and lead to a temporary increase in muscle power. These two compounds are antagonists of skeletal muscle relaxants and are described in the chapter devoted to these compounds (p. 90).

Kidney disorders may be investigated by the use of diagnostic agents. Mannitol, inulin and sodium thiosulphate, for example, are almost completely eliminated from the blood by the glomeruli of the healthy kidney. Damaged glomeruli show much lower elimination rates than normal. Sodium 4-aminohippurate is a compound that is often used to measure the flow of blood plasma through the kidneys. Phenol red and indigocarmine have been used for the same purpose.

Dyes such as azovan blue and Congo red are employed in the determination of blood volume, a factor important in impending shock. The dye, which combines firmly with plasma albumin, is injected intravenously and its subsequent concentration in a blood sample is measured. This gives a measure of the dilution of the dye and thus of the total blood volume.

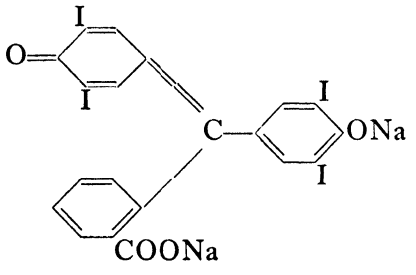
Quinine carbacrylic resin, an ion exchange resin, is employed as an indicator for the detection of excess of gastric acidity. It is the quinine salt of a polyacrylic acid. On oral administration, the quinine is displaced from the resin by the hydrogen ions of free hydrochloric acid present in the stomach. Quinine appears in the urine and may there be estimated photometrically.

Contrast media were introduced soon after the discovery of X-rays in 1895. A detailed radiographic image of the softer parts of the body can only be obtained when a difference in radio-opacity has been achieved. For this purpose, contrast media are introduced into the area. The medium usually renders the area more opaque, but the reverse procedure is occasionally employed. Thus the stomach

can be outlined to some extent by giving the patient a mixture of sodium bicarbonate and tartaric acid and rendering the stomach lining visible against the surrounding tissue because of the carbon dioxide present.

The capacity of an element to absorb X-rays depends upon its atomic number. Substances of high atomic number such as bismuth nitrate, bismuth sulphate and barium sulphate were used, but they are limited to those parts of the body from which they can be directly excreted. Thus barium sulphate is now used only for visualisation of the alimentary canal. Iodine absorbs strongly in the wavelengths used for X-ray diagnosis and iodine compounds are in use as contrast media. Sodium iodide was introduced as an X-ray diagnostic aid but was soon replaced by organic iodo-compounds. Iodised oil was first advocated as a contrast medium by Sicard in 1921, and since then, many iodine addition products of unsaturated vegetable oils have been employed. The main constituent of these products is glyceryl diiodostearate.

The early procedures employed in radiography involved placing the radio-opaque compound at the site to be examined. An easier method was introduced for gall-bladder visualisation by Graham and Cole in 1924. They showed that chlorinated and brominated phenolphthalein were concentrated and excreted by the liver. Thus these substances were possible contrast media. Whitaker and Milliken in 1925 showed that the corresponding iodine compound was less toxic and it came into general use as iodophthalein (I) for oral or intravenous administration. The isomer disodium phenoltetraiodophthalein (II) was also employed.



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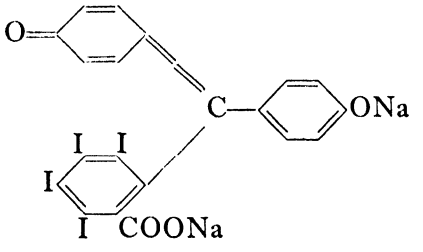


II

The compound pheniodol (XIII) was first used in 1940 and it has now largely replaced iodophthalein. Since the introduction of X-ray contrast media in the early years of the present century there has been considerable expansion in both their numbers and application.

The iodination of a benzene ring by iodine is a substitution reaction liberating one equivalent of hydriodic acid. The latter substance tends to reduce the iodo-compound formed and must therefore be removed. This is done by neutralising with an alkali or by addition of an oxidising agent. When iodine monochloride or iodide-iodate are used, an acid medium is necessary.

Iodised oil.

Preparation. Vegetable oils, such as rape oil, maize oil, and arachis oil have

been iodinated and used as X-ray contrast media. Iodised oil B.P. is an iodine-addition product of poppy-seed oil. It has been prepared by iodination with iodine trichloride (1), but the product then contains chlorine and a better method is that in which hydriodic acid is used (2).

Properties. Iodised oil is a pale yellow clear liquid with no odour and a bland oily taste. It is unstable to air and sunlight. The iodine percentage can vary from batch to batch and the product must have a weight per ml of 1·34 to 1·37 g at 20°. The combined iodine should be 40 per cent. Iodised oil is soluble in ether, chloroform and light petroleum. It is insoluble in water.

Iodised oil is used in the examination of the bronchial passages.

Methiodal sodium. Sodium iodomethanesulphonate. CH_2INaO_3S. (III).

Preparation. Methyl iodide is reacted with sodium sulphite (3, 4).

$$CH_3I + Na_2SO_3 \longrightarrow CH_2INaO_3S$$

III

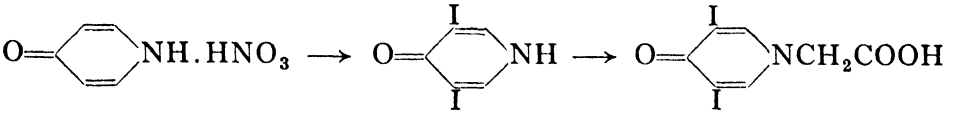
Diiodomethane is formed as an intermediate and has been used as a starting material (5). Other methods have also been employed (6, 7).

Properties. Methiodal sodium is a white odourless crystalline powder, with a slight saline taste and a sweetish after-taste It is unstable to light. It is soluble in water giving a neutral solution. It is soluble in methanol, slightly soluble in ethanol and insoluble in acetone, benzene and ether.

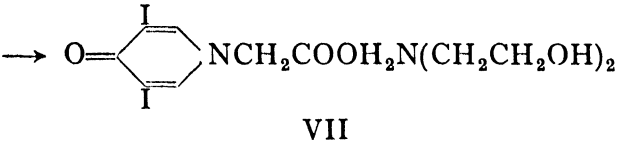
Methiodal is used by injection for the visualisation of the urinary tract.

Diodone. Diethanolamine salt of 1 : 4-dihydro-3 : 5-diiodo-4-oxo-1-pyridyl-acetic acid. $C_{11}H_{16}I_2N_2O_5$. (VII).

Preparation. Investigations into methods available for the commercial production of 3 : 5-diiodo-4-oxo-1-pyridylacetic acid were carried out by Hackman (8) and by Baker (9). The substance was introduced in Germany in 1932 and the German method of preparation has been published (10). Pyridone hydrochloride is converted to the nitrate (IV) and this is iodinated by the reaction between sodium iodide and sodium iodate in sulphuric acid, whereby iodine is liberated. The crude iodopyridone (V) so obtained is purified by precipitation from aqueous alkali by addition of mineral acid and is then reacted with chloroacetic acid. The substituted pyridylacetic acid (VI) obtained as a product melts at 245° to 247°. Reaction with diethanolamine produces diiodone (VII).



IV V VI



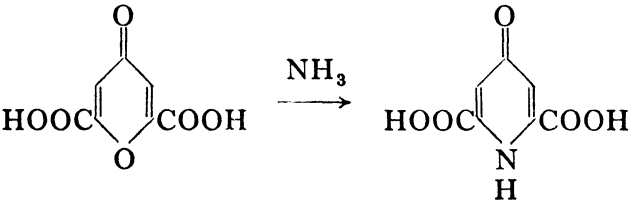
VII

Diodone is employed as an intravenous aqueous injection solution for visualisation of the kidneys and the urinary tract.

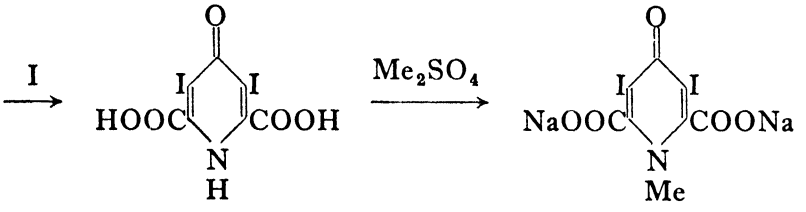
Propyliodone is chemically related to diiodone and is propyl 3 : 5-diodo-4-pyridone-N-acetate. It was introduced in 1953 by Tomich for bronchography. It is a white crystalline solid of m.p. 186° to 187° (dec.). The solubilities in 100 ml of water at 15°, 35° and 95° are 0·014, 0·02 and 0·11 g respectively. It is slightly soluble in serum and saline.

Iodoxyl. Disodium 3 : 5-diiodo-N-methyl-4-pyridone-2 : 6-dicarboxylate. $C_8H_3I_2NNa_2O_5$. (X).

Preparation. Chelidonic acid (VIII) is reacted with aqueous ammonia to yield chelidamic acid (IX) which is iodinated by alternately acidifying and neutralising a solution of chelidamic acid and iodine in alkali (8). Methylation is accomplished by dimethyl sulphate in caustic soda solution. The product, N-methyl-3 : 5-diiodo-chelidamic acid, is easily converted to its disodium salt (X).



VIII IX



X

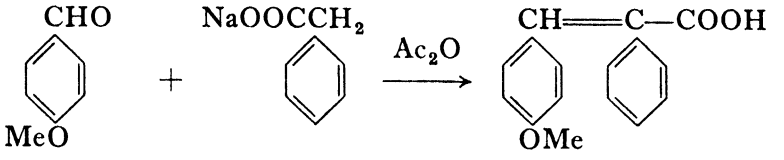
Properties. Iodoxyl is a white odourless powder that is soluble at 20° in 1 part of water and 100 parts of 95 per cent ethanol. It is insoluble in ether and chloroform. The parent dicarboxylic acid melts at 173° to 174°.

Iodoxyl is used particularly for examination of the kidneys and ureter.

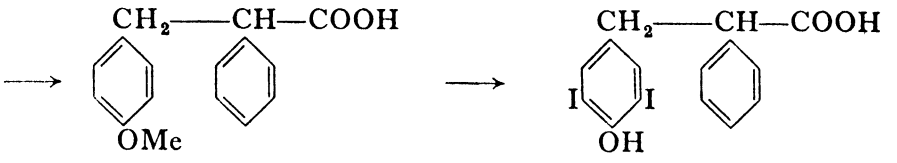
Pheniodol. Iodoalphionic acid. 3 : 5-Diiodophenylphloretic acid. $C_{15}H_{12}I_2O_3$. (XIII).

Preparation. This compound was introduced in 1940 and the method of preparation has been published (11). Anisaldehyde is condensed in a Perkin reaction with sodium phenylacetate in acetic anhydride. The resultant 1-phenyl-2-(methoxyphenyl)acrylic acid (XI) is purified through its sodium salt and then reduced in methanolic solution by hydrogen at 50 atmospheres in the presence of Raney nickel. 4-(Methoxyphenyl)phenylpropionic acid (XII) is obtained. It is demethylated by heating with 48 per cent hydrobromic acid, and then iodinated

by the use of iodine in the presence of aqueous ammonia (12). Other workers (9) have used iodine monochloride. The pheniodol (XIII) formed can be purified by crystallising it from aqueous ethanol.



XI



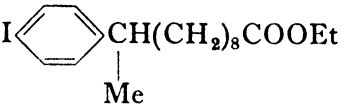
XII XIII

Properties. Pheniodol is a white crystalline powder with a m.p. of 158° to 162° (dec.). It is insoluble in water, soluble in ether and ethanol and not very soluble in benzene, toluene or chloroform. It dissolves in 5·8 parts of benzene at the boiling-point and in 120 parts at room temperature.

Pheniodol contains an optically active carbon atom and the inactive material has been resolved into the optically active isomers (13).

Ethyl iodophenylundecanoate. Iophendylate. Ethyl-10-(4-iodophenyl)-undecanoate. $C_{19}H_{29}IO_2$. (XIV).

Preparation. The corresponding acid is esterified with ethanol to yield the required ester (14).



XIV

Properties. Ethyl iodophenylundecanoate is mainly the compound shown above, but other isomers are present. It is a colourless, odourless oil, with boiling-points of 196° to 198° at 1 mm and 180° at 0·2 mm. The weight per ml is 1·245 to 1·260 g at 20°, and the refractive index is 1·525 to 1·527 at 20°. It is slightly soluble in water and freely soluble in organic solvents.

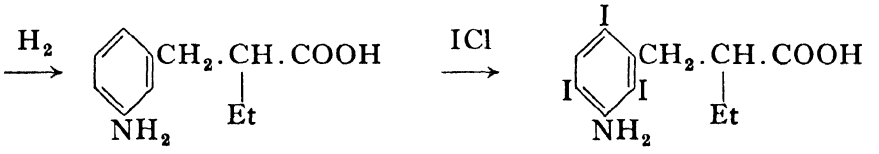
It was introduced in 1942 and is used by injection for visualisation of the spinal canal.

Iopanoic acid. 2-(3-Amino-2 : 4 : 6-triodophenyl)-1-ethylpropionic acid. $C_{11}H_{12}I_3NO_2$. (XVI).

Preparation. 3-Nitrobenzaldehyde is condensed with butyric anhydride in the presence of sodium butyrate in a Perkin reaction (15, 16, 17) to yield the substituted cinnamic acid (XV). This is then reduced by hydrogen at 500 lb/sq. in.

with a Raney nickel catalyst in caustic soda; iodination by iodine monochloride in acid solution leads to iopanoic acid (XVI) which is crystallised from a mixture of chloroform and light petroleum.

XV

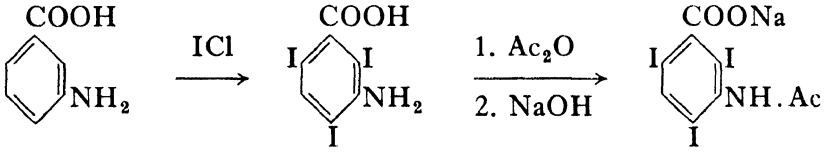


XVI

Properties. Iopanoic acid is insoluble in water and soluble in ethanol, acetone and alkalis. It is a cream coloured powder, odourless and tasteless, with a m.p. of 156° to 158°. It is used orally for visualisation of the gall-bladder and the biliary tract.

Sodium acetrizoate. Sodium 3-acetamido-2 : 4 : 6-triiodobenzoate. $C_9H_5I_3NNaO_3$. (XVII).

Preparation. 3-Aminobenzoic acid is iodinated by iodine monochloride and the amino group is then acetylated by the use of acetic anhydride (18, 19, 20). The acid formed is decolorised by charcoal as the ammonium salt, is reprecipitated by addition of hydrochloric acid and converted to sodium acetrizoate (XVII).



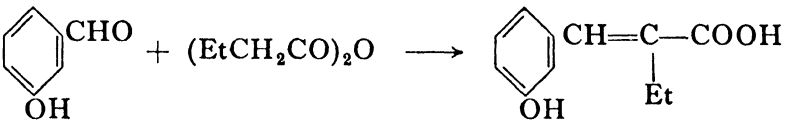
XVII

Properties. Sodium acetrizoate is very soluble in water and is used for intravenous radiography as a 30 per cent or a 70 per cent solution. An aqueous solution is clear and colourless, and has pH 7·0 to 7·4. The corresponding acid melts at 280° (dec.) and its ethyl ester at 207°.

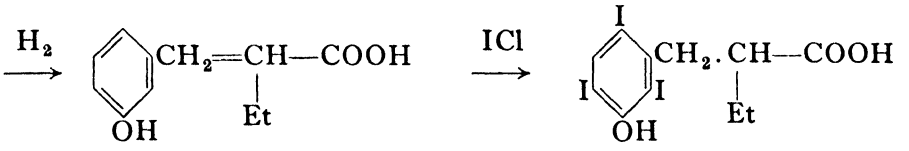
Iophenoxic acid. 1-Ethyl-2-(3-hydroxy-2 : 4 : 6-triiodophenyl)propionic acid. $C_{11}H_{11}I_3O_3$. (XIX).

Preparation. 3-Hydroxybenzaldehyde is condensed with butyric anhydride in the presence of sodium butyrate to give ethylhydroxycinnamic acid (XVIII). This is hydrogenated (21) in 10 per cent caustic soda solution with Raney nickel, at 2 to 3 atmospheres. Iodination of the product by iodine monochloride yields

iophenoxic acid (XIX) which may be recrystallised from a mixture of benzene and light petroleum.



XVIII



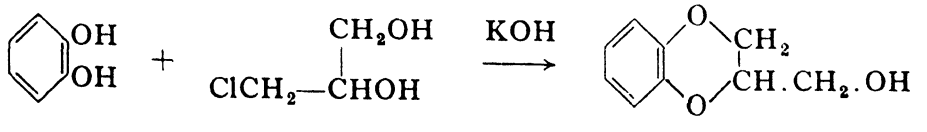
XIX

Properties. Iophenoxic acid is a white crystalline powder with a faint odour and characteristic taste. It melts at 142° to 143°, is slightly soluble in water and freely soluble in ethanol. It is administered orally after a fatty meal and allows the visualisation of the gall-bladder.

Other diagnostic agents

Piperoxane. 2-(1-Piperidylmethyl)-1 : 4-benzodioxane. $C_{14}H_{19}NO_2$. (XXII).

Preparation. Pyrocatechol is treated with glyceryl monochlorohydrin in the presence of potassium hydroxide to yield 2-hydroxymethyl-1 : 4-benzodioxane (XX). Treatment with thionyl chloride in pyridine leads to the 2-chloro compound (XXI) and this, condensed with piperidine, gives piperoxane (XXII). The method has been patented (22).



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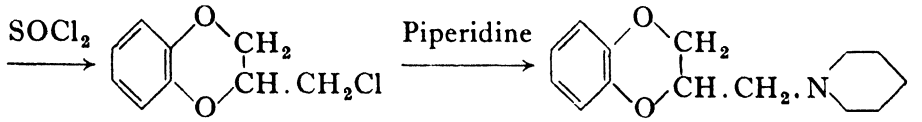
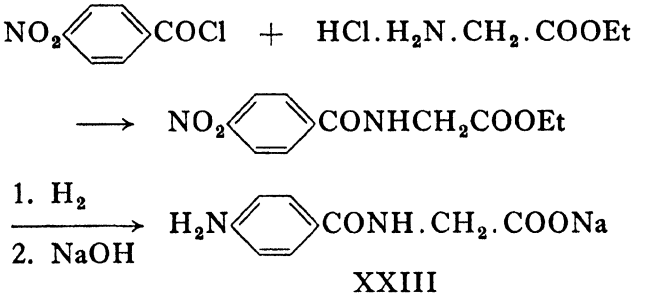


XXI XXII

Properties. Piperoxane in the form of its hydrochloride is a white crystalline material of m.p. 232° to 236° and is used as a diagnostic agent for hypertension due to pheochromocytoma. The picrate melts at 165° to 168°.

Sodium aminohippurate. Sodium 4-aminobenzoylglycinate. $C_9H_{10}N_2O_3$. (XXIII).

Preparation. Nitrobenzoyl chloride is reacted with glycine ethyl ester hydrochloride (23) and the nitro compound is reduced (24) to aminohippuric ester from which the sodium salt (XXIII) is prepared by saponification.



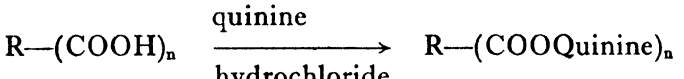
XXIII

The nitro group may be reduced by tin or iron and acid or by hydrogenation using Raney nickel as catalyst.

Properties. Sodium aminohippurate is used to measure the flow of blood plasma through the kidneys. 4-Aminohippuric melts at 198° to 199°. It is soluble in ethanol, chloroform, benzene and acetone and sparingly soluble or insoluble in ether, carbon tetrachloride and water. The ethyl ester melts at 93° to 95°.

Quinine carbacrylic resin. (XXIV).

Preparation. A cationic exchange resin in its acidic form is allowed to react with quinine hydrochloride in aqueous solution (25 to 27). The quininium resin compound (XXIV) is formed.



XXIV

On oral administration the quininium cation is displaced by hydrogen ions in the stomach and is estimated in the urine by a fluorometric technique. By this method gastric acidity can be measured.

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CHAPTER XVIII

Miscellaneous Synthetic Drugs

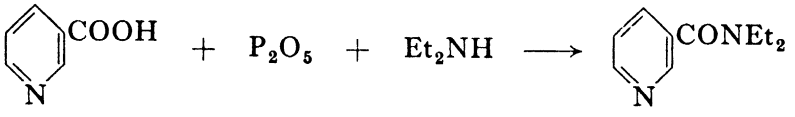
IN this chapter are included certain drugs which do not warrant a chapter to themselves such as the analeptics, the antithyroid drugs, synthetic purgatives and certain groups that are of interest, but have not been explored to a sufficient extent for extended treatment.

ANALEPTICS

These compounds are stimulants of the central nervous system, particularly of that part controlling respiration. They are thus anti-narcotics and convulsants. The main analeptics are strychnine and brucine, picrotoxin, caffeine, theobromine and theophylline among natural compounds (see Part II). The synthetic analeptics nikethamide and leptazol are described below. In addition certain of the sympathomimetic amines, e.g. amphetamine, have analeptic properties.

Nikethamide. NN-Diethylnicotinamide. $C_{10}H_4N_2O$. (I).

Preparation. Nicotinyl chloride may be reacted with diethylamine or its hydrochloride (1), but the preparation of the acyl chloride is not straightforward (2) and other methods of preparation of nikethamide have been used. Nicotinic acid, for example, has been heated with phosphorus pentoxide and diethylamine in toluene (3).



I

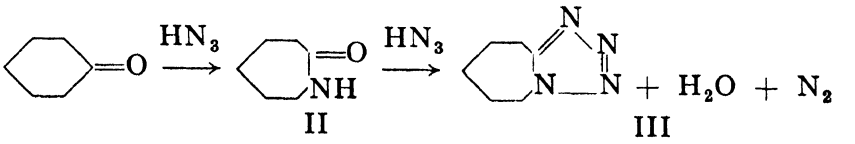
Quinolinic acid anhydride and diethylamine may be reacted together and the product decarboxylated to give nikethamide (4). Other methods have been described (5).

Properties. Nikethamide is a colourless liquid of b.p. 280° and f.p. of 23° to 25°. It has a weight per ml at 20° of 1·060 to 1·063 g. It readily mixes with water, and is soluble in ethanol, ether, chloroform and acetone.

It was introduced in 1924 and is a respiratory stimulant acting against such central nervous system depressants as morphine and the barbiturates.

Leptazol. Pentylenetetrazol. 1 : 5-Pentamethylenetetrazole. $C_6H_{10}O_4$. (III).

*Preparation. cyclo*Hexanone or its oxime is reacted with hydrazoic acid. When the ketone is used, the reaction is as follows:



II III

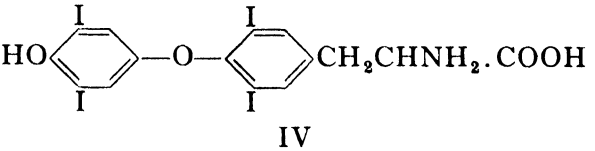
The reaction probably goes by way of the intermediate 2-keto-hexamethylenimine (II) which is not isolated. Hydrazoic acid is explosive when pure, but in solution in a mixture of benzene and light petroleum it is safe to handle. An aqueous solution of sodium azide at 3° is acidified with sulphuric acid. Hydrazoic acid forms and is dissolved out with benzene - light petroleum. A catalytic amount of ferric chloride is added to the hydrazoic acid solution and then the *cyclo*hexanone is added slowly with stirring and cooling. The reaction mixture is finally basified and the product extracted with benzene. It may be distilled at 150° to 153° at 0·45 mm or crystallised from a mixture of benzene and light petroleum (6).

In the alternative method using *cyclo*hexanone oxime (7, 8) the oxime in ethylene dichloride is added to a mixture of sodium azide and chlorosulphonic acid in the same solvent. Excess chlorosulphonic acid is decomposed by the addition of water, and the lower sulphuric acid layer containing the leptazol and some leucine lactam as an impurity is separated from the ethylene dichloride. It is heated to 95° to hydrolyse the lactam to leucine sulphate. Lime is added and the calcium sulphate separates; after treatment with active carbon the aqueous solution of leptazol is concentrated and the required product extracted with ethylene dichloride. Addition of ether precipitates leptazol.

Properties. Leptazol is a colourless crystalline substance possessing a bitter taste. It melts at 58°. With mercuric chloride it forms a white compound, $C_6H_{10}N_4HgCl_2$, of m.p. 175°. At 20° one part dissolves in 1·3 parts of ethanol and 25 parts of water. It is also soluble in chloroform and ether. It was first introduced in 1925 and has been used to counteract respiratory failure during anaesthesia and in barbiturate poisoning. It has also been employed as a convulsant in the treatment of schizophrenia.

ANTITHYROID DRUGS

The endocrine gland, known as the thyroid, secretes the hormone thyroxine (IV). An excess of this hormone in the blood stream leads to the condition known as thyrotoxicosis.



IV

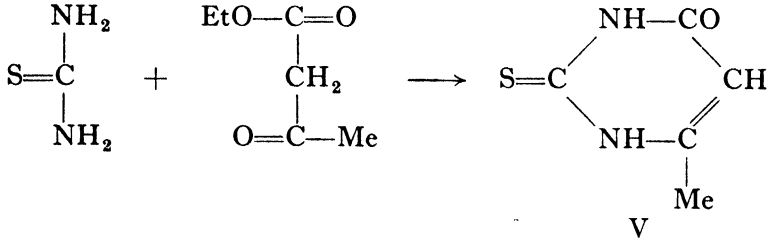
The activity of the thyroid gland can be influenced by chemical substances which have been administered orally. In 1928 Chesney (9) showed that the organic substances present in cabbages have this effect. Later (10) many synthetic substances were shown to be able to interfere with the synthesis of

thyroid hormones in the thyroid gland. Of the many compounds tested, only methylthiouracil, propylthiouracil and methimazole have gained a place in therapeutics.

It has been suggested by Stuckey (11) that antithyroid activity is closely linked with the degree of ionisation of the antithyroid compound at the pH of the blood.

Methylthiouracil. 6-Methyl-2-thiouracil. 4-Hydroxy-2-mercapto-6-methylpyrimidine. $C_5H_6N_2OS$. (V).

Preparation. Thiourea is condensed with ethyl acetoacetate in ethanol in the presence of sodium ethoxide. The reaction mixture is then acidified to pH 4 and the crude product is filtered and recrystallised (12).

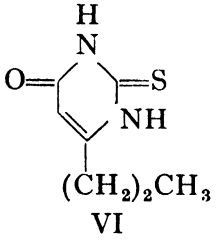


V

Properties. Methylthiouracil melts at 326° to 331° (dec.). It is slightly soluble in ethanol and very slightly soluble in ether or water, but is readily soluble in dilute aqueous sodium hydroxide solution. Methylthiouracil is used in the treatment of thyrotoxicosis and in the preparation of patients for thyroid operations.

Propylthiouracil. 6-Propyl-2-thiouracil. 4-Hydroxy-2-mercapto-6-propylpyrimidine. $C_7H_{10}N_2OS$. (VI).

Preparation. The method used is similar to that employed for methylthiouracil. Ethyl 2-oxohexoate is used instead of ethyl acetoacetate (12).

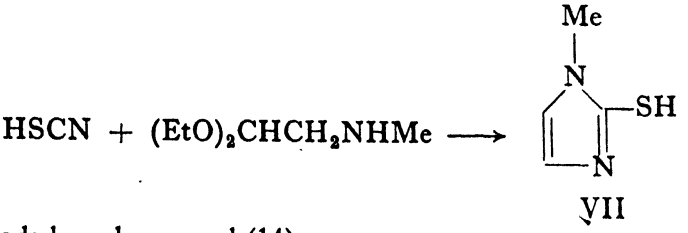


VI

Properties. Propylthiouracil is a white crystalline powder with a bitter taste. It has a m.p. of 218° to 221°. It is slightly soluble in water (1 part in 60 at 100°) and sparingly soluble in ethanol. It is soluble in aqueous solutions of alkali hydroxides and in ammonium hydroxide. Its uses are the same as those of methylthiouracil.

Methimazole. 2-Mercapto-1-methyliminazole. 2-Mercapto-1-methylglyoxaline. $C_4H_6N_2S$. (VII).

Preparation. Methylaminoacetal (prepared from the haloacetal and methylamine) is reacted with potassium thiocyanate and hydrochloric acid in ethanol (13).



VII

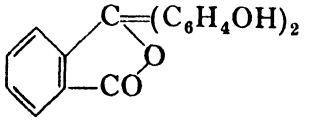
Other methods have been used (14).

Properties. Methimazole is a tasteless white powder with a m.p. of 145° to 148°. It is soluble in water, ethanol and chloroform and fairly soluble in ether. It was introduced in 1949 and is approximately twenty times as potent as propylthiouracil.

SYNTHETIC PURGATIVES

Phenolphthalein. Di-(4-hydroxyphenyl) phthalate. $C_{20}H_{14}O_4$. (VIII).

Preparation. Phenolphthalein, first prepared in 1871, is obtained by the condensation of phthalic anhydride and phenol in the presence of zinc chloride (14).

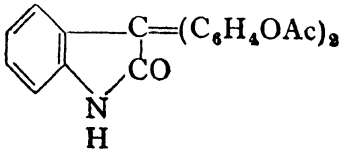


VIII

Properties. Phenolphthalein is almost insoluble in water but soluble in ethanol (1 g in 12 ml), in ether (1 g in 100 ml) and in acetone. It melts at 262° to 264° (corr.). It is colourless in solution below pH 8·5 and becomes red in more alkaline solutions.

Diacetoxydiphenylisatin. $C_{24}H_{19}NO_5$. (IX).

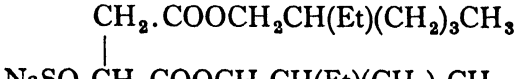
Preparation. The diphenol was first prepared in 1885 by the reaction between phenol and isatin in the presence of concentrated sulphuric acid. Acetylation with acetic anhydride (15) leads to the diacetate.



IX

Properties. This synthetic compound is apparently the active principle of prune juice (16). It is insoluble in water and difficultly soluble in ethanol and ether. It melts at 239° to 240°.

Dioctyl sodium sulphosuccinate. $C_{20}H_{37}NaO_7S$. (X).



X

This compound is a detergent but has a laxative action, as it promotes the penetration of water into the stools. Its preparation has been patented (17).

HYPNOTIC ANTAGONISTS

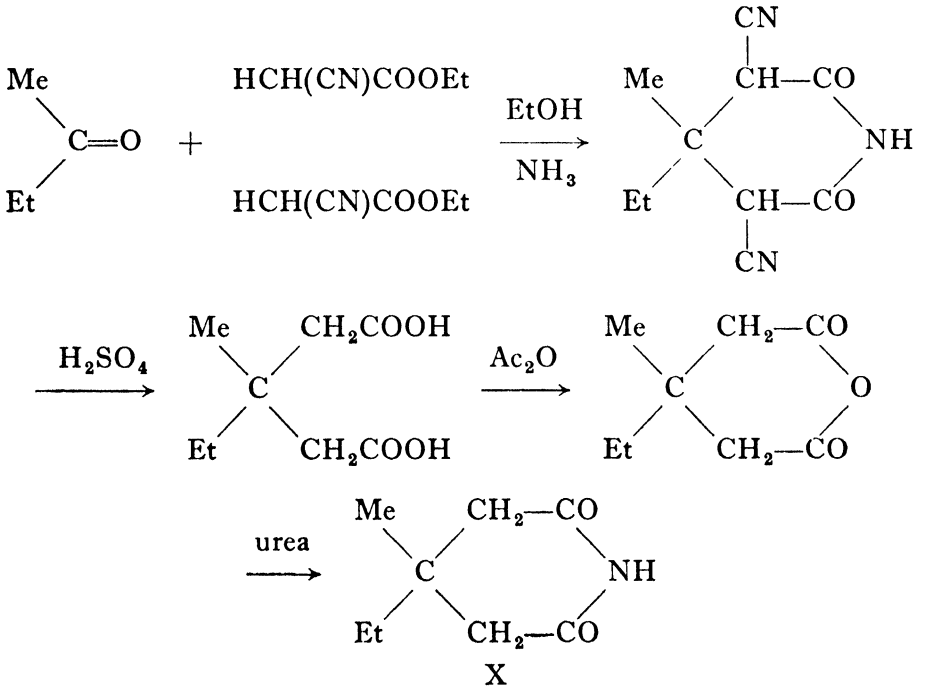
Barbiturates and morphine-like drugs exert a depressant action upon the central nervous system. An overdose can lead to death. Drugs with analeptic activity have an antagonistic effect upon barbiturate poisoning. Recently workers in Australia, whilst investigating the properties of derivatives of glutarimide, discovered that bemegride had no barbiturate-like activity but was in fact a barbiturate antagonist.

Nalorphine, described in Part II, Chapter II, is a morphine antagonist and so also is amiphenazole.

Patients suffering from alcoholism may be treated with sedatives or when a patient finds it emotionally impossible to break the alcohol habit then disulfiram may be useful. After a dose of this drug the subsequent ingestion of alcohol causes a flushing of the skin and of the neck and chest which become bright red. Then follows a severe headache and a rise in blood pressure followed by a precipitous fall in the blood pressure. This gives rise to nausea and vomiting. This physiological shock helps the patient to break the addiction. Ethanol is normally metabolised in the body to acetaldehyde and thence to acetic acid. Disulfiram blocks the latter step and the build-up of acetaldehyde in the body causes the above symptoms. Calcium cyanamide citrate has been recently introduced for the same purpose.

Bemegride. 3-Ethyl-3-methylglutarimide. $C_8H_{13}NO_2$. (X).

Preparation. The method of preparation was introduced by Guareschi in 1900 and has been recently described by other workers (18, 19).



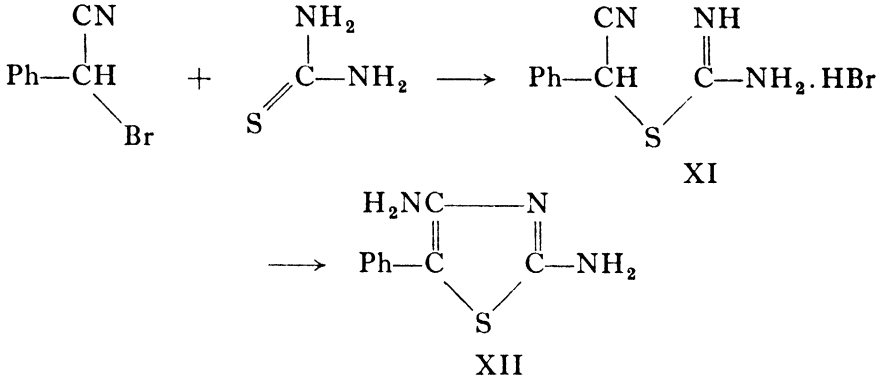
X

Ethylmethylketone is reacted with ethyl cyanoacetate in alcoholic ammonia at 0° to yield 2 : 4-dicyano-3-ethyl-3-methylglutarimide which on hydrolysis with sulphuric acid gives 3-ethyl-3-methylglutaric acid. This is reacted with acetic anhydride to yield the corresponding anhydride which, when heated with urea at 200°, leads to bemegride (X).

Properties. Bemegride, introduced in 1954, is a solid of m.p. 123·5° to 124°. It may be purified by crystallisation from water or sublimation at 100° and 2 mm pressure.

Amiphenazole. 2 : 4-Diamino-5-phenylthiazole. $C_9H_9N_3S$. (XII).

Preparation. Bromobenzylcyanide and thiourea are reacted together to yield the unstable intermediate (XI) which ring closes to amiphenazole hydrobromide from which the free base is obtained by neutralisation (20).



XI

XII

A similar method using benzenesulphonylbenzyl cyanide has been published (21).

Properties. Amiphenazole is a solid of m.p. 163° to 164° (dec.). It may be recrystallised from water or aqueous ethanol. The picrate melts at 189° to 191° and the 2 : 4-diacetamido compound at 233° to 234°. The salts of amiphenazole and mineral acids are water soluble, and may be crystallised from ethanol. The hydrochloride when given together with morphine allows the analgesic activity of morphine to be exerted but counteracts the usual respiratory depression, nausea and constipation.

Disulfiram. Tetraethylthiuram disulphide. $C_{10}H_{20}N_2S_4$. (XIV).

Preparation. Potassium diethyldithiocarbamate (XIII) prepared by the reaction of carbon disulphide with diethylamine in caustic alkali solution is oxidised (22 to 25) to disulfiram.

$$Et_2NH + CS_2 \longrightarrow \underset{\text{XIII}}{Et_2NS_2CK} \longrightarrow \underset{\text{XIV}}{(Et_2NCS)_2S_2}$$

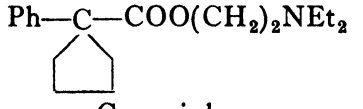
Other methods have also been used (26).

Properties. Disulfiram is a solid of m.p. 70·5°. It is insoluble in water, but may be recrystallised from ethanol or from carbon tetrachloride (27).

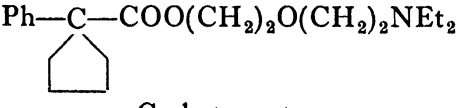
ANTITUSSIVES

Coughing is a reflex response to irritation of the respiratory mucous membranes which causes displacement of phlegm from the air passages. The dry useless cough of early bronchitis, however, is due to hypersensitivity of the bronchial tubes. Cough remedies therefore are designed either to render the sputum more fluid or to suppress useless coughing. The first group, known also as expectorants, includes inorganic salts such as ammonium chloride and potassium iodide and many volatile oils such as eucalyptus and the balsams.

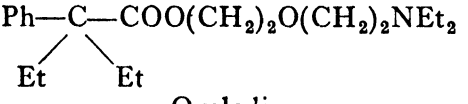
It is in the field of cough suppressants that much recent development has occurred. Certain antihistamines have been included in cough remedies possibly for their bronchodilatory action and for their local sedative effect. Many analgesics and chemically related substances are used as cough suppressants. They include codeine, diamorphine, methadone, dextromethorphan, nalorphine and pholcodine. Caramiphen, an antispasmodic described in Chapter VI, is used in the form of its ethanesulphonate. Two antitussive agents with structures similar to that of caramiphen are carbetapentane and oxeladin:



Caramiphen



Carbetapentane

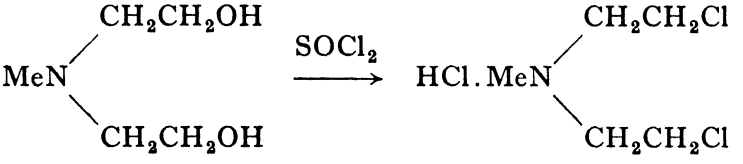


Oxeladin

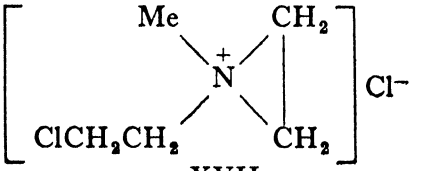
The last two compounds are employed as citrates.

Mustine hydrochloride. Di-(2-chloroethyl)methylamine hydrochloride. $C_5H_{11}Cl_2N.HCl$. (XVI).

Preparation. Diethanolamine is first methylated by the Eschweiler procedure by means of formaldehyde and formic acid to N-methyldiethanolamine (XV) which is then chlorinated to mustine hydrochloride by means of thionyl chloride (28). Studies of the latter reaction on a pilot plant scale have been reported (29).



XV XVI



XVII

Properties. Mustine hydrochloride is a white crystalline solid melting at 110°; it is easily decomposed by water (30) into N-methyldiethanolamine (XV) and 1-(2-chloroethyl)-1-methyl-aziridinium chloride (XVII). Mustine base boils at 59° at 2 mm. Mustine hydrochloride has been used in the treatment of leukemia.

Procainamide hydrochloride. 4-Amino-N-(2-diethylaminoethyl)benzamide hydrochloride. $C_{13}H_{21}N_3O.HCl$. (XIX).

Preparation. The corresponding nitro compound (XVIII) is prepared by the reaction of 4-nitrobenzyl chloride with NN-diethylethylenediamine and the product reduced electrolytically (31) or catalytically (32) to procainamide hydrochloride.

$O_2NC_6H_4CONH(CH_2)_2NEt_2.HCl$ XVIII

$H_2NC_6H_4CONH(CH_2)_2NEt_2.HCl$ XIX

Properties. Procainamide boils at 210° to 215° at 2 mm and melts at 46° to 48°. The dihydrochloride melts at 176·5° to 178° and the monohydrochloride at 165°. The latter compound is a white crystalline solid very soluble in water and soluble in ethanol. It is used as a heart-muscle depressant in cardiac disease.

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PART II

NATURALLY OCCURRING DRUGS

CHAPTER I

Drugs containing Alkaloids. Introduction

THE natural drugs containing alkaloids and the alkaloids derived therefrom form one of the most important groups of substances used in medicine, though the competition of synthetic compounds has almost ousted some of them and has greatly reduced the use of some others. The use of cocaine for example, as a local anaesthetic has been reduced considerably by the introduction of synthetic products. The use of crude drugs and galenical preparations made from them has been steadily declining for many years, but as long as the 'bottle of medicine' is prescribed it seems unlikely that it will be entirely discontinued, but the more accurate dosage provided by tablets or injections made from the pure alkaloids has obvious advantages.

For the present purpose only those alkaloids that are used in medicine have been included, except for a few that, because of their marked physiological action, are of importance in toxicology. Derivatives prepared synthetically from natural alkaloids and some purely synthetic compounds related in structure to natural alkaloids have also been included in this section.

The term 'alkaloid' is somewhat indefinite and cannot be strictly defined, but substances are generally regarded as alkaloids that are nitrogenous basic organic compounds, occurring naturally and almost invariably having a marked pharmacological action; derivatives prepared synthetically from natural alkaloids and related in structure are also regarded as alkaloids. The term is usually confined to substances occurring in the vegetable kingdom which excludes such compounds as adrenaline which would otherwise be included. Purine derivatives such as caffeine and theobromine are not generally regarded as alkaloids, but for convenience they have been described in this section. The simple nitrogenous bases and the amino acids are not regarded as alkaloids; nevertheless the structure of some true alkaloids such as nicotine is comparatively simple.

Much time and labour has been expended in elucidating the structure of the alkaloids; the number remaining whose structure is unknown is steadily diminishing. More recently attention has been paid to the spatial configuration of many alkaloids.

Nearly all alkaloids contain carbon, hydrogen, nitrogen and oxygen, but oxygen is absent from some of the simpler ones.

Many thousands of derivatives of alkaloids have been prepared with a view to modification or improvement of their pharmacological action; occasionally this has led to the production of useful compounds but greater success has been achieved by the preparation of purely synthetic compounds that may or may not bear some structural relation to the natural alkaloid.

Some important groups of alkaloids have been shown to possess a tetracyclic structure related to the steroids and are known as 'steroidal alkaloids'; others occur in combination with sugars and are known as 'glycosidal alkaloids'; hydrolysis removes the sugar group and a sugar-free alkaloid is formed.

Extraction methods. The processes used commercially for the separation of alkaloids usually follow a similar pattern and are based on the following principles. (i) The extraction of the alkaloid from the drug in an impure condition by means of a solvent usually in the presence of an alkali such as lime; (ii) the removal of the alkaloid from the solvent by extraction with dilute acid; (iii) the precipitation of the alkaloid from acid solution by excess of alkali and its extraction by an immiscible solvent and (iv) crystallisation of the alkaloid or of one of its salts. Since most drugs contain a mixture of alkaloids special methods of purification must be applied in order to obtain the alkaloid required in a pure condition. There are some drugs whose properties preclude the application of this simple procedure and for these special methods must be used. A useful method of preparing the hydrochloride of an alkaloid is to dissolve the base in an anhydrous solvent such as acetone and to pass dry hydrogen chloride into the solution; the hydrochloride is precipitated and, after washing with a solvent, is comparatively pure.

Alkaloids are mostly easily crystallisable from organic solvents; their salts are usually crystallisable from water or alcohol and are only slightly soluble in other organic solvents.

Chromatography and ion exchange have both been widely used for the separation of alkaloids from mixtures and from crude drugs (2).

Most alkaloids are optically active. They yield characteristic waves when examined polarographically (1). A few are reduced at the dropping mercury electrode and the usual polarographic technique can be used for their determination, but the majority are not reducible but yield characteristic catalytic waves that are subject to great variation with changing conditions.

Alkaloids often form insoluble compounds with certain reagents, particularly with metallic salts with which insoluble double salts are formed. These compounds often have a characteristic crystalline form under the microscope and provide a useful method for the detection of small amounts of alkaloids. Some of these insoluble derivatives are sufficiently constant in composition to be used for their determination.

The more important reagents for the detection or precipitation of alkaloids are as follows.

Potassium mercuric iodide. (Mayer's reagent.) Yellowish-white, usually amorphous, precipitates are formed at high dilutions with slightly acid solutions of nearly all alkaloids. The purine derivatives are exceptions; many non-alkaloidal bases also form precipitates with this reagent.

Bismuth potassium iodide. (Dragendorff's or Kraut's reagent.) Red or orange precipitates, sometimes crystalline, are formed. This reagent is useful for the detection of theobromine, narceine and coniine by the microscopic form of the crystals.

Cadmium potassium iodide. (Marmé's reagent.) Characteristic crystals are formed with morphine and codeine.

Iodine in potassium iodide solution. (Wagner's reagent.) Brown precipitates are given with the majority of alkaloids except the caffeine group. Homatropine, hyoscyamine, berberine and atropine may be identified by their crystalline form.

Picric acid is a particularly valuable reagent for detecting and for determining the purity of alkaloids. Nearly all the alkaloidal picrates are almost insoluble in water, only slightly soluble in alcohol, but mostly easily soluble in acetone. The picrates crystallise in characteristic forms and have definite melting-points (3).

Styphnic acid (2 : 4 : 6-trinitroresorcinol) forms crystalline salts with many alkaloids (4).

Auric chloride produces orange or yellow precipitates of the aurichlorides, which are often crystalline and have a characteristic melting-point. The aurichlorides of the alkaloids of the solanaceous group are especially valuable as a means of identification. Cocaine, strychnine, caffeine, quinidine, apomorphine, nicotine and sparteine give precipitates of individual crystalline form.

Platinic chloride is generally applicable as a precipitant except in a few cases, notably atropine, whose platinichloride has a marked solubility. This reagent is useful for the identification of pilocarpine, brucine and cinchonidine.

Picrolonic acid forms crystalline precipitates of definite melting-point with many alkaloids.

Potassium permanganate forms crystalline precipitates with cocaine and hydrastinine.

The *hydroferrocyanides* and *hydroferricyanides* of many alkaloids are crystalline and identifiable under the microscope (5).

The *molybdophosphates*, *tungstophosphates* and *tungstosilicates* of alkaloids are usually insoluble compounds.

Colour tests. Some alkaloids may be identified by colour tests. A few of these are very sensitive and characteristic, but many that have been described are only applicable to the pure alkaloid.

Most alkaloids can be titrated with acids; exceptions are the cinchona alkaloids, which do not give a sharp end-point. The determination of alkaloids in crude drugs usually depends on the extraction of the drug with an organic solvent in the presence of an alkali, the transference of the alkaloid to aqueous acid and back into an organic solvent after making alkaline. After evaporating the solvent the alkaloid is dissolved in standard acid and the excess titrated with alkali. When more than one alkaloid is present such a method gives, of course, the total alkaloids. When it is necessary to determine a single alkaloid, advantage must be taken of some difference in a chemical or physical property or the alkaloids must be separated by chromatography. Paper electrophoresis has also been used for the separation of alkaloids.

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CHAPTER II

Opium Alkaloids

OPIUM is the inspissated juice or latex from the unripe capsules of the opium poppy, *Papaver somniferum.* It is produced chiefly in Asia Minor, South-Eastern Europe, Persia, India and China. Medicinal opium is produced almost entirely in Asia Minor and is known as Turkey or Smyrna opium, but the alkaloids are manufactured commercially from Indian or Persian opium. Opium contains numerous alkaloids and these have been extensively studied owing to the ready availability of residues from the manufacture of morphine. Recently, owing to the restrictions on the sale of morphine, the manufacture of codeine has exceeded that of morphine. The following twenty-three alkaloids are the most important of those isolated.

Alkaloid	Formula	Discovered by	Date	Percentage
Morphine	$C_{17}H_{19}O_3N$	Sertürner	1816	7–15
Narcotine	$C_{22}H_{23}O_7N$	Robiquet	1817	2–9
Codeine	$C_{18}H_{21}O_3N$	Robiquet	1832	0·3–4
Narceine	$C_{23}H_{27}O_8N$	Pelletier	1832	0·2
Thebaine	$C_{19}H_{21}O_3N$	Thiboumery	1835	0·1–1
Pseudomorphine	$(C_{17}H_{18}O_3N)_2$	Pelletier	1835	0·02
Papaverine	$C_{20}H_{21}O_4N$	Merck	1848	0·8
Cryptopine	$C_{21}H_{23}O_5N$	Smiles	1864	0·3
Rhoeadine	$C_{21}H_{21}O_6N$	Hesse	1867	—
Lanthopine	$C_{23}H_{25}O_4N$	Hesse	1870	—
Meconidine	$C_{21}H_{23}O_4N$	Hesse	1870	—
Codamine	$C_{20}H_{25}O_4N$	Hesse	1870	—
Laudanine	$C_{20}H_{25}O_4N$	Hesse	1870	—
Laudanosine	$C_{21}H_{27}O_4N$	Hesse	1871	—
Hydrocotarnine	$C_{12}H_{15}O_3N$	Hesse	1871	—
Oxynarcotine	$C_{22}H_{23}O_8N$	Beckett and Wright	1876	—
Protopine	$C_{20}H_{19}O_5N$	Hesse	1878	—
Xanthaline	$C_{20}H_{19}O_5N$	T. & H. Smith	1893	—
Papaveramine	$C_{21}H_{25}O_6N$	Hesse	1903	—
Aporeine	$C_{16}H_{16}O_2N$	Pavesi	1905	—
Neopine	$C_{18}H_{21}O_4N$	T. & H. Smith	1911	—
Porphyroxine	$C_{19}H_{23}O_4N$	Rakshit	1919	—
Narcotoline	$C_{21}H_{21}O_7N$	Wrede	1937	—

Among other alkaloids that have been described as being present in opium gnoscopine has been found to be (±) narcotine while tritopine and laudanidine are (—) laudanine. Pseudopapaverine is identical with papaverine.

The published figures for the percentages of different alkaloids given in the table are only approximate except those for morphine, as the amounts vary widely in different specimens of opium and the methods of their determination have not been, hitherto, very reliable except for a few of the more common constituents.

Opium alkaloids occur in the drug chiefly in the form of meconates and sulphates. Indian opium contains less morphine than the Turkish product, but the morphine content has been raised appreciably by improved methods of collection.

Opium alkaloids may be grouped according to their structure as follows. (i) *Tetrahydro*isoquinoline *derivatives*: hydrocotarnine. (ii) *Benzyl*isoquinoline *derivatives*: papaverine, xanthaline, codamine, laudanine, laudanosine, narcotine, oxynarcotine, narceine and narcotoline. (iii) *Di*-isoquinoline *derivatives*: protopine and cryptopine. (iv) *Morphine sub-group*: morphine, codeine, neopine, pseudomorphine, thebaine and porphyroxine.

Separation of Opium Alkaloids. Water extracts most of the alkaloids from opium but much of the morphine and narcotine remains undissolved. Acids extract all the alkaloids but also much resin-like material. Amyl alcohol on continued extraction extracts all the alkaloids. Other organic solvents such as benzene remove narcotine and some other alkaloids but leave morphine undissolved. Strong alkalis remove morphine, codeine and narceine but not other alkaloids. Codeine is dissolved by ammonia solution but not morphine.

In the determination of morphine in opium the extraction is carried out with lime-water which dissolves the morphine and some of the codeine but leaves most of the other alkaloids undissolved. The meconic acid is precipitated as calcium meconate. The addition of ammonium chloride reduces the pH to about 9 which causes the morphine to be precipitated; shaking with ether extracts codeine and other alkaloids and the morphine crystallises in an almost pure condition.

Narcotine, papaverine and narceine are very weak bases; the first two are readily extracted from acid solutions by chloroform and are precipitated by the addition of sodium acetate to solutions of their salts. Narceine, on account of its solubility in water, is difficult to separate, but after removal of the other alkaloids it may be precipitated as picrate which may be converted to the hydrochloride.

In a method that is stated to have been in use in a German factory (1), raw opium is extracted in the cold with 2 to 3 volumes of methylene chloride which removes papaverine, narcotine and gum. The residue, after removal of the methylene chloride, is agitated with water and milled with ten volumes of lime-water at a temperature below 20°. The residue is extracted with sulphuric acid to remove residual morphine, the solution is concentrated and added to the batch later. The lime-water extract contains morphine, codeine and thebaine and is extracted several times with benzene to remove codeine and thebaine and neutralised to

pH 8·0. The crude morphine is thus precipitated and is filtered; the filtrate is evaporated *in vacuo* and extracted with amyl alcohol, yielding more crude morphine. The combined crude morphine is dissolved in dilute hydrochloric acid and filtered through charcoal. Alcohol is added to the filtrate which is neutralised with ammonia when the morphine precipitates. The morphine is dissolved in dilute hydrochloric acid to give a saturated solution and, on cooling, morphine hydrochloride crystallises and is recrystallised.

The first two methylene chloride extracts obtained in the original extraction of the opium are combined and evaporated; the papaverine and narcotine are extracted from the residue with hot dilute hydrochloric acid. The solution is treated with charcoal and filtered; the filtrate is neutralised with ammonia and the precipitate is filtered off. From this residue the papaverine is extracted with hot alcohol, precipitated as acid oxalate and purified by recrystallisation. The crude narcotine in the residue from the alcohol extraction is similarly purified.

The benzene extracts obtained earlier are evaporated and the residue treated with hot alcohol, cooled and filtered. The filtrate is treated with sulphuric acid which precipitates codeine sulphate which is filtered off. The filtrate is treated with tartaric acid which precipitates thebaine acid tartrate.

Methods for the separation of opium alkaloids have been published by Merck (2), Hesse (3), Plugge (4), and others. Manufacturing methods have been described by Schwyzer (5), Barbier (6), Chemnitius (7), Busse and Busse (8), and by Dott (9). A method of separation by chromatography has been described by Borke and Kirch (10).

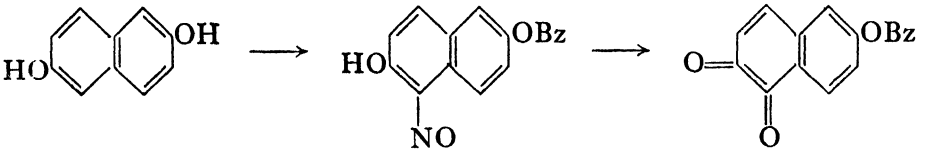
Morphine. $C_{17}H_{19}O_3N$. Morphine is the most important alkaloid of opium; it is also the most abundant, from 7 to 15 per cent being present, according to the source of the drug. It still has a considerable use in medicine though it has to some extent been replaced by synthetic compounds. The restrictions on its sale owing to the operation of the Dangerous Drugs Act have also had an effect in this direction. Morphine exerts a depressing action on the central nervous system; the depression affects the brain, especially the sense of pain, and the respiration; it is habit-forming and its prolonged use may lead to addiction.

Morphine was the first alkaloid to be isolated from opium. Seguin in 1804 probably obtained it in a fairly pure condition, but Sertürner was the first to publish a description of it and to recognise it as a 'vegetable alkali' in 1817.

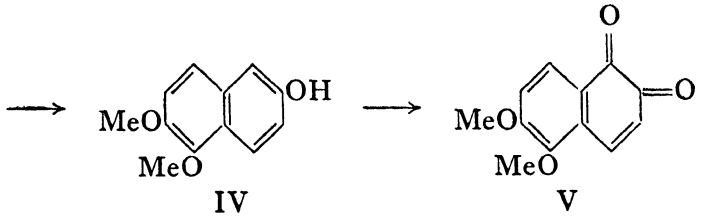
Morphine contains two hydroxyl groups, one of which is phenolic and the other is a secondary alcohol group. Morphine therefore forms a diacetyl compound, *diamorphine*, and because of the phenolic group is soluble in excess of alkali, a property which distinguishes it from most other alkaloids. The phenolic group can be methylated forming *codeine*. Morphine is a phenanthrene derivative; its constitution was the subject of controversy for many years, but the formula proposed by Gulland and Robinson in 1923 (XIX) is now accepted and has been confirmed by synthesis.

Synthesis. The starting-point of the synthesis finally announced by M. Gates and G. Tschudi (11) was 2 : 6-dihydroxynaphthalene (I) which on benzoylation and nitrosation gave (II) which was reduced and then oxidised with $FeCl_3$ to form 6-benzoyloxy-1 : 2-naphthoquinone (III). This was reduced to the

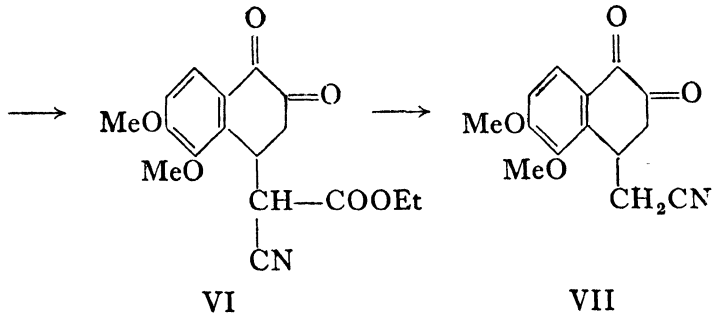
hydroquinone, methylated with dimethyl sulphate and the benzoyloxy group hydrolysed to form 5 : 6-dimethoxy-2-naphthol (IV).



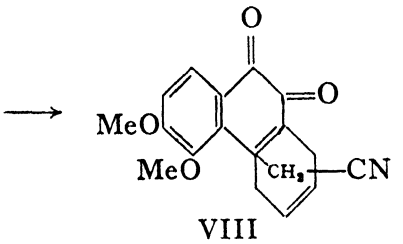
I II III



IV V



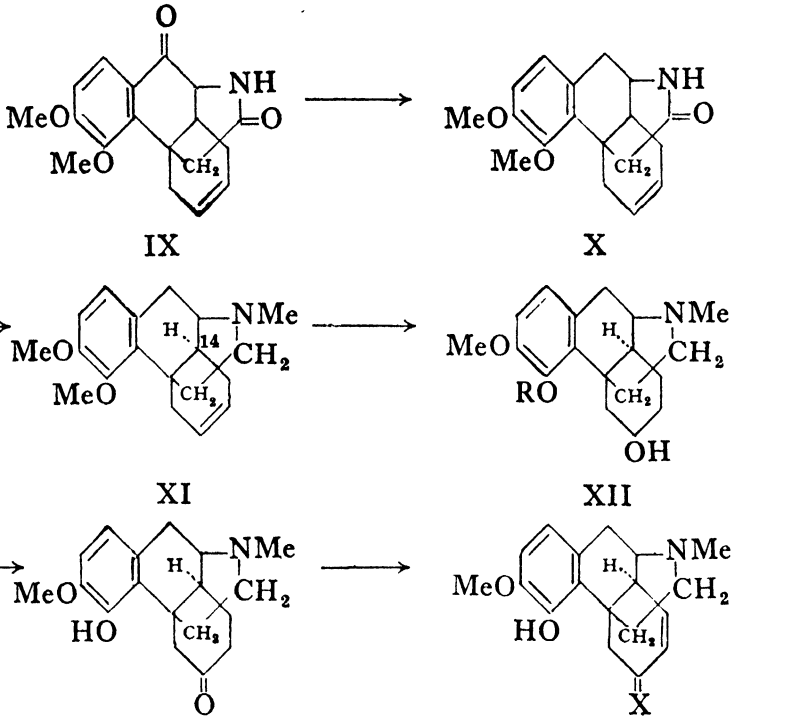
VI VII



VIII

This compound is then treated as in steps II and III to give 5 : 6-dimethoxy-1 : 2-naphthoquinone (V), which with ethyl cyanoacetate gives VI. Claisen's alkali treatment gives VII which then condenses with butadiene to form 3 : 4-dimethoxy-9 : 10-dioxo-13-cyanomethyl-5 : 8 : 9 : 10 : 13 : 14-hexahydrophenanthrene (VIII). Hydrogenation gives the ketolactam (IX) which on reduction and remethylation yields the lactam (X); reduction with $LiAlH_4$ followed by methylation with formaldehyde - formic acid gives (±)-β-Δ^6-dihydroxydeoxycodeine methyl ether (XI). This was resolved, the (+) form being identical with the substance obtained from natural sources. On hydration with dilute sulphuric acid this yields β-dihydrothebainol methyl ether (XII,

R=Me) which, on vigorous treatment with potassium hydroxide in diethylene glycol yields β-dihydrothebainol (XII, R=H); oxidation with the potassium *tert.*-butoxide - benzophenone system gives β-dihydrothebainone (XIII). On bromination with two moles of bromine followed by treatment with 2 : 4-dinitrophenylhydrazine a dinitrophenylhydrazone (XIV) is formed identical with that obtained from thebainone (XV). That this remarkable reaction has produced epimerisation at C_{14} (*trans*→*cis* fusion of rings II and III) is clearly shown by cleavage of the dinitrophenylhydrazone with acetone and acid to produce 1-bromothebainone, which was reduced to dihydrothebainone (XVI).



IX X

XI XII

XIII XIV

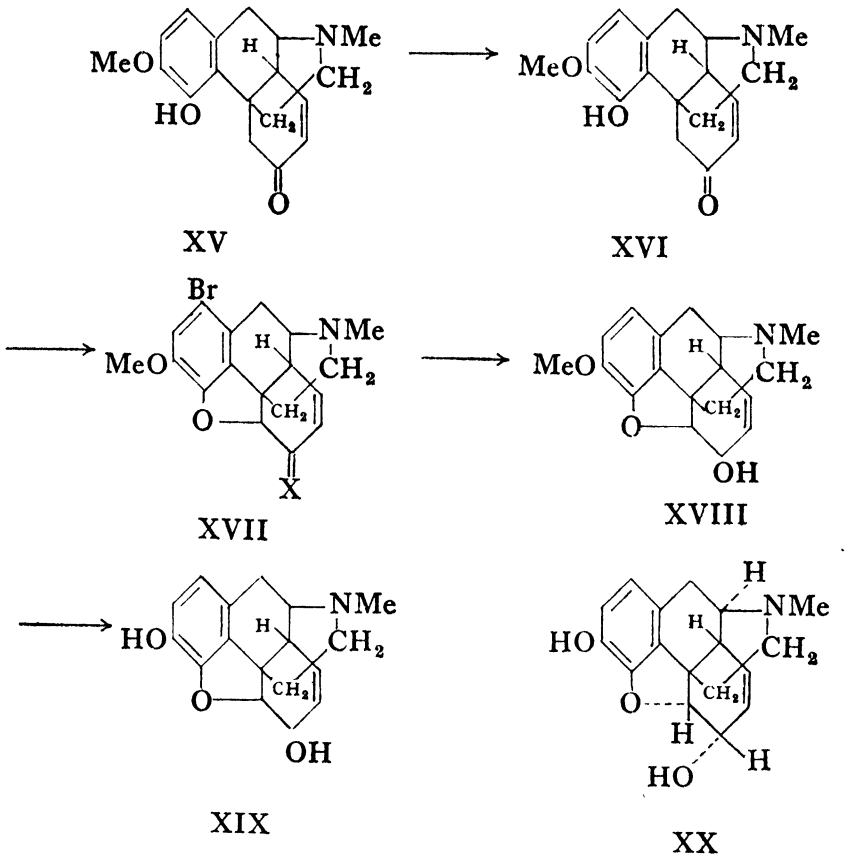
[X=2:4:1-$(NO_2)_2C_6H_3NHN$]

Bromination of XVI followed by treatment with 2 : 4-dinitrophenylhydrazine gave a small yield of 1-bromocodeine-2 : 4-dinitrophenylhydrazone (XVII); this was reduced to codeine (XVIII) which can be demethylated to morphine (XIX).

X-ray crystallography indicates that (—) morphine has the stereochemistry (XX) or its mirror image (12) and a consideration of molecular-rotation differences establishes that (XX) represents the stereochemical structure of the natural alkaloids (13).

An alternative synthesis of (—) dihydrothebainone has been published by Elad and Ginsburg (14).

Preparation of morphine. Morphine is usually prepared from opium by treatment with calcium chloride solution when the alkaloids are extracted as soluble



hydrochlorides while meconic acid and other compounds are precipitated as insoluble calcium salts. The solution of the hydrochlorides is evaporated to a low volume *in vacuo*, care being taken to prevent oxidation, for which purpose sodium sulphite is added. Narcotine and papaverine may be removed from this liquor by the addition of sodium acetate but care must be taken that the liquid does not become alkaline or morphine will be precipitated. Crude morphine is precipitated from the filtrate by the addition of a carefully adjusted amount of alkali and filtered off. The crude morphine is neutralised with hydrochloric acid and dissolved in boiling water. On cooling under protection from oxidation morphine hydrochloride crystallises out. Morphine may be regenerated from the hydrochloride by the addition of ammonia to the solution or the hydrochloride may be recrystallised from water. Morphine may be freed from codeine by washing with benzene or ether in which the latter is soluble, but in which morphine is practically insoluble.

A considerable amount of morphine is prepared from the whole poppy capsules which contain from 0·2 to 0·4 per cent of morphine. The capsules are powdered and thoroughly extracted by percolation with water; the aqueous extract is concentrated to about one-twentieth of its volume and extracted with methylene chloride, from which the alkaloids are extracted with dilute sulphuric

acid; the acid extract is brought to pH 9 with ammonia and the crude morphine which precipitates is purified in the usual way.

Properties. Morphine crystallises in white needle-shaped crystals with one molecule of water of crystallisation, which it loses on heating to 120°. M.p. 230° (dec.). The solubility at 20° in water is about 0·015 g per 100 ml and in 95 per cent ethanol 0·4 g per 100 ml. Morphine is only slightly soluble in ether, chloroform, benzene or acetone, but rather more soluble in amyl alcohol and much more soluble in benzyl alcohol (21·8 g per 100 ml at 20°); it also dissolves in a mixture of two volumes of chloroform and one volume of dehydrated ethanol (2·3 g per 100 ml), by which it may be extracted from aqueous solutions made alkaline with ammonia. Morphine is precipitated from solution on the addition of alkali, reaching its maximum insolubility at pH 9; as the pH increases beyond this point the alkaloid redissolves owing to the presence of a phenolic hydroxyl group.

Colour tests. When a crystal of morphine is dissolved in strong nitric acid an orange-red colour is formed; it also gives a greenish-blue colour when ferric chloride solution is added to a neutral solution and a deep blue colour with a dilute solution of potassium ferricyanide containing a trace of ferric chloride; iodic acid is reduced with liberation of iodine, the colour being deepened by excess of ammonia. When to a dilute solution of morphine in dilute hydrochloric acid is added a small quantity of sodium nitrite followed by an excess of ammonia, a red colour is produced (Radulescu's test). Sulphuric acid containing a trace of formaldehyde gives a reddish-violet coloration.

Morphine is distinguished from nearly all other alkaloids by its slight solubility in organic solvents; the usual reagents give no characteristic crystals, but microscopic crystals of characteristic form appear on adding cadmium potassium iodide solution (Marmé's reagent).

SALTS OF MORPHINE

Morphine hydrochloride, $C_{17}H_{19}O_3N.HCl.3H_2O$, is a white crystalline powder containing from 75 to 76 per cent of anhydrous morphine; it is soluble in water (1 g in 25 ml): in ethanol (1 g in 50 ml).

Morphine sulphate, $(C_{17}H_{19}O_3N)_2.H_2SO_4.5H_2O$, forms white feathery crystals or cubical masses. It contains 75 per cent of anhydrous morphine: it is soluble in water (1 g in 24 ml): slightly soluble in ethanol.

Morphine tartrate, $(C_{17}H_{19}O_3N)_2.C_4H_6O_6.3H_2O$, is an efflorescent salt, containing 73 to 74·5 per cent of morphine. It is soluble in water (1 g in 11 ml) and slightly soluble in ethanol.

MORPHINE DERIVATIVES

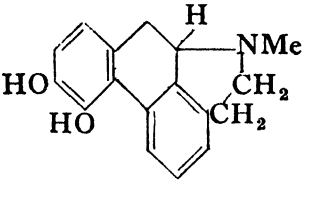
Diamorphine. Diacetylmorphine. This derivative is always found in commerce as the hydrochloride, $C_{17}H_{17}NO_3(COCH_3)_2.HCl$. It may be prepared by heating morphine with acetic anhydride to 85° for 6 hours, when the two hydroxyl groups become acetylated. The excess of acetic anhydride and the acetic acid are distilled off *in vacuo*; the residue is dissolved in water and

the crude base precipitated with ammonia. This is decolorised with charcoal, recrystallised from ethanol and converted to the hydrochloride by passing dry hydrochloric acid gas into an acetone solution. The base melts at 171° and the hydrochloride at 231° to 233°. Owing to the widespread use of diamorphine by drug addicts its manufacture and sale are prohibited in many countries.

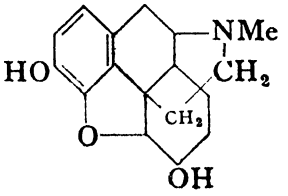
Ethylmorphine, $C_{19}H_{23}O_3N$, is prepared by the action of ethyl iodide or other ethylating agent on morphine. Its structure is that of codeine except that it contains an ethoxy group in place of the methoxy group in the latter. It resembles codeine in its physiological action. The hydrochloride, $C_{19}H_{24}O_3NCl.2H_2O$, melts at 123°.

Apomorphine, $C_{17}H_{17}O_2N$, is prepared from morphine by removing the elements of water by heating in a sealed tube to 140° to 150° with 25 per cent hydrochloric acid. After cooling, the solution is neutralised with sodium bicarbonate and extracted with ether, benzene or chloroform. The separated base is then combined with hydrochloride acid to form the hydrochloride. Precautions are taken to avoid oxidation in the process. The hydrochloride is a greyish-white powder, becoming green on exposure to air; it is soluble in water (1·4 g in 100 ml) or in ethanol (2 g in 100 ml).

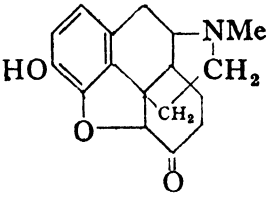
Apomorphine contains two hydroxyl groups and a tertiary nitrogen atom and has the constitution XXI. It has a similar pharmacological action to morphine, but is chiefly used for producing emesis on account of its stimulating action on the medulla.



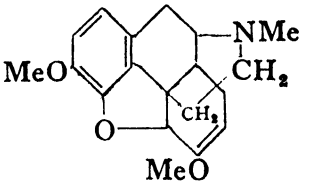
XXI



XXII



XXIII



XXIV

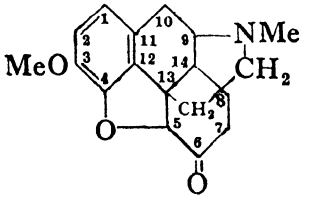
Dihydromorphinone, $C_{17}H_{19}NO_3$, (XXIII), is stated not to be so liable to cause addiction as morphine.

Preparation. It has been claimed that the oxidation of the secondary alcohol group of morphine and codeine together with the reduction of the 7 : 8 double bond can be accomplished by heating the alkaloids in ethanolic solution with noble metal catalysts (15). A better method appears to be that introduced by

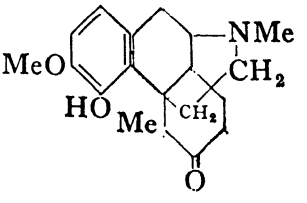
Rapoport (16), in which morphine is first converted to dihydromorphine (XXII) by hydrogenation and this is then oxidised by the Oppenauer technique with potassium tertiary butoxide as catalyst and benzophenone as oxidant when dihydromorphinone is formed.

Dihydromorphinone melts at 266° to 267° and has $[\alpha]_D^{25}$ —194° (in dioxan). It is used as the hydrochloride (B.HCl).

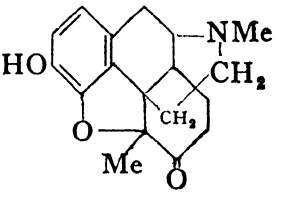
Dihydrocodeinone is prepared from codeine by a similar method. Alternatively thebaine can be converted to dihydrothebaine (XXIV) which, on hydrolysis, yields dihydrocodeinone (XXV) (17). The base melts at 197° to 198°, the oxime at 264° to 265°, the methiodide at 253° to 255°. The $[\alpha]_D^{26}$ is —208·2°. Dihydrocodeinone hydrochloride melts at 125° (dec.) and its dihydrate at 82°. The acid tartrate (m.p. 146° to 148°) crystallises with $2\frac{1}{2}H_2O$; it is also used in medicine as an antitussive.



XXV



XXVI



XXVII

Methyldihydromorphinone. $C_{18}H_{21}O_3N$. (XXVII).

Preparation. This compound is one of a large number prepared by Small and his associates (18) during their search for a non-addicting analgesic comparable to morphine. They found that when a substance such as dihydrothebaine (XXIV) which has a double bond in the 6 : 7 position is heated with a large excess of methyl magnesium iodide the 4 : 5 oxide link is broken and 5-methyldihydro-thebainone (XXVI) together with some of the 7-isomer is formed. The compound (XXVI) is then brominated and yields a 1 : 5-dibromo derivative which, on reaction with alkali, gives 1-bromo-5-methyldihydrocodeinone; thus the oxide link has been rebuilt. The 1-bromo group is next removed by catalytic hydrogenation and then the 3-methoxy group is dealkylated with hydrobromic acid to give 5-methyldihydromorphinone (XXVII). Similar methods have been published by other workers (19).

Properties. The base melts at 243° to 245° and has $[\alpha]_D^{24}$ —140·7° (ethanol). The hydrochloride melts at 315° to 318° (dec.) and has $[\alpha]_D^{24}$ —104·8° (water). It is very soluble in water and sparingly soluble in ethanol.

Nalorphine. N-allylnormorphine. $C_{19}H_{21}O_3N$. (XXIX).

Preparation. When morphine reacts with cyanogen bromide the N-methyl group is replaced by -CN which can be removed by the action of hydrochloric acid forming normorphine (XXVIII). Alkylation with allyl bromide under pressure leads to nalorphine (XXIX) (20).

Properties. Nalorphine melts at 208° to 209°. It is soluble in chloroform, ethanol and dilute alkali, but sparingly soluble in ether or water. It is used as the hydrochloride or hydrobromide as an antagonist to narcotics such as

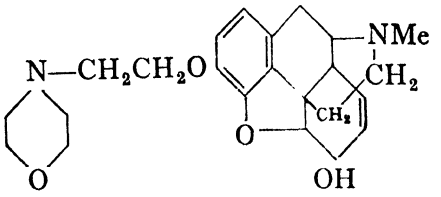
morphine, pethidine or amidone. The hydrochloride is soluble in water and in ethanol. The hydrobromide melts at 258° to 259°. Diacetylnalorphine is also used. It is obtained by the action of acetic anhydride on nalorphine; it forms a hemihydrate (m.p. 148° to 155°).

Pholcodine. Morpholinoethylmorphine. $C_{23}H_{30}N_2O_4.H_2O$. (XXX).

Pholcodine was introduced in France in 1950 as an antitussive agent.

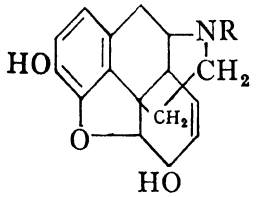
Preparation. Sodium morphinate is prepared by the addition of morphine to a hot solution of sodium ethoxide in ethanol and to this solution is added an ethanolic solution of morpholinoethyl chloride. The precipitated sodium chloride is filtered off and the ethanol is distilled under reduced pressure. The residue of crude pholcodine is dissolved in hot water in the presence of activated charcoal, filtered and cooled. The slow addition of aqueous sodium hydroxide causes precipitation of pholcodine (XXX) (20a).

Properties. Pholcodine is a white microcrystalline powder which melts at 98°; $[\alpha]_D$ −94·5° (2 per cent in ethanol). It is soluble in water (1 in 54 at 20°) and in boiling water (1 in 8·5), in benzene (1 in 18), and in ether (1 in 180); it is readily soluble in acetone, ethanol and chloroform. Spot tests have been described by Cooper (20b). The tartrate, $C_{23}H_{30}O_4N_2.(C_4H_6O_6)_2,3H_2O$, is a white crystalline powder, soluble in water (1 in 8 at 20°), but less soluble in ethanol and only sparingly soluble in chloroform or ether. It has $[\alpha]_D$ −33° (c=1 in H_2O).

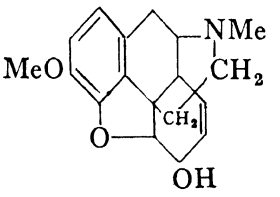


XXX

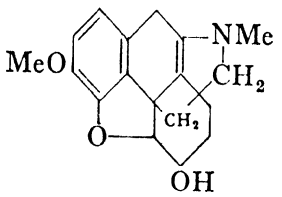
For other compounds related to morphine see Part I, Chapter III.



XXVIII R=H
XXIX R=—$CH_2CH:CH_2$



XXXI



XXXII

Codeine. $C_{18}H_{21}O_3N.H_2O$. (XXXI). Codeine is methyl morphine and differs from morphine in containing a methoxy group in place of the phenolic hydroxy group. Direct alkylation of morphine with methyl iodide or similar alkylating agents converts the tertiary nitrogen atom to the pentavalent condition whereupon the ring system is liable to be destroyed. The use of a quaternary methylating agent such as phenyltrimethylammonium chloride prevents this loss and gives high yields of codeine. The reaction is carried out at 60 lb pressure in an

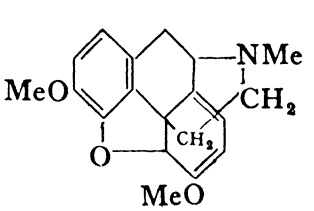
ethanolic solution of sodium ethylate; at the end of the reaction the ethanol and dimethylaniline are distilled off, the codeine is extracted with benzene and unconverted morphine is removed by washing with sodium hydroxide solution; the codeine is then extracted as the sulphate with dilute sulphuric acid and purified by crystallisation.

From 0·1 to 3 per cent of codeine is found in opium. It may be extracted from the filtrate from the precipitated morphine by means of toluene or chloroform, converted to the sulphate and purified by recrystallisation.

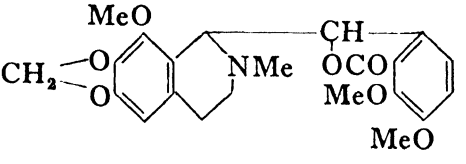
Codeine occurs in colourless crystals melting at 155°; it is slightly soluble in water (0·9 g in 100 ml), more soluble in toluene (5·8 w/v), in chloroform (53 w/v), 90 per cent ethanol (28·5 w/v) and in ether (2·6 w/v). Codeine has no phenolic properties like morphine and does not reduce ferric chloride. It is strongly basic, the most important salts being the *hydrochloride*, $B.HCl.2H_2O$, soluble in water (3·5 w/v), $[\alpha]_D^{22.5}$ −108·2° (water); the phosphate, $B.H_3PO_4.2H_2O$, soluble in water (28·5 w/v), and the sulphate, $B_2.H_2SO_4.5H_2O$, soluble in water (2·5 w/v), $[\alpha]_D^{15}$ −101·2° (water). Codeine picrate melts at 196° to 197°. On warming a crystal of codeine with sulphuric acid containing a trace of ferric chloride a characteristic blue colour is formed.

Neopine. $C_{18}H_{21}O_3N$. (XXXII). This alkaloid has been shown (21) to be an isomer of codeine, from which it differs in having a double bond at 8 : 14 instead of at 7 : 8. It melts at 127° and is optically inactive. It is not used in medicine.

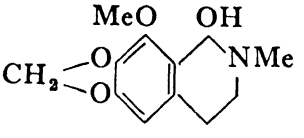
Thebaine. $C_{19}H_{21}O_3N$. (XXXIII). This alkaloid occurs in opium in amounts varying from 0·1 to 1 per cent. It is precipitated with other alkaloids by alkali from the solution of mixed opium alkaloids after the removal of morphine and codeine. After pecipitation of the papaverine and narcotine the thebaine can be



XXXIII



XXXIV



XXXV

separated by crystallisation as the acid tartrate. Thebaine is closely related to morphine and codeine, being a methyl ether of the enolic form of codeinone.

Thebaine melts at 193° and has $[\alpha]_D^{15}$ −218·6° (ethanol). The picrate melts at 189° to 191°. The salicylate and acid tartrate are only slightly soluble in water. Thebaine is not used in medicine.

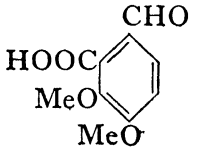
Narcotine. $C_{22}H_{23}O_7N$. (XXXIV). Apart from morphine narcotine is the most abundant alkaloid in opium, in which it occurs in amounts varying from 1 to 9 per cent; it has little pharmacological action, but forms derivatives of

medicinal value. Narcotine and papaverine are separated from the alkaloidal mother liquors after the separation of morphine and codeine, by the addition of sodium acetate. The mixture of alkaloids is dissolved in dilute acid and the papaverine removed by precipitation as acid oxalate in ethanolic solution or as ferricyanide. The narcotine may then be precipitated by ammonia and recrystallised from ethanol.

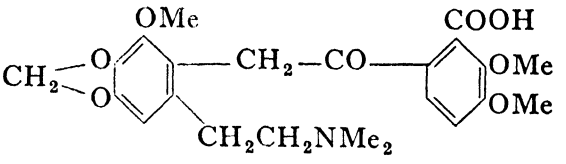
Narcotine occurs in prismatic crystals melting at 176°; the picrate melts at 174°. It is a very weak base and may be extracted from acid solutions with chloroform. Narcotine is racemised in boiling acetic acid to (±) narcotine which was formerly known as gnoscopine. By the action of dilute nitric acid on narcotine cotarnine (XXXV) is formed together with opianic acid (XXXVI).

Cotarnine in the form of the chloride or phthalate was formerly used as a styptic but its value is doubtful.

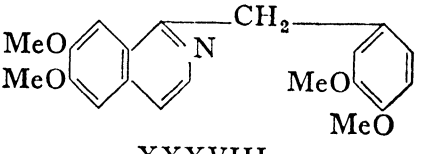
Narceine. $C_{23}H_{27}O_8N.H_2O$. (XXXVII). Narceine is closely related to narcotine whose methylchloride is converted to narceine by treatment with sodium hydroxide. About 0·2 per cent is present in opium. It is a feeble base and is not extracted by organic solvents from alkaline solutions. The base melts at 170° to 171° and the picrate at 195°. It is not used in medicine.



XXXVI



XXXVII

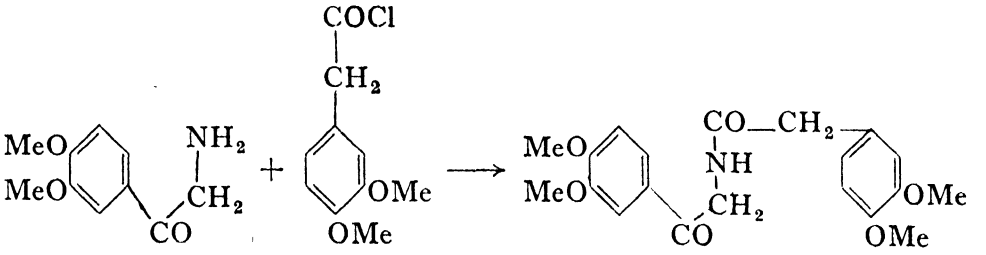


XXXVIII

Papaverine. $C_{20}H_{21}O_4N$. (XXXVIII). About 0·8 per cent of papaverine occurs in opium. It is separated together with narcotine after the removal of morphine and codeine by the addition of sodium acetate to the solution. Papaverine may be separated from narcotine by precipitation as the acid oxalate in ethanolic solution or as the ferricyanide.

Papaverine was originally synthesised by Pictet and Gams (22). *o*-Dimethoxybenzene (veratrole) was treated with acetyl chloride in the presence of aluminium chloride to form 4 : 5-dimethoxy-acetophenone, the oximino derivative of which, on reduction, gave aminoacetylveratrole (XXXIX); the latter was condensed with homoveratroyl chloride (XL) to form homoveratroylaminoacetylveratrole (XLI) which, after reduction of one carbonyl group, was boiled with phosphoric acid in xylene solution when it lost two molecules of water and underwent ring-closure with the formation of papaverine (XXXVIII).

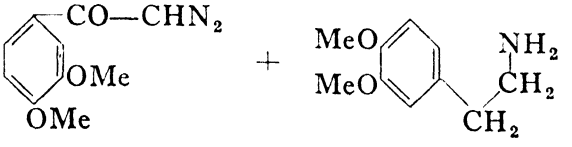
Several other syntheses of papaverine have since been published, e.g. that of Späth and Berger (23), but the most interesting is that of Arndt and Eistert (24)



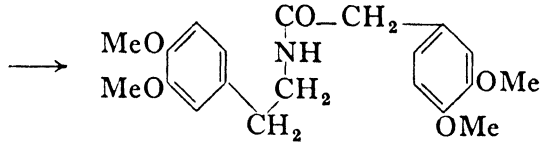
XXXIX XL XLI

in which veratroyl chloride is treated with diazomethane forming the diazoketone (XLII); this is condensed with 1 : 2-dimethoxy-4-aminoethylbenzene (XLIII) to produce the compound (XLIV) which by loss of water is converted to papaverine (XXXVIII).

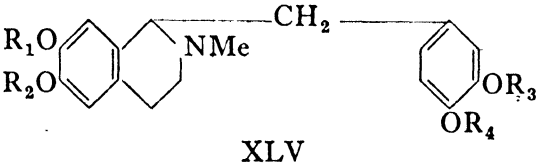
Papaverine melts at 147° and is optically inactive. It slowly forms a rose-red colour with sulphuric acid containing a trace of formaldehyde; it gives an insoluble lemon-yellow ferricyanide. The hydrochloride, B.HCl, melts at 210° to 211° and the picrate at 181° to 183°. Papaverine is slightly analgesic and narcotic and has a relaxing action on smooth muscle; it is valuable for its antispasmodic activity.



XLII XLIII



XLIV

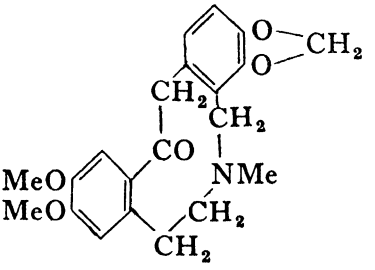


XLV

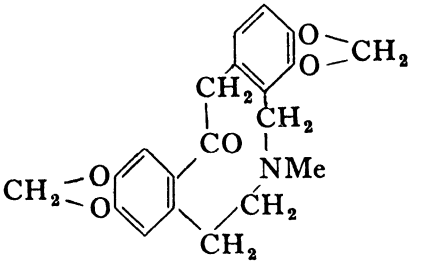
Laudanosine	$R_1=R_2=R_3=R_4=Me$
Laudanine	$R_1=R_2=R_4=Me$, $R_3=H$
Pseudolaudanine	$R_1=H$, $R_2=R_3=R_4=Me$
Codamine	$R_1=R_3=R_4=Me$, $R_2=H$

Laudanosine, Laudanine, Pseudolaudanine and Codamine. These alkaloids are all closely related to papaverine; their structure is represented by XLV. They are not used in medicine.

Cryptopine, $C_{21}H_{23}O_5N$, and **Protopine**, $C_{20}H_{19}O_5N$, are two closely related alkaloids that are of interest on account of their relationship to berberine and the chelidonium alkaloids. Their constitution is represented by XLVI and XLVII respectively.



XLVI



XLVII

These alkaloids have been synthesised (25); they are not used in medicine.

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CHAPTER III

Strychnos Alkaloids

THE two most important alkaloids occurring in *Strychnos* species are the closely related compounds strychnine and brucine, the former being the only one of importance in medicine. The following are the chief alkaloidal constituents of various *Strychnos* species:

S. nux-vomica	Strychnine and brucine.
S. Ignatii	Strychnine and brucine.
S. Tieute	Strychnine and a little brucine.
S. ligustrina	Brucine.
S. Rheedei	Brucine.
S. aculeata	Brucine.
S. Henningsii	A bitter alkaloid.
S. toxifera	Curarines, toxiferines, etc.
S. Castelnaei	Curarines, toxiferines, etc.

The curarising alkaloids from *Strychnos* spp. are not of any importance in medicine (see Chapter VIII).

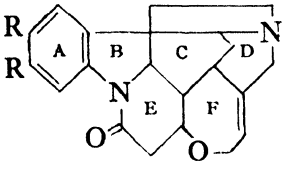
The alkaloids vomicine (1), $C_{22}H_{24}O_4N_2$, α- and β-colubrine, $C_{22}H_{24}O_3N_2$, and ψ-strychnine (2), $C_{21}H_{22}O_3N_2$ or $C_{21}H_{24}O_3N_2$, have been isolated from the strychnine mother liquors. Novacine, $C_{24}H_{28}O_5N_2$, occurring in *S. nux-vomica* is N-methyl-*sec.*-ψ-brucine (3).

Nux Vomica. The seeds of *Strychnos nux-vomica* grow in the East Indies and contain about 2 or 3 per cent of total alkaloids, of which rather less than half is strychnine, the remainder being mostly brucine.

Ignatius Beans (*S. Ignatii*) are also obtained from the East Indies, and contain a similar percentage of total alkaloids, but the proportion of strychnine may be as high as two-thirds of the total.

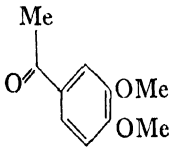
Strychnine, $C_{21}H_{22}O_2N_2$. Strychnine was discovered in 1817 by Pelletier and Caventou.

Manufacture. Strychnine is extracted from *S. nux-vomica* or *S. Ignatii* seeds by grinding them after treatment with steam or hot water, making into a paste



Strychnine R = H
Brucine R = MeO

I



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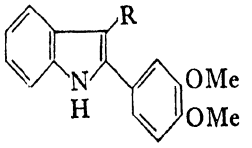

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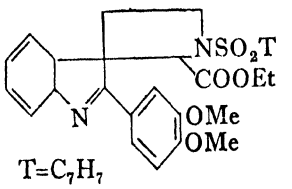

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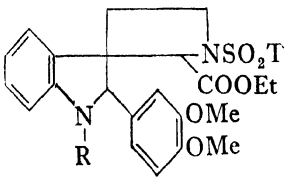

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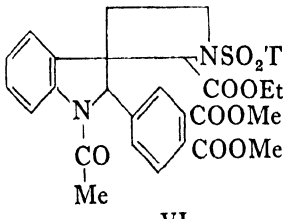

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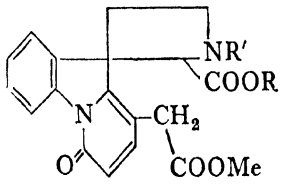

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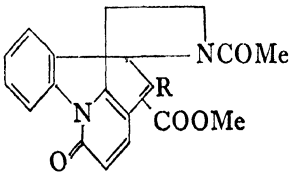

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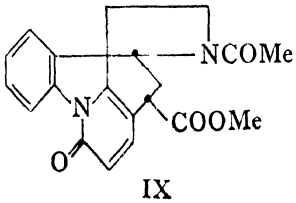

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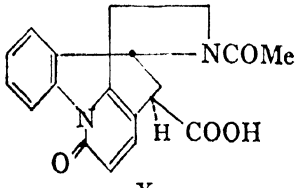

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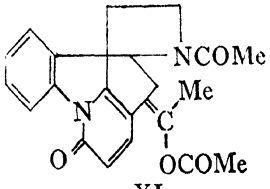

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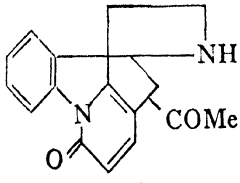

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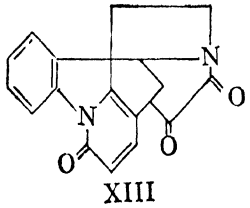

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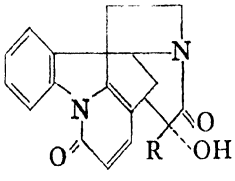

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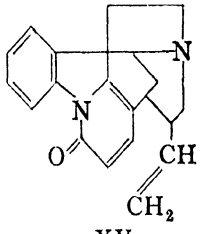

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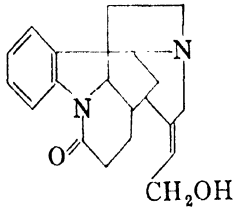

XVI

with slaked lime, and exhausting with hot naphtha or chloroform. The alkaloids are removed from the solvent with dilute sulphuric acid; strychnine sulphate crystallises in a fairly pure condition, while brucine sulphate remains for the most part in solution. The alkaloid is precipitated with alkali and recrystallised from ethanol until the brucine is removed. Alternatively a crude mixture of alkaloids may be obtained by precipitating the acid extract with sodium

hydroxide; treatment of this with dilute ethanol extracts most of the brucine leaving the strychnine undissolved.

Synthesis. Strychnine has been for many years the object of intensive study and controversy and it is only recently that the constitution has been established as (I). The total synthesis has been achieved by Woodward and his colleagues in the following steps (4).

2-Veratrylindole (III, R=H) is prepared from acetveratrone (II) by condensation with phenylhydrazine in the presence of polyphosphoric acid and thence converted by formaldehyde and dimethylamine to the gramine (III, $R=CH_2NMe_2$) from which the methiodide (III, $R=CH_2NMe_3I$) is formed; this with sodium cyanide in dimethylformamide gives the nitrile (III, $R=CH_2CN$). Reduction of the nitrile with lithium aluminium hydride gave 2-veratryltryptamine (III, $R=CH_2CH_2NH_2$) which with ethyl glyoxalate in benzene gave the Schiff base (III, $R=CH_2CH_2N{=}CHCOOEt$). This compound was transformed directly by toluenesulphonyl chloride and pyridine into the indolenine (IV). Reduction of IV with sodium borohydride gave the indoline (V, R=H) which was converted to the N-acetyl derivative (V, $R=CH_3CO$) and ozonised to give the muconic ester (VI). Treatment with methanolic hydrogen chloride gave the pyridone (VII, R=Et, $R'=SO_2T$) ($T=-C_6H_4CH_3$). Rings A, B and E of the strychnine skeleton are now complete.

Vigorous hydrolysis with hydriodic acid and red phosphorus, re-esterification with methanolic hydrochloric acid and acetylation resulted in VII, (R=Me, $R'=CH_3CO$) which was converted by methanolic sodium methoxide to the enol-ester (VIII, R=OH), whose tosylate (VIII, $R=OSO_2T$) gave with sodium benzylmercaptide the thiobenzyl ether (VIII, $R=SCH_2C_6H_5$). Desulphurisation by Raney nickel produced the unsaturated ester (VIII, R=H) which was reduced by hydrogen in the presence of palladium - charcoal to the *cis* ester (IX), hydrolysed with alkali to form the racemic *trans* acid (X) which was resolved by way of the quinidine salt. The (−) acid was identical with a compound obtained by oxidation of dehydrostrychninone.

When the acid (X) was heated with acetic anhydride in pyridine it was converted to the enol acetate (XI), which, on vigorous hydrolysis produced an oily mixture of stereoisomeric methyl ketones (XII). From these, by oxidation with selenium dioxide in ethanol dehydrostrychninone (XIII) was obtained. Addition of sodium acetylide formed the tertiary carbinol (XIV, $R=-C{\equiv}CH$), which was hydrogenated over the Lindlar catalyst to the vinyl carbinol (XIV, $R=-CH{=}CH_2$). Reduction of this by lithium aluminium hydride gave the carbinol (XV) which, when treated with hydrobromic acid in acetic acid followed by boiling dilute sulphuric acid, was rearranged to *iso*strychnine (XVI); this was then isomerised by ethanolic potassium hydroxide to strychnine (I, R=H).

Properties. Strychnine crystallises in colourless prisms, melting at 268° to 290° according to the rate of heating. $[\alpha]_D$ −109·9° (in 80 per cent ethanol); −139·3° (in chloroform). It has an intensely bitter taste, which can be detected at a dilution of 1 in 700,000. It is very slightly soluble in water (1 in 7000), and soluble

in 90 per cent ethanol (1 in 150), in boiling 90 per cent ethanol (1 in 12), in dehydrated ethanol (1 in 350), in chloroform (1 in 6) and almost insoluble in ether. Two colour tests are characteristic; with a 1 per cent solution of ammonium vanadate in sulphuric acid a deep violet-blue colour appears, changing to deep purple and, on dilution with water, to a cherry-red colour; when dissolved in sulphuric acid on a porcelain tile an intense violet colour is produced when a crystal of potassium dichromate is moved slowly through the solution. It is not coloured by sulphuric acid alone. Although containing two nitrogen atoms strychnine behaves as a monoacidic base.

Strychnine hydrochloride, $C_{12}H_{22}O_2N_2,HCl,2H_2O$, is a white crystalline powder, soluble in water (1 in 40) and in ethanol (1 in 80).

Strychnine sulphate, $(C_{21}H_{22}O_2N_2)_2,H_2SO_4,5H_2O$, forms colourless crystals, soluble in water (1 in 50) and in ethanol (1 in 135).

Brucine, $C_{23}H_{26}O_4N_2$, is dimethoxystrychnine; it contains two methoxy groups attached to ring A of strychnine (I). It melts at 178° (anhydrous). It is distinguished from strychnine by being readily oxidised by dilute nitric acid with the formation of an intense red colour.

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CHAPTER IV

Cinchona Alkaloids

THE group of alkaloids known as the cinchona alkaloids is derived from various species of *Cinchona* and *Remijia*. The cinchona species is indigenous to South America, but different varieties have been introduced into other parts of the world, such as Java and India. The bulk of cinchona bark used in the manufacture of quinine is now, in fact, derived from Java.

The most important species of cinchona are:

Cinchona officinalis, yielding 'pale' or 'crown' bark. It contains about 6 per cent of alkaloids, of which more than half is quinine.

Cihchona Calisaya, yielding 'yellow' or Calisaya bark, containing about 6 to 7 per cent total alkaloids, containing a high proportion of quinine.

Cinchona Ledgeriana, a variety of the above, is very rich in alkaloids, yielding from 6 to 10 per cent or more of total alkaloid, containing a high proportion of quinine.

Cinchona succirubra, which gives the 'red' bark, containing about 6·5 per cent of total alkaloids. The quinine content of this bark is low, and the cinchonidine is high.

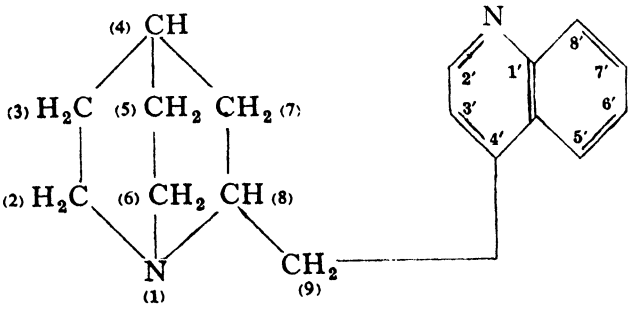
Cuprea bark, yielded by *Remijia pedunculata*, is not a cinchona bark, but contains quinine and cupreine.

For many years, until recently, attention was directed to the cultivation of species yielding the highest percentages of quinine, but now that the value of the other alkaloids is becoming more evident, the cultivation of *C. succirubra* is in some places being extended. Numerous alkaloids have been isolated from these barks, and from other species, viz.

ALKALOIDS	FORMULA
Paricine	$C_{16}H_{18}ON_2$
Cinchonine, cinchonicine, cinchonidine, homocinchonidine	$C_{19}H_{22}ON_2$
Cinchotine, cinchamidine, cinchonamine	$C_{19}H_{24}ON_2$
Cupreine	$C_{19}H_{22}O_2N_2$
Quinamine, conquinamine	$C_{19}H_{24}O_2N_2$
Quinine, quinidine, quinotoxine	$C_{20}H_{24}O_2N_2$
Chairamine, conchairamine, chairamidine, conchairamidine	$C_{22}H_{26}O_4N_2$
Cusconine, concusconine, aricine	$C_{23}H_{26}O_4N_2$
Dicinchonine	$C_{38}H_{44}O_2N_4$
Diconquinine	$C_{40}H_{46}O_4N_4$
Javanine, cuscamine, cuscamidine, cusconidine	Unknown.

The quinine alkaloids may be considered as derived from the parent substance, Ruban (I). All those whose constitutions are known may be regarded as

derived from Q-CHOH-Q′ where Q is a quinoline or methoxyquinoline group and Q′ is a 3-vinyl or a 3-ethyl quinuclidine group (the bridged piperidine ring in formula II). Ruban (1) is thus 4′-quinolyl-quinuclidine.



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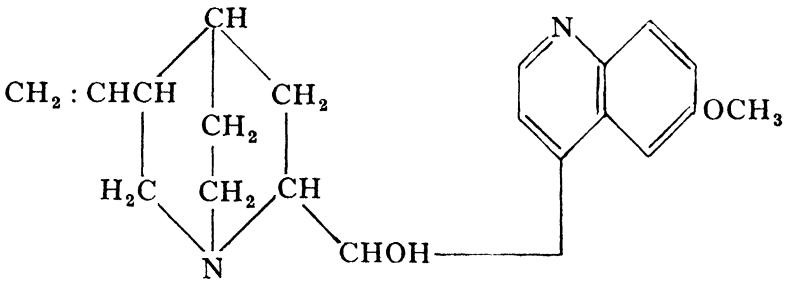


II

Quinine and *quinidine* are isomeric and of opposite optical rotation, and have the constitution (II), i.e. they are 6′-methoxy-3-vinyl-9-rubanol. It is probable that they are stereoisomerides. *Hydroquinine* and *hydroquinidine* correspond with quinine and quinidine, but the vinyl-group is hydrogenated to a CH_3CH_2 group. They are, therefore, 6′-methoxy-3-ethyl-9-rubanol.

Cinchonine and *cinchonidine* are also isomeric and of opposite optical rotation. They differ from quinine and quinidine respectively, in that they do not contain the methoxy group. They are, therefore, 3-vinyl-9-rubanol. *Hydrocinchonine* and *hydrocinchonidine* are 3-ethyl-9-rubanol, and bear the same relationship to cinchonine and cinchonidine as hydroquinine and hydroquinidine bear to quinine and quinidine.

Cupreine contains a hydroxy group in place of the methoxy group of quinine. It is, therefore, 6′-hydroxy-3-vinyl-9-rubanol, and quinine is the methyl ether of cupreine. Nevertheless, when the methoxy group of quinine is converted into a hydroxyl group by heating with 60 per cent sulphuric acid *apoquinine* and iso*apoquinine* are formed. Similarly *apoquinidine* and iso*apoquinine* are formed from quinidine (1). Apoquinine is not hydrogenated in the presence of nickel, as is cupreine. Probably the difference between apoquinine and cupreine is

connected with the vinyl group and is not stereochemical. Hydroquinidine can be converted to hydrocinchonine by removal of the methoxyl group by heating with ammonium bisulphite (2). By the same method cupreine yields cinchonidine.

Quinine, $C_{20}H_{24}O_2N_2 . 3H_2O$. Quinine is the most important alkaloid of the cinchona group, and is found in greater abundance than any of the other cinchona alkaloids.

Quinine was originally prepared in a crude state in 1792 by Fourcroy. Pelletier and Caventou in 1820 investigated the crude product and separated from it two alkaloids, which they called quinine and cinchonine. Quinine is chiefly manufactured from barks of the Ledgeriana type, which are specially selected on account of their quinine content. The bark is stripped and dried in the sun. It is then crushed to powder and mixed with lime and caustic soda solution. The alkaloids are extracted from the mass by repeated digestion with hot petroleum, the mixture being vigorously stirred in a rotating ball-mill heated by steam for some hours. After allowing time for the separation of the petroleum, the latter is drawn off. When the bark is sufficiently exhausted, the united petroleum extracts are extracted with dilute sulphuric acid in a lead-lined vessel provided with a powerful stirrer. When extraction is complete the oil is again separated and used again for extracting the bark. The acid aqueous liquid, while still hot, is neutralised to the reaction of the neutral sulphates of the alkaloids and allowed to crystallise. Crude quinine sulphate, containing cinchonidine and cinchonine sulphates and colouring matter, crystallises out. It is redissolved in water, decolorised with charcoal, and recrystallised until the cinchonidine and cinchonine are reduced to the required percentage. Quinine is prepared from the sulphate by precipitation with alkali, washing and drying. It crystallises with 3 molecules of water, melting at 57°, but this hydrate soon loses water on exposure to the air. Dried over sulphuric acid, a hydrate containing 1 molecule of water is formed. At 110° all the water is lost, and the anhydrous quinine melts at 172·8°. The specific rotation depends to a large extent, on the solvent, the temperature and the pH, but at 15° in 99 per cent alcohol its $[\alpha]_D$ is −158°.

Solutions of quinine in sulphuric, tartaric, phosphoric and certain other oxy-acids show a strong blue fluorescence, which is still perceptible even at high dilutions. Hydrochloric or other halogen acids destroy the fluorescence. Quinidine and hydroquinine give a similar fluorescence; cinchonine and cinchonidine do not.

Thalleioquin Test. This is the most important colour test for quinine, but, unless the conditions are right, it is liable to be uncertain in its indications. It is best carried out by taking 10 ml of the quinine solution and adding 0·5 ml of saturated bromine water. After shaking, one drop of strong ammonia is added, or enough to make the liquid distinctly alkaline. A green colour is formed, unless the quinine solution is concentrated, when a green precipitate comes down. If carefully carried out, this test is said to be capable of detecting one part of quinine in 1,000,000. The thalleioquin test is given also by quinidine, hydroquinine, hydroquinidine, quinamine, quinotoxine and cupreine, but not by cinchonine, hydrocinchonidine, cinchonidine, cinchonicine or cinchonamine.

Quinine gives crystals of characteristic form in dilute solutions with sodium phosphate or potassium chromate. Quinine iodosulphate or 'herapathite' also has a characteristic microscopic form. Quinine picrate melts at 125° to 126°.

Quinine is more soluble in ether and in ammonia solution than the other cinchona alkaloids. Pure quinine has been prepared by precipitation from the commercial salt as periodide, and recovery of the base from the latter, or by recrystallisation of the (+)-camphor sulphonate and recovery of the quinine.

Quinine is distinguished from the other cinchona alkaloids by the following characters:

From *cinchonine* by the blue fluorescence with sulphuric acid, by its laevorotation, by the thalleioquin test, by its solubility in ether and ammonia, and the insolubility of its neutral tartrate.

From *cinchonidine* by the blue fluorescence, and by its greater solubility in ether and ammonia.

From *quinidine* by its laevorotation, by yielding no crystalline precipitate with potassium iodide, and by the insolubility of quinine sulphate in chloroform.

From *quinamine* by its laevorotation, its solubility in ether and the insolubility of its neutral tartrate.

From *cupreine* by the blue fluorescence and by the insolubility of the alkaloid when precipitated in excess of sodium hydroxide.

Quinine has been completely synthesized by R. B. Woodward and W. E. Doering (3) according to the scheme on pp. 223 to 225.

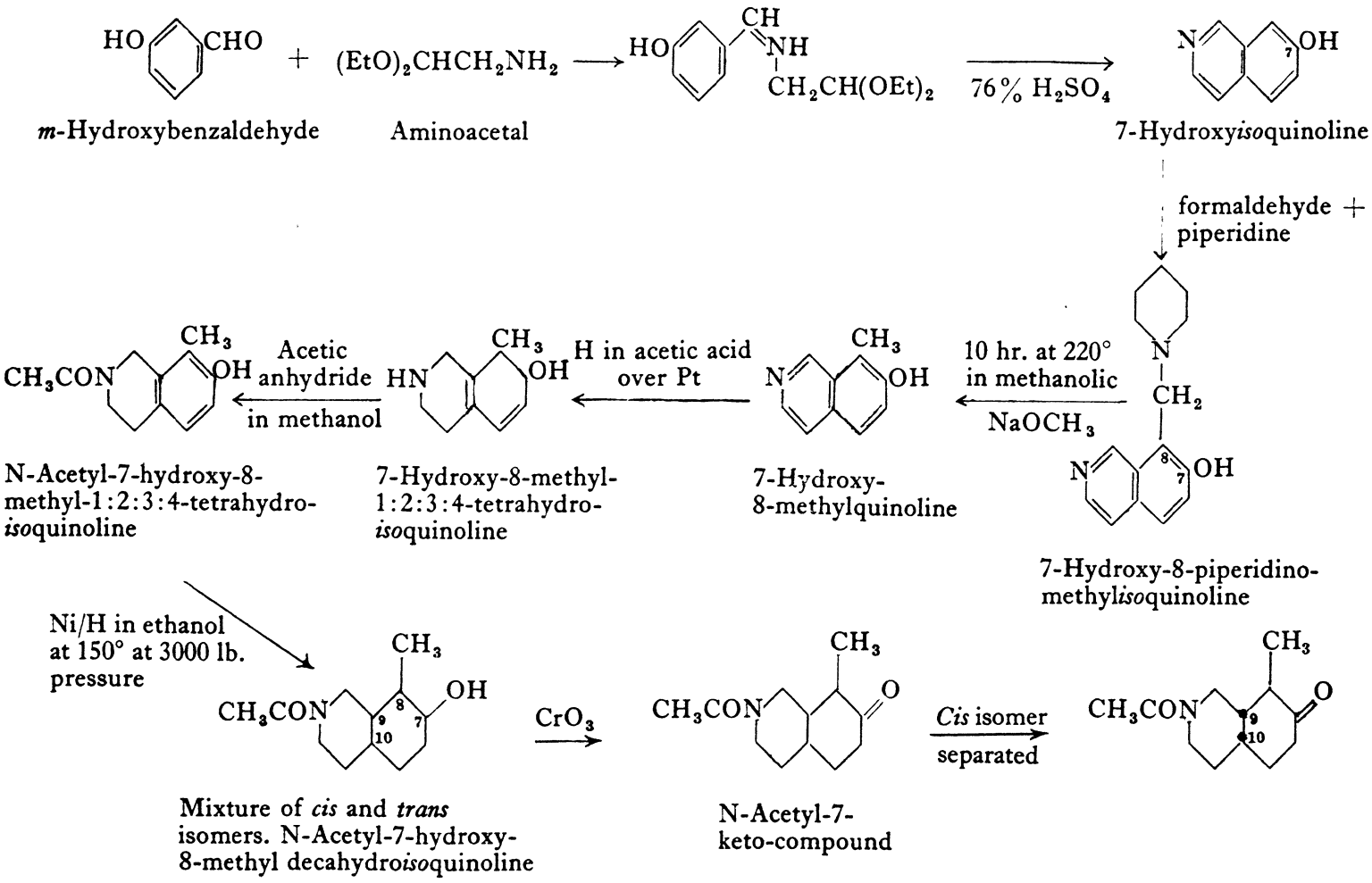
Quinine sulphate, $(C_{20}H_{24}O_2N_2)_2.H_2SO_4.2H_2O$. Quinine sulphate is the most important salt of quinine, and is used in medicine in large quantities. Its preparation on the commercial scale has been described above. Commercial quinine sulphate is never pure, but always contains a certain proportion of other cinchona alkaloids, chiefly cinchonidine and hydroquinine. Certain empirical tests are laid down by the various pharmacopœias in order to keep these impurities below a certain limit; these tests depend on the greater solubility of quinine in ether and ammonia, as compared with its impurities. Quinine sulphate occurs in light silky white crystals. 1 gram dissolves completely in 7 ml of a mixture of chloroform (2 volumes) and absolute alcohol (1 volume). Quinine sulphate contains 73·5 per cent of anhydrous quinine. $[\alpha]_D^{15°}$ —216·5° calculated to the pure dry salt (c=M/40 in water).

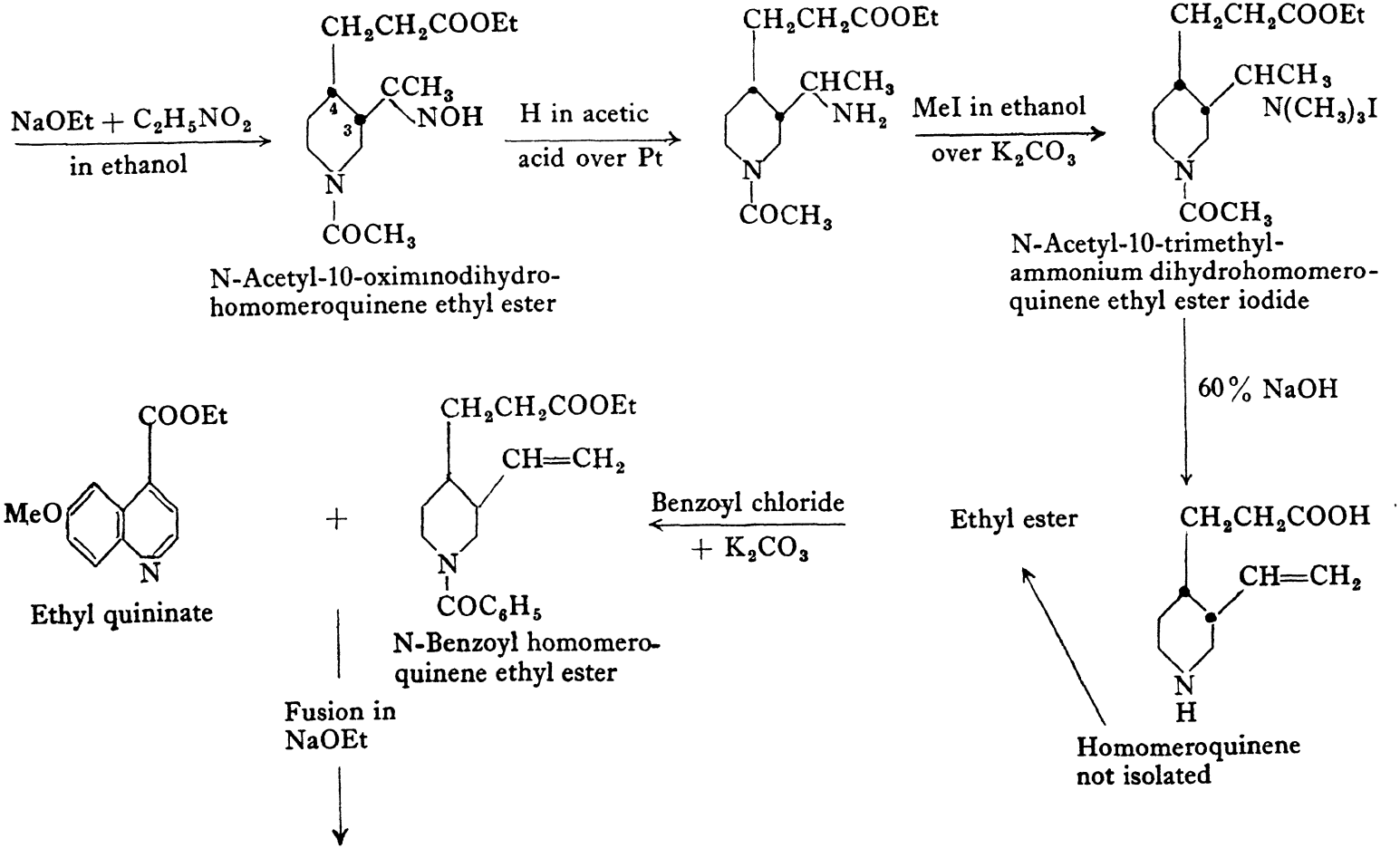
Quinine hydrochloride, $C_{20}H_{24}O_2N_2.HCl.2H_2O$. This salt is much more soluble than the sulphate. It forms white silky crystals. The salt contains 81·7 per cent of anhydrous quinine. M.p. 158° to 160° $[\alpha]_D^{17°}$ —133·7° (in water).

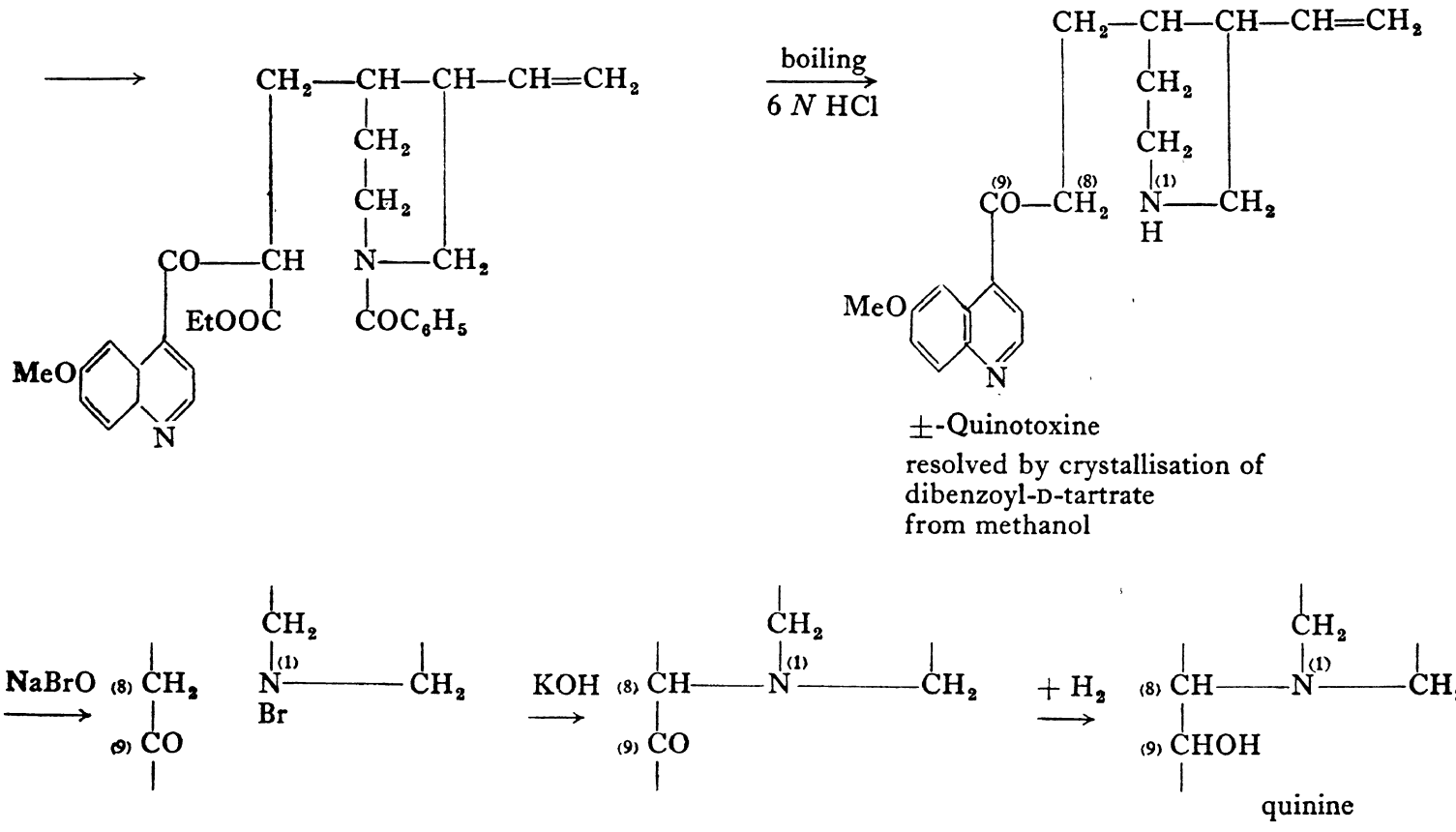
The *dihydrochloride* or *acid hydrochloride*, $C_{20}H_{24}O_2N_2.2HCl$, and the *bisulphate* or *acid sulphate*, $C_{20}H_{24}O_2N_2.H_2SO_4.7H_2O$, are sometimes used on account of their greater solubility. Numerous other salts of quinine are used, such as the hydrobromide, glycerophosphate, phosphate, hypophosphite and salicylate.

Quinine Ethyl Carbonate, $C_2H_5CO_3.C_{20}H_{23}ON_2$, is almost tasteless. The double hydrochloride of quinine and urea, $C_{20}H_{24}O_2N_2.HCl.CO(NH_2)_2.HCl.5H_2O$, is used for injection.

Quinidine, $C_{20}H_{24}O_2N_2$, occurs in small amount in certain cinchona barks.


m-Hydroxybenzaldehyde
Aminoacetal
76% H2SO4
7-Hydroxyisoquinoline
formaldehyde + piperidine
10 hr. at 220° in methanolic NaOCH3
7-Hydroxy-8-piperidinomethylisoquinoline
H in acetic acid over Pt
7-Hydroxy-8-methylquinoline
7-Hydroxy-8-methyl-1:2:3:4-tetrahydroisoquinoline
Acetic anhydride in methanol
N-Acetyl-7-hydroxy-8-methyl-1:2:3:4-tetrahydroisoquinoline
Ni/H in ethanol at 150° at 3000 lb. pressure
Mixture of cis and trans isomers. N-Acetyl-7-hydroxy-8-methyl decahydroisoquinoline
CrO3
N-Acetyl-7-keto-compound
Cis isomer separated


NaOEt + $C_2H_5NO_2$
in ethanol
CH_2CH_2COOEt
CCH_3
NOH
4
3
N
$COCH_3$
N-Acetyl-10-oximinodihydro-homomeroquinene ethyl ester
H in acetic acid over Pt
CH_2CH_2COOEt
$CHCH_3$
NH_2
N
$COCH_3$
MeI in ethanol over K_2CO_3
CH_2CH_2COOEt
$CHCH_3$
$N(CH_3)_3I$
N
$COCH_3$
N-Acetyl-10-trimethyl-ammonium dihydrohomomero-quinene ethyl ester iodide
60% NaOH
Ethyl ester
CH_2CH_2COOH
$CH=CH_2$
N
H
Homomeroquinene not isolated
COOEt
MeO
N
Ethyl quininate
+
CH_2CH_2COOEt
$CH=CH_2$
N
COC_6H_5
N-Benzoyl homomero-quinene ethyl ester
Benzoyl chloride
+ K_2CO_3
Fusion in NaOEt



The conversion of (±)-quinotoxine to quinine had already been accomplished by Rabe & Kindler (4).

The root barks always contain more quinidine than the stem barks; in fact the stem bark of *Cinchona succirubra* contains no quinidine, whereas the root bark contains about 0·4 per cent. Quinidine remains in the mother liquor obtained in the manufacture of quinine after the quinine and cinchonidine sulphates have been crystallised out. On precipitating these liquors with sodium hydroxide and extracting with ether, quinidine and cinchonidine are dissolved. The alkaloids are removed from the ether with dilute sulphuric acid, and the acid solution neutralised with ammonia. The cinchonidine is then precipitated with sodium potassium tartrate. The quinidine is precipitated from the filtrate as the hydriodide by the addition of potassium iodide solution. The base is recovered and recrystallised from alcohol. Quinidine, when anhydrous, melts at 171·5°. It is slightly soluble in water, more soluble in 80 per cent alcohol and in ether. It is dextrorotatory $[\alpha]_D$ +274·7° in alcohol - chloroform (1 : 2). Quinidine picrate melts at 137° to 138°.

Quinidine sulphate, $(C_{20}H_{24}N_2O_2)_2.H_2SO_4.2H_2O$, occurs as white silky needles or hard prisms, slightly soluble in water, more soluble in alcohol and in chloroform. M.p. 206°. The solution in water acidified with sulphuric acid shows a blue fluorescence. Commercial quinidine sulphate always contains hydroquinidine sulphate.

Quinidine is more effective than quinine in benign tertian malaria, and has been found useful in the treatment of auricular fibrillation.

Cinchonine, $C_{19}H_{22}ON_2$, occurs in nearly all cinchona barks. Cinchonine is prepared from the mother liquors after the crystallisation of crude quinine sulphate. The cinchonidine is removed as tartrate. The cinchonine is separated from quinidine by taking advantage of the slight solubility of the former in ether. It is recrystallised from alcohol. Cinchonine crystallises in needles or prisms, which sublime at 220° and melt at 255°. Cinchonine is almost insoluble in water, more soluble in alcohol and chloroform, and only slightly soluble in ether. $[\alpha]_D$ +229° in dry alcohol. Cinchonine gives characteristic crystals in dilute solutions with potassium ferrocyanide and with Wagner's reagent. Cinchonine picrate melts at 193° to 194°.

Cinchonidine, $C_{19}H_{22}ON_2$, occurs in the largest amount in *Cinchona succirubra*, but occurs in most cinchona barks. It is prepared from the mother liquor from the crystallisation of quinine sulphate by precipitation as neutral tartrate with sodium potassium tartrate. The tartrate is washed with water and decomposed with ammonia, and the base dried at a low temperature. On dissolving the base in 2·1 ml of 50 per cent sulphuric acid and 11 ml of absolute alcohol for each gram of base, and allowing to cool, pure cinchonidine tetrasulphate crystallises out. Cinchonidine is recovered from the sulphate by precipitation with sodium hydroxide and recrystallisation from alcohol. Cinchonidine crystallises in short prisms, almost insoluble in water. Cinchonidine picrate melts at 208° to 209°. Cinchonidine has been found to be more effective than quinine in the treatment of benign tertian malaria.

Hydroquinine, $C_{20}H_{26}O_2N_2.2H_2O$. Hydroquinine was first obtained by Hesse in 1882 from the alkaloids of *Cinchona Ledgeriana*. Hydroquinine is one of the chief impurities present in commercial quinine sulphate, in which it is

present to an amount of 1 to 2 per cent. Hydroquinine is best prepared by the hydrogenation of quinine. In the presence of palladium black an acid solution of quinine sulphate is readily hydrogenated to hydroquinine (5).

Hydroquinine is prepared by this method for use in the preparation of the hydrocupreines.

Hydroquinine may be separated from quinine by repeated crystallisation of the sulphate. The mother liquors are freed as far as possible from quinine and treated in the cold with permanganate, which oxidises the quinine, but has no action on hydroquinine. Hydroquinine melts at 172·3° when anhydrous. $[\alpha]_D$ in alcohol −42·2°. Hydroquinine closely resembles quinine. It gives the thalleioquin reaction and its solution in sulphuric acid shows a blue fluorescence. It forms similar salts to those of quinine. Hydroquinine is stated to be more effective than quinine in malign tertian malaria.

Hydrocinchonine or **Cinchotine**, $C_{19}H_{24}ON_2$. This alkaloid has been found in several varieties of cinchona bark, having been discovered by Hesse in 1873. It accompanies cinchonine in the separation of the alkaloids and is found in commercial cinchonine, from which it may be separated by fractional crystallisation from alcohol, the remaining cinchonine being removed by cold oxidation with permanganate. Hydrocinchonine, however, is best prepared by hydrogenation of cinchonine by the method used for hydroquinine. Hydrocinchonine melts at 286°. $[\alpha]_D$ in 97 per cent alcohol +192°.

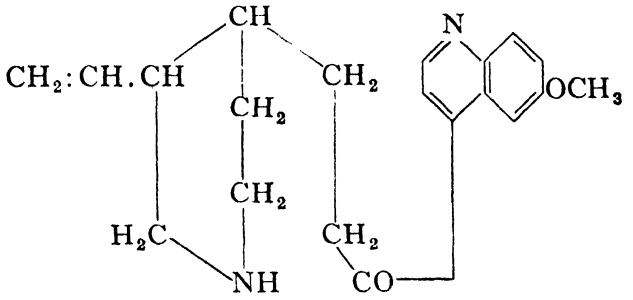
Hydrocinchonidine, $C_{19}H_{24}ON_2$, was found by Forst and Böhringer in 1881 in *Cinchona Ledgeriana* bark, and occurs also in other varieties. As in the case of the other 'hydro' cinchona alkaloids, it is best prepared by the hydrogenation of the corresponding dehydrogenated alkaloid cinchonidine. Hydrocinchonidine accompanies cinchonidine in the commercial process for the separation of the alkaloids, and is found in commercial cinchonidine sulphate, from which it may be separated by fractional precipitation of the tartrates. The residual cinchonidine is removed by oxidation with permanganate in the cold. Hydrocinchonidine melts at 229°. $[\alpha]_D$ −98·4° in alcohol. Like cinchonidine, the sulphate does not show a blue fluorescence in solution, nor does it give the thalleioquin test. The salts resemble those of cinchonidine.

Hydroquinidine, $C_{20}H_{26}O_2N_2.2\frac{1}{2}H_2O$. Forst and Böhringer in 1881 found this alkaloid as an impurity in quinidine. It occurs in considerable amount in commercial quinidine sulphate, from which it may be separated by fractional crystallisation by the same method as is used for the separation of hydroquinine from quinine. Quinidine may be readily hydrogenated to hydroquinidine. Hydroquinidine melts at 166° to 167° when anhydrous. $[\alpha]_D$ +230°. Like quinidine, it shows a blue fluorescence in sulphuric acid solution, and gives the thalleioquin reaction. The salts resemble those of quinidine.

Cupreine, $C_{19}H_{22}O_2N_2.2H_2O$. Cupreine occurs in the bark of *Remijia pedunculata* or cuprea bark. Cupreine may be prepared from the sulphuric acid solution of the total alkaloids extracted from the bark. The solution consists of the sulphates of cupreine and quinine, and on careful neutralisation of the sulphates a compound of cupreine and quinine (known as homoquinine) crystallises out. The crystals are dissolved in dilute sulphuric acid, and the alkaloids are

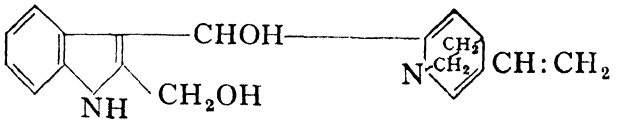
precipitated with an excess of sodium hydroxide and extracted with ether. The quinine is dissolved while the cupreine remains in solution. The alkaline solution is neutralised with sulphuric acid, and cupreine sulphate crystallises out. The alkaloid may be purified by crystallisation from alcohol. Cupreine melts at 198°, when anhydrous. $[\alpha]_D$ in 1·5 per cent solution in absolute alcohol −175·5°. Cupreine is soluble in alcohol, and in excess of sodium hydroxide, but not in ammonia. It is only slightly soluble in ether and chloroform. Cupreine gives the thalleioquin reaction, but the sulphate is not fluorescent.

Quinotoxine or **Quinicine**, $C_{20}H_{24}O_2N_2$. Pasteur in 1853 found that on heating the acid quinine sulphate a new alkaloid was formed. This alkaloid is also formed by heating quinidine acid sulphate, and has been found in cinchona bark. Quinotoxine has toxic properties, and as it is formed by heating quinine in acid solution, it is liable to occur in solutions of acid salts of quinine which have been sterilised by heat. Similar compounds are formed from the homologues of quinine. Quinotoxine (III) is 6′-methoxy-3-vinyl-rubatoxan-9-one.



III

Quinamine (6). Quinamine differs from the other cinchona alkaloids in containing an indole nucleus in place of the usual quinoline nucleus. Kirby (7) suggests the structure (IV).



IV

Cinchonicine, 3-vinyl-rubatoxan-9-one, is formed in a similar way from cinchonine or cinchonidine. Similar changes occur in the other alkaloids, e.g. cupreine forms *cupreicine*, hydrocupreine forms *hydrocupreicine*.

Comparisons between the quinine alkaloids (8) in their effectiveness in the treatment of bird malaria have been carried out, though it does not necessarily follow that the effectiveness in human malaria would show the same relationships. Hydroquinine was the most effective, quinine, quinidine, cinchonine, and cinchonidine being of equal value.

The series of alkaloids formed by the mild oxidation of quinine, quinidine,

cinchonine and cinchonidine—viz. quitenine, quitenidine, cinchotenine, and cinchotenidine—in which the vinyl group is replaced by a carboxyl group, have been shown to be ineffective in bird malaria, but the alkylation of the carboxyl group restores the activity, which increases as the homologous series is ascended, reaching a maximum at butyl or amyl.

It has also been shown (9) that in all cases in which the alcoholic hydroxyl group of quinine is replaced or protected the antimalarial properties of the alkaloid disappear.

Cinchona 'Febrifuge'. Mixtures of cinchona alkaloids are largely used in India and other countries in the treatment of malaria. These febrifuges are manufactured from the mother liquors from the crystallisation of quinine and cinchonidine sulphates in the manufacture of quinine from cinchona bark. They therefore do not represent the total alkaloids of the drug (10). The typical analysis of such a preparation is:

	Per cent
Quinine	8·5
Cinchonidine	7·0
Cinchonine	28·3
Quinidine	8·6
Amorphous alkaloids	44·7

Totaquine and **Quinetum** are preparations containing the total alkaloids of cinchona.

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CHAPTER V

Ergot Alkaloids

ERGOT consists of the mycelia of *Claviceps purpurea*, a fungus which is found growing on many cereals and grasses, but principally on rye. Ergot has been used for centuries for its pressor action, and in particular for its stimulating action on the muscles of the uterus.

The constituents of ergot have been the subject of numerous researches and in early years many products of doubtful purity were described. Wenzell (1) in 1864 prepared two bases which he called *ergotine* and *ecboline*, but the first crystalline substance was a base prepared by Tanret (2) which he named *ergotinine*; this was later shown by Kobert (3) to be devoid of pharmacological activity. Jacobi's *secaline* and the *picrosclerotine* of Dragendorff and Podwyssozki also consisted of ergotinine. Tanret, however, isolated from the mother liquors from ergotinine an amorphous base, *cornutine*, which Kobert found to be active. This base, as well as similar products prepared by others, such as the *sphacelotoxine* of Jacobi, consisted of impure ergotoxine on which their activity depended. Ergotoxine was first obtained crystalline by Barger and Carr (4); it was also isolated almost simultaneously by Kraft (5), who thought that it was converted into ergotinine by the loss of a molecule of water; hence he named it *hydroergotinine*. A second active alkaloid, *ergotamine*, was isolated by Stoll (6) in 1920.

The stimulating activity on the uterus of aqueous extracts of ergot, which apparently contained no ergotoxine or ergotamine, was a puzzle for many years until the water-soluble alkaloid *ergometrine* was almost simultaneously discovered by Dudley and Moir (7) in 1935, by Kharasch and Legault (8) who named it *ergotocine*, by Stoll and Burckhardt (9) and by Thompson (10) who called it *ergobasine* and *ergostetrine* respectively. Because of these conflicting claims the name *ergonovine* was officially adopted in the U.S.A. but ergometrine was retained in the B.P.

Ergotoxine has been shown by Stoll and Hofmann (11) to be a mixture of three alkaloids, *ergocornine*, *ergocrystine* and *ergocryptine*. Consequently ergotinine is also a mixture. The name ergotoxine is, however, still used to denote the product used in medicine.

Ergot also contains a number of non-alkaloidal nitrogenous bases including *p*-hydroxy-β-phenylethylamine (tyramine), ergothioneine and histamine; it also contains about 33 per cent of lipids of which about 0·3 per cent is ergosterol.

The ergot alkaloids exist in pairs which are isomeric and interconvertible. One member is laevorotatory and very active pharmacologically while the second member is strongly dextrorotatory and only mildly active.

Ergot alkaloids possess two types of pharmacological activity, (*a*) their stimulating activity on smooth muscle, especially that of the uterus, and (*b*) a stimulating

Alkaloid	Formula	$[\alpha]_{5461}$	M.p.	Isomer	$[\alpha]_{5461}$	M.p.
Ergotoxine group						
Ergocristine	$C_{35}H_{39}O_5N_5$	$-217°$	165–170° (dec.)	Ergocristinine	$+460°$	226° (dec.)
Ergocryptine	$C_{32}H_{41}O_5N_5$	$-226°$	212–214° (dec.)	Ergocryptinine	$+508°$	240–242° (dec.)
Ergocornine	$C_{31}H_{39}O_5N_5$	$-226°$	182–184° (dec.)	Ergocorninine	$+512°$	228° (dec.)
Ergotamine group						
Ergotamine	$C_{33}H_{35}O_5N_5$	$-181°$	213–214° (dec.)	Ergotaminine	$+450°$	252° (dec.)
Ergosine	$C_{30}H_{37}O_5N_5$	$-193°$	228° (dec.)	Ergosinine	$+522°$	228° (dec.)
Ergometrine group						
Ergometrine (ergonovine)	$C_{19}H_{23}O_2N_3$	$-62{\cdot}6°$*	212° (dec.)	Ergometrinine	$+520°$	195–197° (dec.)

* In dehydrated alcohol.

action on the motor terminations of the sympathetic nerves, which in large doses are paralysed. Ergometrine and its homologues exert only the first type of activity, for which purpose they are used in medicine. By hydrogenation of ergotoxine and ergotamine this activity is suppressed and only the second type is observed.

The specific rotation is determined where not otherwise stated in chloroform. The melting-point is not a reliable characteristic of ergot alkaloids. They tend to crystallise with combined solvent which is difficult to remove. The figures in the table are determined on the alkaloid from which the solvent has been removed.

In addition to the alkaloids in the above table, a further alkaloid, *ergomonamine*, has been found by Holden and Diver (12) which differs from the others in not giving indole colour reactions. The most important of these colour reactions is the blue colour given with a solution of 1 per cent dimethylaminobenzaldehyde in sulphuric acid containing a trace of ferric chloride. This is given by all the alkaloids except ergomonamine and by the decomposition products ergine and lysergic acid.

The change from the (−) to the (+) type of alkaloid can be effected by boiling with methanol or by standing in aqueous ethanolic potassium hydroxide; the reverse change is effected by boiling with ethanol containing phosphoric acid.

Constitution. When the ergot alkaloids of the (−) series are hydrolysed lysergic acid is obtained together with other compounds which differ in each alkaloid. The following table shows the constituents that accompany lysergic acid.

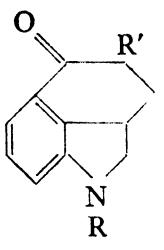
Ergocrystine	dimethylpyruvic acid	(+)proline (−)phenylalanine
Ergocryptine	dimethylpyruvic acid	(+)proline (−)leucine
Ergocornine	dimethylpyruvic acid	(+)proline (−)valine
Ergotamine	pyruvic acid	(+)proline (−)phenylalanine
Ergosine	pyruvic acid	(+)proline (−)leucine
Ergometrine	*l*-(+)-2-aminopropan-1-ol	

The alkaloids of the (+) or pharmacologically inactive series yield the same compounds and *iso*lysergic acid.

Lysergic acid, $C_{16}H_{16}O_2N_2$, (IV). In 1932 Smith and Timmis (13) showed that all the then known ergot alkaloids gave a basic degradation product, which they named *ergine*, by the action of methanolic alkali (this is now called iso*ergine* since it is an amide of *iso*lysergic acid). In 1934 Jacobs and Craig (14) showed that ergometrine was a hydroxypropylamide of lysergic acid and in 1938 Stoll and Hofmann (15) synthesised ergometrine from lysergic acid and *l*-(+)-2-amino-

propan-1-ol thus showing that lysergic acid is the fundamental constituent of the (—) series of ergot alkaloids.

Lysergic acid has been synthesised by Kornfeld *et al.* (16). The reaction of N-benzoyl-3-(β-carboxyethyl)dihydroindole with thionyl chloride followed by aluminium chloride gave I, (R = $-COC_6H_5$; R′ = H); this was brominated to give I, (R = $-COC_6H_5$; R′ = Br) which by reaction with methylaminoacetone ethylene ketal was converted to I, [R = $-COC_6H_5$; R′ = $-N(Me)CH_2C(Me)OCH_2CH_2O$]; hydrolysis yielded the diketone [I, R = H; R′ = $-N(Me)\ CH_2COCH_3$] which by treatment with sodium methoxide gave the tetracyclic ketone (II, R = H). Acetylation yielded II, (R = $-COCH_3$) and reduction gave the alcohol (III, R = $-COCH_3$; R′ = OH). Treatment of the hydrochloride of this with thionyl chloride followed by sodium cyanide in liquid hydrogen cyanide gave the nitrile (III, R = $-COCH_3$; R′ = CN) which by methanolysis produced the ester (III, R = H; R′ = $-COOCH_3$); this was hydrolysed with alkali and dehydrogenated catalytically with deactivated Raney nickel giving (±)-lysergic acid (IV). From the synthetic acid, treatment with diazomethane followed by hydrazine gave (±)-*iso*lysergic acid hydrazide. This compound was resolved by Stoll and Hofmann (17) by the use of the di-*p*-toluoyl tartrates into its optical isomers which were converted into the corresponding lysergic hydrazides by treatment with ethanolic alkali. *iso*Lysergic acid differs from lysergic acid in the spatial arrangement of the substituents at position 8.



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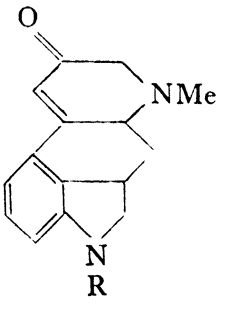

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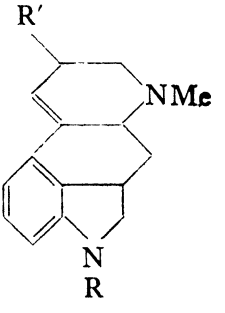

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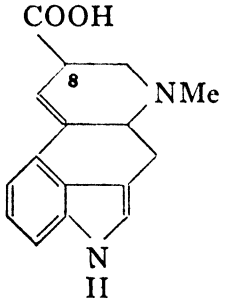


IV

All the alkaloids of ergot, as well as the hydrogenated components of ergotoxine have been separated by chromatography (18).

The stereochemistry of the lysergic acids and their derivatives have been discussed by Stoll and his associates (19).

Ergometrine. Ergonovine. $C_{19}H_{23}O_2N_3$. This alkaloid has the simplest structure of all those occurring naturally in ergot, being the amide of (+)-lysergic acid and *l*-(+)-2-aminopropan-1-ol. It differs from the other alkaloids in being water-soluble and in its pharmacological action. It is also more reliable in its action when given by the mouth than the other alkaloids.

Ergometrine crystallises from benzene in colourless needles and from ethyl methyl ketone in prisms; both these forms contain combined solvent and melt at 162° to 164° (dec.). It may also be crystallised from ethyl acetate at −4° in plates containing no combined solvent which melt at 160° to 161°. By crystallisation from acetone and drying *in vacuo* at 140° a form is obtained which melts at 212° (dec.). The optical rotation is $[\alpha]_D^{20}$ (c=1·5 in dehydrated ethanol) +40° to +43° calculated to solvent-free material or $[\alpha]_{5461}^{20}$ +60° to +63°.

Ergometrine picrate exists in two forms, a hydrated form melting at 148° (dec.) and an anhydrous form melting with sudden decomposition at 188° to 189°.

Ergometrine and its salts are easily oxidised and readily discolour on exposure to air and light; the maleate is the most stable salt. Aqueous solutions of the salts have a blue fluorescence.

Ergometrine maleate. $C_{19}H_{23}O_2N_2.C_4H_4O_4$. This salt is soluble in water (about 1 in 36) and melts at 195° to 197° (dec.); $[\alpha]_D^{20}$ +53° to +56° (when dried *in vacuo* at 110°: c=1·5 w/v in water).

Methods for the preparation of ergometrine and its maleate have been patented (20).

Ergometrine was synthesised by Stoll and Hofmann (21) from lysergic acid and *l*-(+)-2-aminopropan-1-ol. Lysergic acid amide is prepared by diazotisation of the hydrazide and this is condensed with the aminopropanol in the presence of alkali.

Methyl ergometrine tartrate, (+)-Lysergic acid-*n*-butanol-2-amide. This compound is stated to have an action on the uterus one and a half to two times as powerful as ergometrine, and the action is also more prolonged.

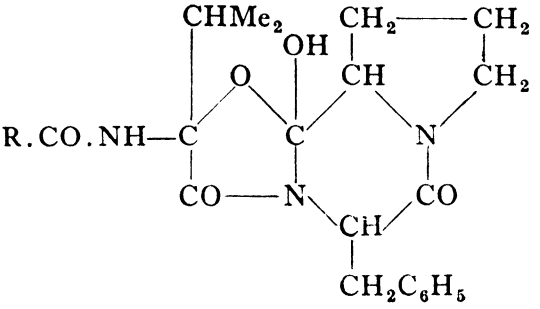
Ergotamine, $C_{33}H_{35}O_5N_5$. There are two strains of ergot, one containing alkaloids of the ergotoxine group and the other yielding ergotamine (22). The ergot collected from the tall fescue grass of New Zealand also contains ergotamine (23). Ergotamine may be prepared by the method described by Stoll (24). The coarsely ground ergot (2 kg) is mixed with a solution of aluminium sulphate (200 g) in 300 ml of water and finely ground; the mass is moistened with benzene (1500 ml) and thoroughly extracted with benzene to remove fat, etc. The mass is then stirred with benzene (4 litres) and brought to an alkaline reaction with ammonia, the extraction with benzene being continued until no more alkaloid is removed. The benzene extracts are concentrated *in vacuo* to a volume of 50 to 100 ml, when the greater part of the alkaloid crystallises; the remainder is precipitated from the mother liquor by the addition of petroleum spirit. The alkaloid is dried *in vacuo* and recrystallised from aqueous acetone.

Ergotamine crystallises from aqueous acetone in rectangular plates with two molecules of acetone and two molecules of water.

Ergotamine is a weak monoacidic base; the optical rotation (c=1·0 in chloroform) is $[\alpha]_D^{20}$ −160° or $[\alpha]_{5461}^{20}$ −192°.

Ergotamine tartrate, $(C_{33}H_{35}O_5N_5)_2,C_4H_6O_6$, is the salt generally used; it is readily soluble in water.

Ergotoxine. This was formerly regarded as a single alkaloid but has been found to be a mixture of three alkaloids, *ergocristine*, $C_{35}H_{39}O_5N_5$, *ergocryptine*, $C_{32}H_{41}O_5N_5$, and *ergocornine*, $C_{31}H_{39}O_5N_5$. The constituent parts of these alkaloids have been given on p. 232. Ergocristine has the structure (V). These alkaloids were isolated from commercial ergotoxine by Stoll and Hofmann (24) by crystallisation of the di-(*p*-toluyl) (−)tartrates.



R.COOH = Lysergic acid

V

Dihydro derivatives of ergot alkaloids. These compounds are readily formed by hydrogenation of the double bond in the lysergic acid part of the molecule of ergot alkaloids. The dihydro derivatives of ergotamine and of the ergotoxine group of alkaloids have been used in medicine. The pharmacological action is modified so that the action on smooth muscle is suppressed and the sympathicolytic activity remains; they therefore reduce the blood pressure and have been used in hypertension.

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CHAPTER VI

Solanaceous Alkaloids

OF the plants yielding solanaceous alkaloids, only belladonna root and leaves, and the leaves of *Hyoscyamus niger* and *Datura stramonium* are in common use in medicine. *Hyoscyamus muticus*, the Egyptian henbane, is the chief source of commercial hyoscyamine. Hyoscine is best obtained from *Datura Metel*, or from *Duboisia* species. The following is a list of the chief plants yielding solanaceous alkaloids. The composition of the alkaloids in the plants is liable to variation in the same species at different times or in different plants:

Plant	Part of Plant	Percentage of Alkaloids	Chief Alkaloids
Atropa acuminata (Indian Belladonna)	Whole	0·3 to 0·5	Hyoscyamine
Atropa Belladonna	Leaves	0·15 to 0·60	Hyoscyamine and hyoscine
	Roots	0·1 to 0·7	
	Seeds	0·8	
Datura fastuosa	Fruits	0·24	Hyoscine
Datura Metel	Fruits	0·12	Hyoscine
	Leaves	0·2 to 0·5	Hyoscine
Datura meteloides	—	0·4	Hyoscine, and meteloidine
Datura quercifolia	Leaves	0·42	Hyoscine and hyoscyamine
	Seeds	0·29	Hyoscine and hyoscyamine
Datura stramonium	Leaves	0·2 to 0·45	Hyoscyamine
	Seeds	0·2 to 0·5	Hyoscyamine
Duboisia myoporoides	Roots	—	Hyoscine, hyoscyamine
Duboisia Leichardii	Leaves	2·0	Hyoscyamine
Hyoscyamus albus	Leaves	0·2 to 0·56	Hyoscyamine and hyoscine
	Seeds	0·16	Hyoscyamine and hyoscine
Hyoscyamus muticus	Leaves	1·4	Hyoscyamine
	Seeds	0·87 to 1·34	Hyoscyamine
Hyoscyamus niger	Leaves	0·045 to 0·08	Hyoscyamine
	Seeds	0·06 to 0·10	Hyoscyamine
Mandragora officinarum	Leaves	—	Hyoscyamine and hyoscine
Scopolia carniolica	Rhizomes	0·43 to 0·51	Hyoscyamine and hyoscine
Scopolia japonica	Leaves	0·18	Hyoscyamine

The chief alkaloids belonging to the 'solanaceous' group are (—)-hyoscyamine, atropine [(±)-hyoscyamine], hyoscine (scopolamine), apoatropine (atropamine), belladonnine, *nor*hyoscyamine, *nor*atropine, and meteloidine. All these alkaloids

are esters formed by the combination of an acid with an amino alcohol as shown in the following table:

Alkaloid	Acid	Amino Alcohol
Hyoscyamine Atropine	Tropic	Tropine
Norhyoscyamine	Tropic	*nor*Tropine
Hyoscine	Tropic	Scopine
Meteloidine	Tiglic	Teloidine
Apoatropine (Atropamine)	Atropic	Tropine
Belladonnine	β-Isatropic	Tropine

The alkaloids of this group possess the power of dilating the pupil when applied to the eye, and are hence often known as the 'mydriatic' alkaloids. They are easily hydrolysed, and the conditions of their extraction must be such as to avoid this possibility. Further, (—)-hyoscyamine is readily converted into its inactive form, atropine, in the process of extraction. It is, in fact, doubtful if atropine is ever present in the growing plant in more than minute quantities, if at all.

Methods of preparation. The total alkaloids may be extracted from a solanaceous drug by the following process: the finely powdered drug is exhausted with hot alcohol, the solvent being then removed by distillation *in vacuo* at a low temperature. The syrupy extract is now mixed with dilute hydrochloric or sulphuric acid of about 0·5 to 1·0 per cent strength. The liquid is filtered and extracted with light petroleum. The aqueous solution is then neutralised with ammonia and allowed to stand for some time in order to allow certain resinous matter to separate. After filtering, the solution is made slightly alkaline with ammonia, and the alkaloids extracted with chloroform. The chloroform solution is extracted with dilute acid, the aqueous extract is again made alkaline with ammonia and again extracted with chloroform. The solvent is distilled off at a low temperature, leaving a residue of mixed alkaloids. In order to obtain hyoscyamine from the mixture, the required quantity of oxalic acid is added to convert the whole of the alkaloids into the normal oxalates, and the salt is recrystallised from water until it has the m.p. of (—)-hyoscyamine oxalate (176°). The base is then regenerated, extracted with chloroform, combined with the required amount of sulphuric acid to form the neutral sulphate, and crystallised from alcohol.

For the preparation of atropine, the total alkaloids and those recovered from the mother liquors after the crystallisation of hyoscyamine oxalate, are dissolved in 90 per cent alcohol containing 0·8 per cent sodium hydroxide. Racemisation proceeds slowly, and the solution is allowed to stand until it is optically inactive. The alkaloid is then neutralised with oxalic acid, and the alcohol is distilled off *in vacuo*. The atropine oxalate is crystallised from water until the m.p. is 196° to 197°. The base is then regenerated and converted into the sulphate.

Hyoscyamine and hyoscine are both strongly adsorbed on a silica column from

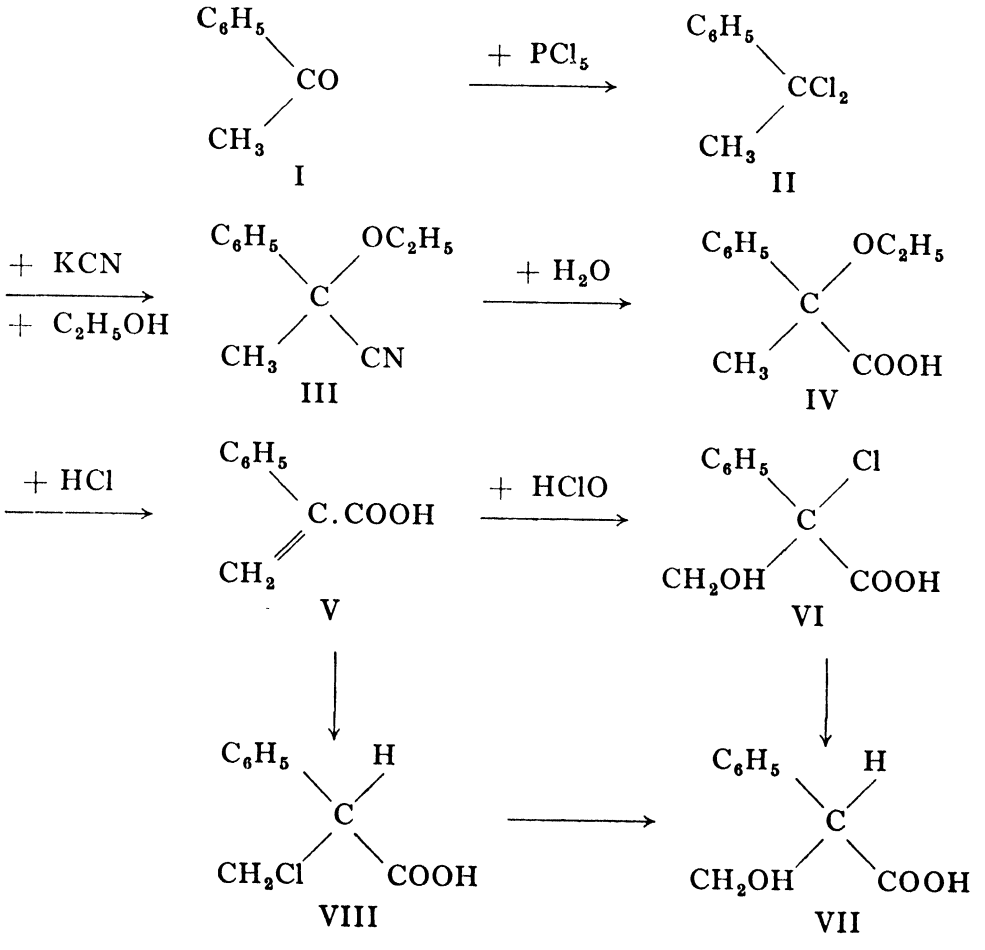
benzene solution and are separated by elution with dehydrated ethanol; the hyoscine is removed rapidly but the hyoscyamine only slowly (1).

Constitution. When atropine is hydrolysed by warming with acids or dilute alkalis, it is decomposed into tropine and tropic acid:

$$\underset{\text{Atropine}}{C_{17}H_{23}O_3N} + H_2O \longrightarrow \underset{\text{Tropine}}{C_8H_{15}ON} + \underset{\text{Tropic acid}}{C_9H_{10}O_3}$$

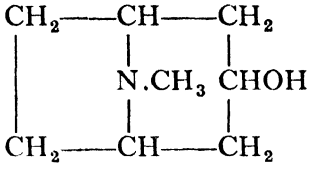
Tropic acid loses water at high temperature, and atropic acid, $C_9H_8O_2$, is formed.

Tropic acid and atropic acid have been synthesised by Ladenburg (2) by the following method: Acetophenone (I) is converted into α-dichloroethylbenzene (II) by the action of phosphorus pentachloride. Potassium cyanide in alcohol reacts with II to form ethoxycyanoethylbenzene (III), which is readily hydrolysed to ethylatrolactic acid (IV). Strong hydrochloric acid converts the latter into atropic acid (V). Atropic acid reacts with hypochlorous acid to form chlorotropic acid (VI), which on reduction passes into tropic acid (VII).

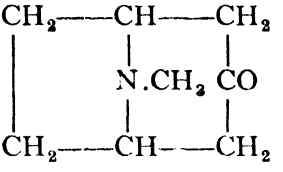


Alternatively, atropic acid (V) may be treated in ethereal solution with hydrochloric acid, which causes the formation of β-chlorohydratropic acid (VIII), which is converted into tropic acid by boiling with sodium carbonate.

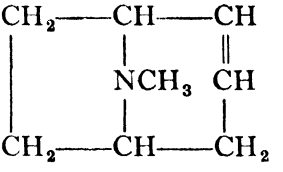
The constitution of the base tropine, $C_8H_{15}ON$, produced by the hydrolysis of atropine, is not so simply determined. Tropine, when heated with strong hydrochloric or sulphuric acid, is converted into tropidine, $C_8H_{13}N$. Tropidine methiodide is decomposed by potassium hydroxide into tropilene, $C_7H_{10}O$, and dimethylamine, showing the presence of the group $:NCH_3$ in tropine. Oxidation of tropine by chromic acid gives tropinone, $C_8H_{13}ON$. Tropinone, on reduction with sodium amalgam, forms *pseudo*tropine, which is identical with the base obtained from tropacocaine by hydrolysis. When electrolytically reduced, however, tropinone produces tropinic acid, $C_8H_{13}O_4N$. The constitution of tropine was finally settled by Willstätter (3), who adopted the formula IX, and showed it to satisfy all requirements.



IX

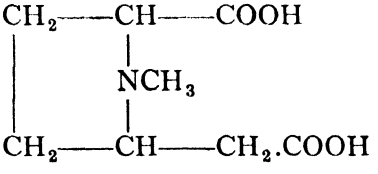


X



XI

Tropinone has, therefore, the structure X, tropidine XI, and tropinic acid XII. The parent compound from which the tropines are derived known as tropane, may be represented by XIII:



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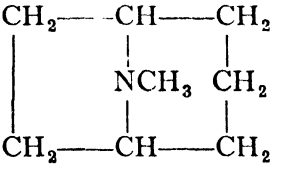
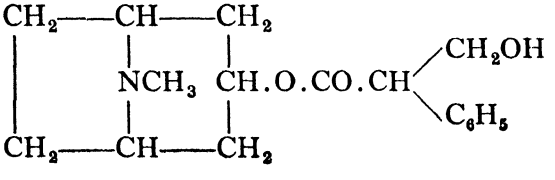


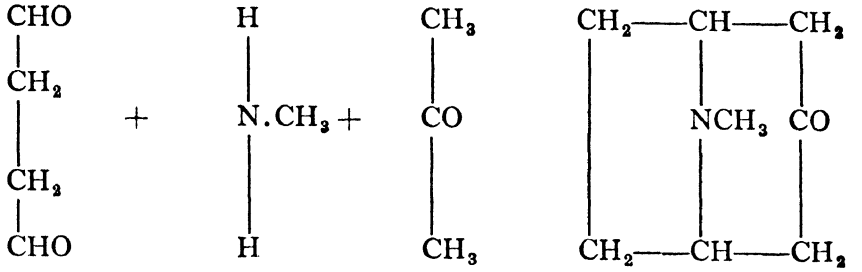
XIII

Atropine and hyoscyamine are, therefore, represented by XIV. In *nor*atropine or *nor*hyoscyamine the methyl group attached to the nitrogen atom is replaced by hydrogen.



XIV

Robinson (4) observed the formation of tropinone in small quantity by the interaction of succindialdehyde, methylamine and acetone.



Succindialdehyde Methylamine Acetone Tropinone

A better yield is obtained by using calcium acetone dicarboxylate in place of acetone and decarboxylating the dibasic acid by heating in acid solution (5).

The practical difficulties of the preparation of the appropriate dialdehyde were such that the method was not suitable for large-scale use, but recently succindialdehyde has been prepared from furan which is commercially available (6). Furan (XV) is reacted with bromine or chlorine in dry ethanolic solution at −25° and ammonia is added to neutralise the acid formed; after filtration from ammonium bromide or chloride distillation yields 2 : 5-diethoxydihydrofuran (XVI). This is hydrogenated in the presence of Raney nickel at 150° and 2000 lb per sq in. pressure to give 2 : 5-diethoxytetrahydrofuran (XVII). Hydrolysis leads to succindialdehyde (XVIII).

This work has made possible the development of a process for the manufacture of synthetic atropine. Robinson's synthesis (see above) yields tropinone which is easily reduced to tropine (IX) (7). Atropine may then be prepared by the straightforward esterification of tropine hydrochloride with acetyltropyl chloride. Acetylatropine is formed and is hydrolysed to atropine. The acetyltropoyl chloride is obtained by the reaction between acetyltropic acid and thionyl chloride.

Tropine is readily esterified by acids and numerous synthetic tropeines, as these esters are called, have been prepared. The only member of the group that has found application in medicine is phenylglycollyltropeine, known as homatropine (q.v.).

Hyoscine, like atropine, is readily hydrolysed, but in this case the products are tropic acid and a different base, oscine (scopoline) (XIX), but it has been shown by Willstätter and Berner (8) that in hyoscine itself a base scopine (XX) is present, which in the course of hydrolysis undergoes rearrangement to oscine. Hyoscine, therefore, has the constitution XXI. The configuration of hyoscine has been elucidated by making use of its hydrogenolysis into (±)-3α: 6β-dihydroxytropane, and is represented by XXVIII.

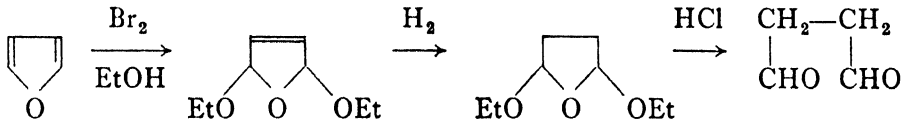
The total synthesis of hyoscine has been accomplished by Fodor *et al.* (9). (±)-6β-Hydroxytropan-3-one was converted into the phenylurethane (XXII), which gave rise on hydrogenation to (±)-6β-phenylcarbamyloxy-3α-hydroxytropane (XXIII, R=$C_6H_5NH.CO$) which was then acetylated to XXIV,

($R=C_6H_5NH.CO$, $R'=CH_3CO$). Distillation in a vacuum yielded (±)-3α-acetoxy-6β-hydroxytropane (XXIV, $R=H$, $R'=CH_3CO$). The *p*-toluenesulphonic ester (XXIV, $R=MeC_6H_4SO_2$, $R'=CH_3CO$) was prepared and cleaved in collidine at 180° in a sealed tube to 6-tropen-3-yl acetate (XXV). The trifluoroacetate of this compound was oxidised in acetonitrile with a solution of trifluoroperacetic acid in methylene chloride to scopyl acetate (XXVI) which was identical with the salt obtained by the acetylation of scopine hydrochloride obtained by mild hydrolysis of natural scopolamine. Hydrolysis with *N* NaOH in acetone for two days at 20° gave scopine (XXVII) together with some oscine. When heated for four days at 60° with a large excess of acetyltropeyl chloride in nitrobenzene acetylscopolamine was formed which was deacetylated with *N* HCl for 20 hours at 30°. The (±)-scopolamine formed was purified from scopine and oscine by partition chromatography and resolved by King's method (10) yielding (−)-hyoscine (XXVIII).

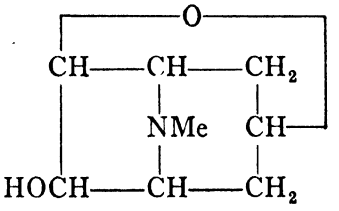
The stereochemical notation for the tropane alkaloids is based on the >NR bridge as the reference group; substituents are denoted by β or α according to whether they are on the same side or opposite sides, respectively, of the general plane of the ring as the reference group.

Atropine. (±)-Hyoscyamine. $C_{17}H_{23}O_3N$. Atropine probably does not occur as such in the plant. It is formed from hyoscyamine during the extraction. It is obtained commercially by treating crude hyoscyamine with dilute alkali when the latter is racemised to atropine. The atropine is then purified by recrystallisation of the oxalate. Atropine melts at 117° to 118°, and is optically inactive. On hydrolysis it forms tropine and tropic acid. If atropine is evaporated to dryness on the water-bath with nitric acid, and the dry residue is treated with a drop of alcoholic potash, a violet colour is formed (Vitali's test). This test is given by atropine, hyoscyamine, and hyoscine. Homatropine does not give it. Veratrine gives a somewhat similar colour. A delicate test for atropine, and, of course, for the other mydriatic alkaloids, is its power of producing mydriasis in the eye. This effect is produced in very dilute solutions; a solution containing 1 in 40,000 of atropine is sufficient to dilate the pupil of a cat in less than an hour. Atropine is a strong base, and the free alkaloid reddens phenolphthalein. The alkaloid may be titrated to methyl red. A saturated solution of bromine in hydrobromic acid (Wormley's reagent) gives a yellow amorphous precipitate with atropine or hyoscyamine, which rapidly becomes crystalline, and shows rosettes of needles or leaf-like crystals under the microscope. Hyoscine also gives a similar amorphous precipitate, which crystallises after a slightly longer period and forms similar rosettes of crystals. Atropine gives a crystalline precipitate of characteristic form with a solution of iodine in potassium iodide, a solution of 1 : 8,000 giving numbers of small crystals. When auric chloride is added to a solution of atropine in dilute hydrochloric acid, an oily precipitate is at first formed, which soon crystallises. The aurichloride melts at 137° to 139°. Atropine picrate forms rectangular plates, melting at 175° to 176°. The platinichloride melts at 197° to 200°.

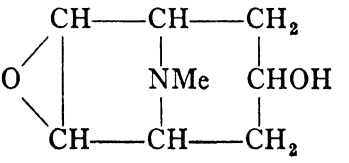
Atropine sulphate, $(C_{17}H_{23}O_3N)_2.H_2SO_4.H_2O$. This is the salt of atropine most commonly used in medicine. M.p. (when anhydrous) 195° to 196°.



XV XVI XVII XVIII



XIX



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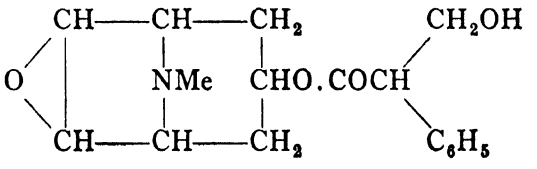
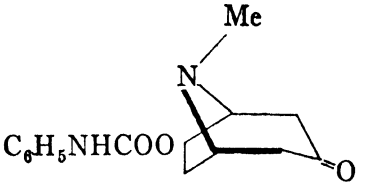


XXI



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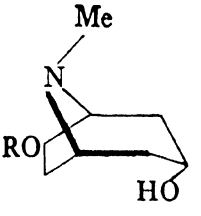

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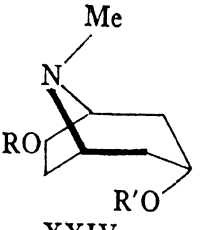

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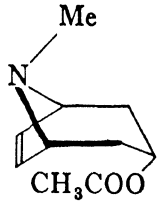

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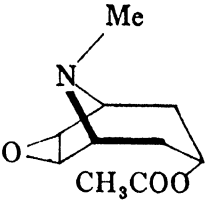

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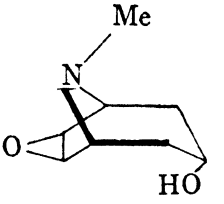

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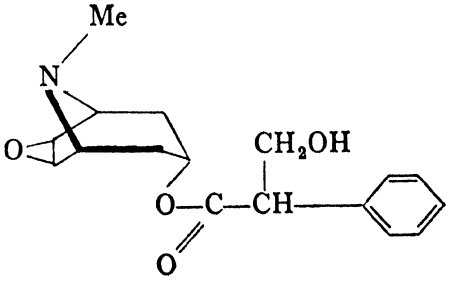


XXVIII

Atropine hydrochloride, $C_{17}H_{23}O_3N.HCl$, forms colourless needles melting at 162°.

Atropine hydrobromide, $C_{17}H_{23}O_3N.HBr$, melts at 163° to 164°.

Atropine methylbromide, $C_{17}H_{23}O_2N.CH_3Br$, melting at about 222°, and the *methylnitrate*, $B.CH_3NO_3$, are also used as mydriatics.

Hyoscyamine. (—)-Hyoscyamine, $C_{17}H_{23}O_3N$. Hyoscyamine is obtained commercially from *Hyoscyamus muticus*, or Egyptian henbane, in which about 1 per cent is found. Hyoscyamine crystallises from alcohol or petroleum ether in long silky needles. M.p. 108·5°. It is very similar to atropine in its solubilities. Hyoscyamine gives Vitali's test (see Atropine) and dilates the pupil of the eye. The physiological activity is greater than that of atropine, into which it is readily converted by treatment with alkali. Hyoscyamine on hydrolysis gives tropine and tropic acid. The $[\alpha]_D$ is —22° in 50 per cent alcohol. The aurichloride is precipitated in crystals immediately, and melts at 165°. The picrate forms quadrangular plates, melting at 165°. Hyoscyamine platinichloride melts at 206°.

Hyoscyamine forms small crystals with iodine in potassium iodide, resembling those formed by atropine, but, as a rule, somewhat larger.

(—)-Hyoscyamine sulphate, $(C_{17}H_{23}O_3N)_2.H_2SO_4.2H_2O$, is the most important salt of hyoscyamine. It crystallises in white hygroscopic needles, is soluble in water (200), and in alcohol (22). M.p. 206°. $[\alpha]_D$ —27·8° (in water).

Hyoscine. (—)-Scopolamine, $C_{17}H_{21}O_4N$. Hyoscine occurs as the (—)- modification in many solanaceous plants, especially in the Datura species, particularly in *Datura Metel*, and in certain Australian corkwood trees *Duboisia myoporoides* and *D. Leichardii* in which it is more abundant than in belladonna or datura. It is usually prepared from the mother liquor after the hyoscyamine has been removed. The alkaloid is liberated with sodium bicarbonate and neutralised with hydrobromic acid. On concentration of the solution hyoscine hydrobromide crystallises out. (—)-Hyoscine crystallises with one molecule of water, but is usually obtained as a syrup. $[\alpha]_D^{20°}$ —28° (in water). On hydrolysis hyoscine forms tropic acid and scopine, the latter being readily converted into oscine.

(—)-Hyoscine forms an aurichloride melting at 208° to 209°, and a picrate forming masses of needles melting at 187·5° to 188·5°. The platinichloride is amorphous. The gold chloride test is very sensitive, much more so than with atropine or hyoscyamine; crystals are formed from a 1 : 1,000 solution, consisting of rosettes of plates with coarse saw-like edges. Crystals are not formed with iodine in potassium iodide solution as readily as by atropine or hyoscyamine. Wormley's reagent (bromine in hydrobromic acid) gives an amorphous precipitate, which soon becomes crystalline. Hyoscine gives Vitali's test, and dilates the pupil of the eye. It is racemised by alkali in the same way as hyoscyamine.

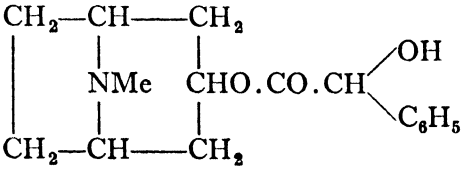
Hyoscine hydrobromide, $C_{17}H_{21}O_4N.HBr.3H_2O$, is the salt chiefly used in medicine. When anhydrous it melts at 193° to 194°. $[\alpha]_D^{20°}$ —25·9° (in water).

Apoatropine, Atropamine, $C_{17}H_{21}O_2N$. Apoatropine occurs in belladonna root. It is an anhydride of atropine, forming tropine and atropic acid on hydro-

lysis. M.p. 60°. Apoatropine forms a series of easily crystallisable salts. It is optically inactive, and does not dilate the pupil of the eye. Apoatropine is formed from atropine by heating with acetic or phosphoric anhydrides. The aurichloride melts at 110° to 112°.

Norhyoscyamine, $C_{16}H_{21}O_3N$. The presence of norhyoscyamine has been shown in several species of solanaceous plants by Carr and Reynolds (11), notably *Datura Metel* and *D. meteloides*. It may be separated from hyoscyamine by extracting the greater part of the latter with ether, and then converting into the oxalates and fractionally crystallising. Norhyoscyamine differs from hyoscyamine in that a hydrogen atom is attached to the nitrogen atom in place of a methyl group. Norhyoscyamine melts at 140°. $[\alpha]_D$ −23·0° (in 50 per cent alcohol). It is slightly soluble in water, but soluble in alcohol, chloroform, or ether. The aurichloride melts at 178° to 179°, and the picrate at 220°. On hydrolysis *nor*hyoscyamine gives *nor*tropine and tropic acid. It is racemised by alkali to *nor*atropine. On treatment with methyl iodide, hyoscyamine is formed.

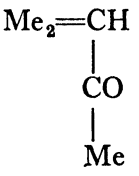
Homatropine, $C_{16}H_{21}O_3N$. Phenylglycollytropeine or mandelyltropeine. Homatropine (XXIX) is the most important of the artificial tropeines. It may be prepared by passing hydrogen chloride gas for three to four hours through a mixture of 7 parts of tropine, 10 parts of mandelic acid and 2 parts of water.



XXIX

It will be seen that homatropine differs from atropine in containing a hydroxyl group in place of the $-CH_2OH$ group of tropic acid. Homatropine crystallises in prisms. M.p. 99° to 100°. It is slightly soluble in water, and readily soluble in alcohol, ether or chloroform. Homatropine does not give Vitali's test. It resembles atropine in its physiological actions, and is a powerful mydriatic. Homatropine aurichloride is first precipitated as an oil, which afterwards becomes crystalline. Homatropine hydrobromide, $C_{16}H_{21}O_3N.HBr$, is the salt most commonly used in medicine. It melts at 217° to 218°, and is readily soluble in water. Homatropine methylbromide, $C_{17}H_{24}O_3NBr$, melts at 191° to 192°.

Eucatropine hydrochloride, $C_{17}H_{25}O_3N.HCl$, (XXXIV), is 4-mandeloxy-1 : 2 : 2 : 6-tetramethylpiperidine hydrochloride. The salt melts at 183° to 190°; it is very soluble in water, alcohol or chloroform. The starting-point of the synthesis is mesityl oxide (XXX) which reacts with ammonia to form diacetonamine (XXXI) whose acid oxalate is reacted with diethylacetal in ethanol to form vinyldiacetonamine (XXXII); reduction to the secondary alcohol and methylation with methyl iodide gives XXXIII, which is condensed with mandelic acid in hydrochloric acid at 80° to form eucatropine (12). Eucatropine hydrochloride is used as a mydriatic.



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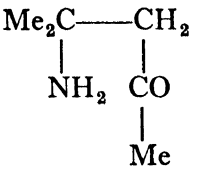

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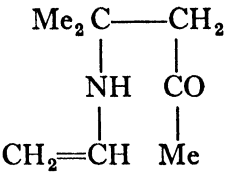

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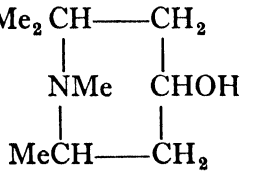

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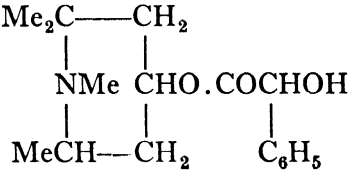

XXXIV

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CHAPTER VII

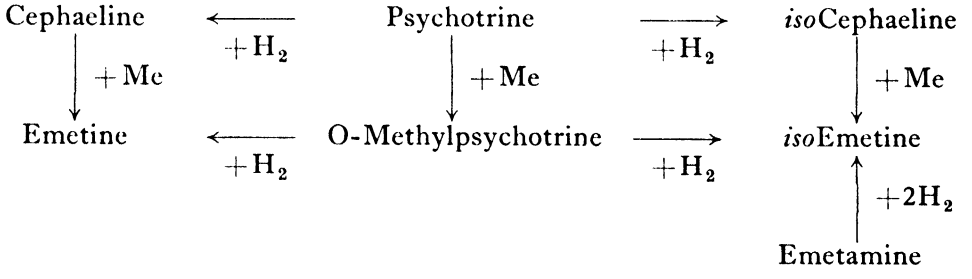
Ipecacuanha Alkaloids

IPECACUANHA root is obtained from *Cephaelis ipecacuanha* (Brot.), A. Rich, which grows in Brazil. The variety known as Rio or Matto Grosso ipecacuanha is obtained from this species and contains 2 to 3 per cent of total alkaloids of which 66 to 72 per cent is emetine. Minas ipecacuanha is very similar but the proportion of emetine is about 60 per cent of the total alkaloids. Carthagena ipecacuanha (probably from *Psychotria acuminata* Karsten) and the Nicaragua variety, which is very similar, contain only from 30 to 40 and 20 to 25 per cent of total alkaloids respectively. The Indian or Johore variety is very similar in appearance and the alkaloids contain about 50 per cent of emetine.

The alkaloids of ipecacuanha are:

emetine	$C_{29}H_{40}O_4N_2$
cephaeline	$C_{28}H_{38}O_4N_2$
psychotrine	$C_{28}H_{36}O_4N_2$
O-methylpsychotrine	$C_{29}H_{38}O_4N_2$
emetamine	$C_{29}H_{36}O_4N_2$

The relationship of these alkaloids is illustrated in the following diagram.

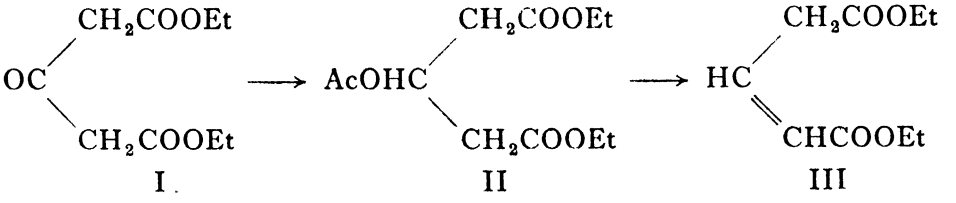


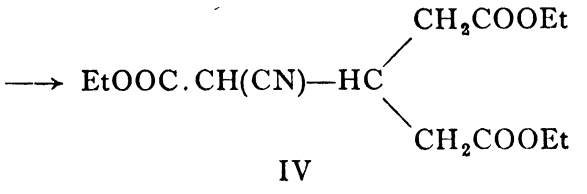
Emetine, *iso*emetine, O-methylpsychotrine and emetamine each contain four methoxy groups; cephaeline, *iso*cephaeline and psychotrine contain three methoxy groups and one hydroxyl group and are therefore known as the 'phenolic alkaloids'. The total alkaloids may be extracted from powdered ipecacuanha by extraction with ethanol, amyl alcohol or a mixture of benzene and light petroleum; the solvent is extracted with dilute hydrochloric acid which is made alkaline with ammonia and the alkaloids are extracted with ether. All the alkaloids, with the exception of psychotrine, are dissolved by the ether; psychotrine may be extracted from the aqueous liquid with chloroform and crystallised from acetone. The ethereal solution is shaken with sodium hydroxide in which the

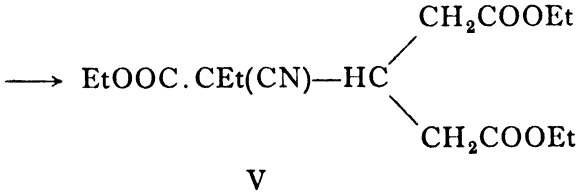
cephaeline dissolves; after the addition of ammonium chloride the cephaeline can be extracted with ether and crystallised. The ethereal solution containing the remainder of the alkaloids is concentrated and the residue is converted into the hydrochloride, hydrobromide or hydriodide; the emetine salt crystallises out and the remaining alkaloids are converted into the acid oxalates in ethanolic solution; the crystalline acid oxalates of O-methylpsychotrine and emetamine are deposited. These are separated (1 to 7) by fractional extraction from chloroform solution by dilute acid.

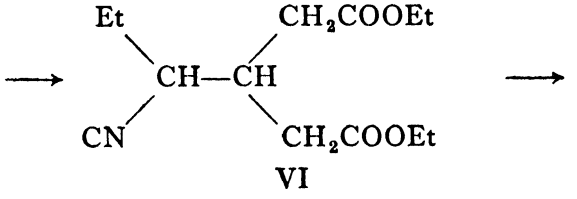
Emetine. $C_{29}H_{40}O_4N_2$. (XIII, R=Me). Emetine contains two *iso*quinoline rings; it is converted to O-methylpsychotrine on gentle oxidation but by boiling with ferric solution a red compound ***rubremetine*** is formed; in this reaction eight hydrogen atoms are lost, one nitrogen atom becomes non-basic and the other quaternary.

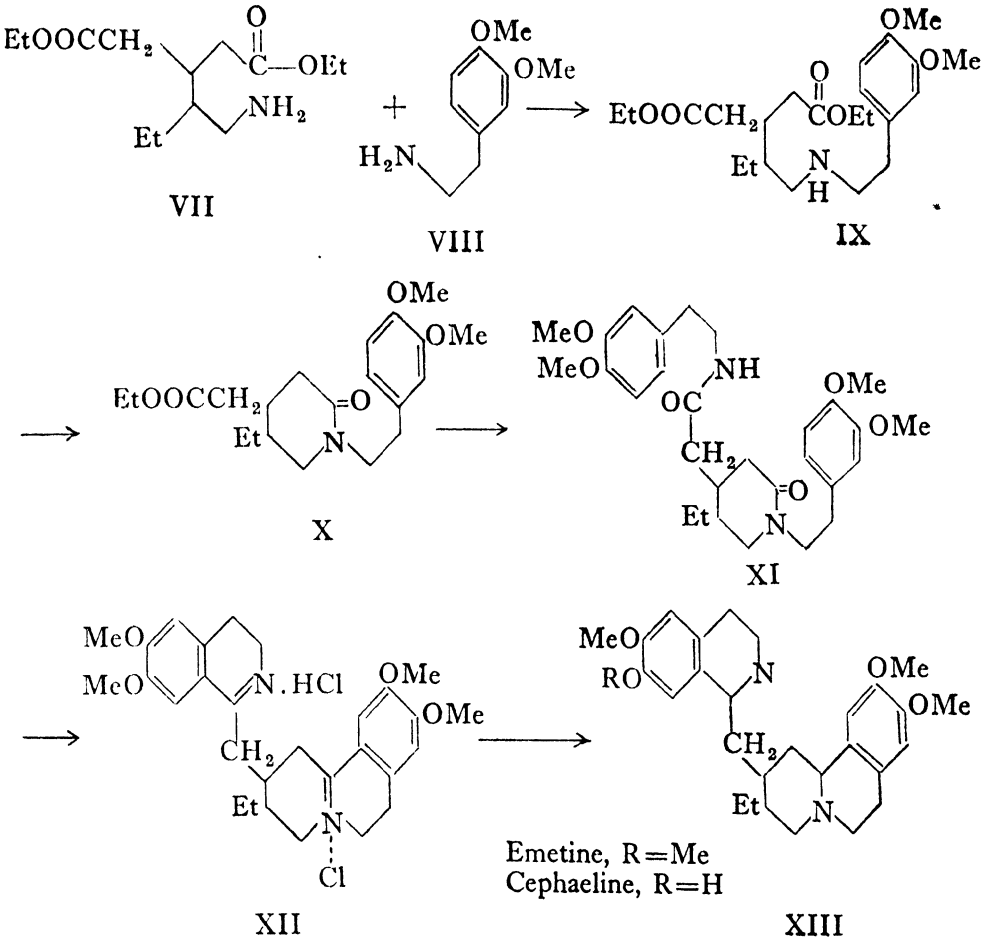
Synthesis. The structure of emetine was established by degradation in 1949 (8, 9) and has been confirmed by synthesis by Evstigneeva and his colleagues in Russia in 1952 (10). Emetine contains four asymmetric carbon atoms and is therefore one of sixteen possible optical isomers. The route followed for the preparation of the isomer that occurs in nature was as follows.











2-Oxoglutaric ester (I) was hydrogenated in the presence of Raney nickel and the hydroxy ester obtained was acetylated to give 2-acetoxyglutaric ester (II) which, when heated with potassium hydrogen sulphate, lost one molecule of acetic acid to yield glutaconic ester (III). Ethyl cyanoacetate reacted across the double bond and the compound IV produced was ethylated with ethyl iodide in the presence of sodium ethoxide to give the triester (V). One ester group was now hydrolysed and the acid formed was decarboxylated at 180° to give the key intermediate ethyl 2-(1-cyanopropyl)glutarate (VI). This was now reacted with homoveratrylamine in the presence of Raney nickel and hydrogen under pressure. The nitrile group may be assumed to have been reduced to the corresponding primary amine (VII) which then combined with one molecule of homoveratrylamine (VIII) with the loss of ammonia and the formation of a secondary amine (IX); the ring then closed with the elimination of ethanol to yield (X). A second molecule of veratrylamine now reacted, this time with the terminal ester group to give a mixture of isomeric amides (XI); this mixture was extracted with toluene and the insoluble isomer was treated with phosphorus oxychloride, by

which the enolic hydroxyl groups were chlorinated and elimination of hydrogen chloride led to ring closure and the formation of a quaternary chloride (XII). As a final step the unsaturation at the two nitrogen atoms was reduced with the formation of emetine (XIII) identical with the natural alkaloid.*

Properties. Crystalline emetine has been prepared by Foster and Norgrove (11). It melts at 104° to 105° and has $[\alpha]_D^{20} = -24{\cdot}4°$ (c=1·8 in 50 per cent ethanol). Commercial emetine is amorphous and has a lower melting-point. On exposure to air it slowly becomes yellow. It is a strong base and forms stable crystalline salts. It gives a green colour with Fröhde's reagent. The *hydrochloride*, $B.2HCl.7H_2O$, melts at 235° to 255° (dec.) and has $[\alpha]_D^{20}$ +11° to +21° (c=1 to 8 in water), but the hydrochloride prepared from crystalline emetine has $[\alpha]_D^{20} = 17{\cdot}7°$ (c=5 in water). The hydriodide is sparingly soluble in water and melts at 235° to 238°.

Emetine bismuth iodide is a double iodide of emetine and bismuth; it is prepared by adding a solution of bismuth carbonate in hydrochloric acid and potassium iodide to a solution of emetine hydrochloride. An orange-red precipitate is formed which is filtered and washed. It contains from 25 to 28 per cent of emetine and from 18 to 21 per cent of bismuth. It is used in the treatment of amoebic dysentery.

Cephaeline. $C_{28}H_{38}O_4N_2$. (XIII, R=H). This alkaloid is of importance because it may readily be converted into emetine by methylation, thus increasing the yield of the costly alkaloid emetine from ipecacuanha. Treatment with methyl sulphate forms emetine together with N-methylcephaeline and N-methylemetine. Cephaeline melts at 120° to 130° and the $[\alpha]_D$ is −43·4° (in chloroform).

* For another synthesis of emetine and a discussion of its stereochemistry see M. Barash and J. M. Osbond (*Chem. & Ind.* 1958, 490) and A. Brossi *et al.* (*ibid.*, 491).

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CHAPTER VIII

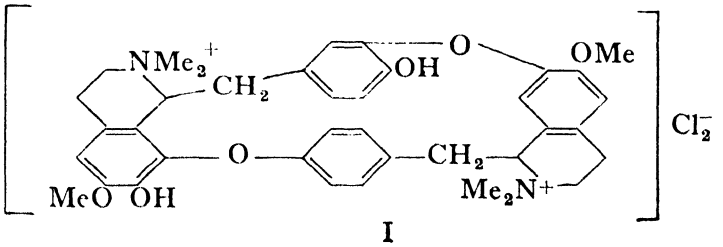
Curare Alkaloids

CURARE is an extract prepared from various plants by the Indians of South America and used by them as an arrow poison. The characteristic physiological action of curare is the loss of the normal motor-nerve control of the voluntary muscles. The botanical source of curare was for long a mystery, partly because the ingredients vary in different regions and because many innocuous plants are added. Humboldt believed that the toxic constituents were members of the genus *Strychnos*, especially *S. toxifera*. While members of this genus are undoubtedly used, present-day knowledge makes it certain that the most valuable ingredients are species of *Chondrodendron* particularly *Ch. tomentosum*, which is the main source of the valuable alkaloid (+)-tubocurarine. This alkaloid is the most effective in producing the characteristic curarising action on the muscles without other undesirable pharmacological effects, though other alkaloids of curare are more potent.

Formerly, three varieties of curare were recognised in commerce, named from the type of container in which they appeared, bamboo—or tube-curare, calabash curare and pot-curare. Though this distinction no longer holds, most curare being filled into tins, the constituents of these varieties are different and most of the published work refers to one or other variety.

It has been known for many years that curare contains two chief types of physiologically active alkaloids; those of the first type are quaternary bases known as 'curarines', and produce the typical muscle paralysis; those of the second type are tertiary bases known as 'curines' and have a direct effect on the blood pressure.

In so far as the constitution of curare alkaloids has been elucidated, many of them have a bisbenzyl*iso*quinoline structure and have been classified by H. King (1) into two types—the bebeerine type (I) and the *iso*chondrodendrine type (II). The alkaloids (+)-tubocurarine, (+)- and (−)-bebeerine [(−)-curine] and (−)-chondrofoline belong to the bebeerine group, (+)-protocuridine, neoprotocuridine and (+)-*iso*chondrodendrine to the *iso*chondrodendrine type.



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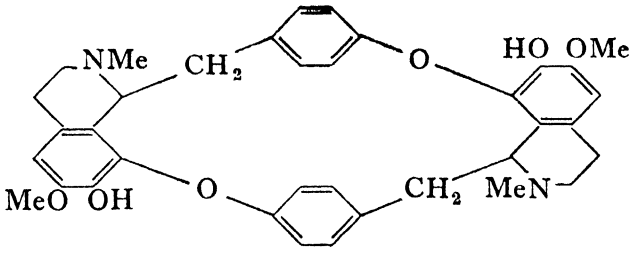

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Other alkaloids occurring in curare are the toxiferins and curarines isolated from calabash-curare. Alkaloids closely related to tubocurarine have been isolated by King and others from various species of *Chondrodendron.*

Tubocurarine. (+)-Tubocurarine commonly occurs in *Ch. tomentosum*, but H. King (2) has reported on a specimen of this species from Northern Peru which contained (−)-tubocurarine. The constitution of tubocurarine has been elucidated by H. King (3) and confirmed by J. D. Dutcher (4). When (+)-tubocurarine is methylated, (+)-tubocurarine dimethyl ether is formed in which the two OH groups are methylated.

The salt used in medicine is (+)-tubocurarine chloride, (I), $C_{38}H_{44}O_6N_2Cl_2.5H_2O$. M.p. 274° to 275° with effervescence. $[\alpha]_D^{20}$ (c=1·2 in water) +210° to +220° calculated to the anhydrous salt.

(+)-Tubocurarine may be extracted from curare by the following process described by H. King (5). The total alkaloids are extracted from the drug by means of dilute tartaric acid. The tertiary alkaloids are removed by treatment with sodium bicarbonate and extraction with organic solvents. The quaternary bases are precipitated first as phosphotungstates and then as their mercuric chloride double compounds. The latter are suspended in water and decomposed by hydrogen sulphide. Mercuric sulphide is precipitated and the aqueous solution after evaporation to small bulk deposits crystals of (+)-tubocurarine chloride (6).

(+)-Tubocurarine chloride gives a blue colour with the Folin-Ciocalteu phenol reagent. (+)-Tubocurarine dimethyl ether is more potent in curarising action than (+)-tubocurarine.

For a review of the chemistry of the curare alkaloids see Karrer (7).

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CHAPTER IX

Coca Alkaloids

THE coca leaves of commerce are obtained from species of *Erythroxylon*—viz. *E. coca*, and *E. truxillense*. These were originally all derived from South America, but are now grown in Java and Ceylon. Peruvian coca leaves contain a large proportion of cocaine, and are derived from *E. truxillense*. Java leaves contain chiefly cinnamyl cocaine and little cocaine. The percentage of total alkaloids in coca leaves varies from 0·6 to 2·0 per cent or more, according to the source. The following alkaloids have been found in coca leaves.

Cocaine, $C_{17}H_{21}O_4N$.
Cinnamyl cocaine, $C_{19}H_{23}O_4N$.
α-Truxilline, $C_{38}H_{46}O_8N_2$. γ-Isatropyl cocaine.
β-Truxilline, $C_{38}H_{46}O_8N_2$. δ-Isatropyl cocaine.
Benzoyl ecgonine, $C_9H_{14}(CO.C_6H_5)O_3N$.

These constitute the cocaine group, and are all derivatives of ecgonine.

Tropacocaine, $C_{15}H_{19}O_2N$. Benzoyl-ψ-tropeine.

This alkaloid, being a derivative of ψ-tropine, is more readily related to the atropine group.

Hygrine, $C_8H_{15}ON$.
β-Hygrine, $C_{14}H_{24}ON_2$.
Cuscohygrine, $C_{13}H_{24}ON_2$.

The last three form a group quite distinct from the other alkaloids. They have no physiological action.

Cocaine. $C_{17}H_{21}O_4N$.

Manufacture. Cocaine is chiefly prepared from Java coca leaves, but some crude alkaloid is made in South America from Peruvian leaves and exported for further purification (1, 2). Bignon's method for the manufacture of cocaine is as follows: the powdered leaves are thoroughly digested with lime or sodium carbonate and a little water, and then thoroughly extracted with light petroleum. The alkaloids pass into the solvent, from which they are removed by shaking with dilute hydrochloric acid, avoiding excess. The acid solution is then evaporated, and a strong solution of the crude alkaloidal hydrochlorides is obtained. If the coca leaves used are rich in cocaine, as is the case with the Peruvian leaves, the larger portion of the cocaine may be crystallised out at this point in a crude condition and purified by recrystallisation. The mother liquor may then be treated by the same process as for Java leaves. Since Java leaves

contain little cocaine, the mixed hydrochlorides consist chiefly of cinnamyl cocaine. This mixture is, therefore, hydrolysed to ecgonine by boiling for an hour with dilute hydrochloric acid. On pouring into water truxillic acid is thrown down. The liquid is filtered and evaporated. Ecgonine hydrochloride crystallises out, and is washed with alcohol. The ecgonine is set free by adding sodium carbonate and extracting with dilute alcohol. The solvent is evaporated off, and the ecgonine is then benzoylated by digesting with benzoic anhydride for one hour. The excess of benzoic anhydride and benzoic acid is removed by extraction with ether.

$$\underset{\text{Cinnamyl cocaine}}{C_9H_{13}O_3N(CH_3).C_9H_7O} \xrightarrow{HCl} \underset{\text{Ecgonine}}{C_9H_{15}O_3N} + \underset{\text{Cinnamic acid}}{C_9H_8O_2} + CH_3OH$$

$$\underset{\text{Ecgonine}}{C_9H_{15}O_3N} + (C_6H_5CO)_2O \longrightarrow \underset{\text{Benzoylecgonine}}{C_9H_{14}O_3N.COC_6H_5} + C_6H_5COOH$$

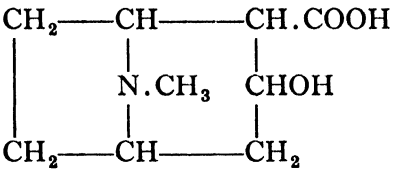
The residue consists of benzoyl ecgonine containing some ecgonine. The latter is removed by washing with water. The benzoyl ecgonine is now methylated by treatment with methyl iodide and sodium in methyl alcohol. Cocaine is obtained in quantitative yield:

$$\underset{\text{Benzoylecgonine}}{C_9H_{14}O_3N.CO.C_6H_5} + CH_3I \longrightarrow \underset{\text{Cocaine}}{C_9H_{13}O_3N(CH_3).COC_6H_5} + HI$$

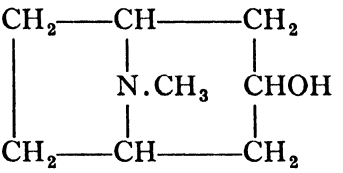
The cocaine thus obtained is purified by recrystallisation of the hydrochloride (3).

The crude cocaine obtained from Peruvian coca leaves in South America is obtained by extracting the leaves with dilute sulphuric acid, making alkaline with sodium carbonate, and extracting the alkaloid with petroleum. The alkaloid is again removed from the petroleum by thorough shaking with dilute sulphuric acid, and the crude base is reprecipitated by sodium carbonate. In all methods for the separation of cocaine prolonged contact with acid or alkali must be avoided owing to the ease with which it undergoes hydrolysis.

Constitution. Cocaine is readily hydrolysed with the formation of ecgonine, benzoic acid and methyl alcohol. It is, therefore, considered to be the benzoyl derivative of the methyl ester of ecgonine. Ecgonine, $C_9H_{15}O_3N.H_2O$, melts at 205° (when anhydrous). Ecgonine readily reacts with acid chlorides or acid anhydrides to form acyl derivatives. It is also readily esterified. These facts point to the presence of a carboxyl and a hydroxyl group in ecgonine. A molecule of water is easily removed from ecgonine to form anhydroecgonine, $C_9H_{13}O_2N$, which still contains the carboxyl group. When anhydroecgonine is heated with hydrochloric acid at 280°, tropidine is formed (see Atropine). Evidently, therefore, ecgonine is a carboxylic acid of hydroxytropidine. When ecgonine is oxidised with chromic acid tropinone, $C_8H_{13}ON$, tropinic acid, $C_8H_{13}O_4N$, and ecgoninic acid, $C_7H_{11}O_3N$, are formed. With permanganate *nor*ecgonine, $C_8H_{13}O_3N$, is formed. Ecgonine is represented by formula I. The relationship to tropine (II) is evident.

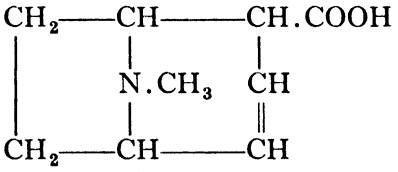


I

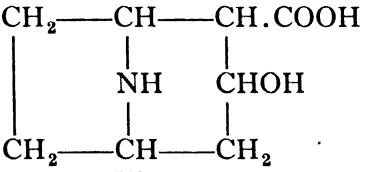


II

Anhydroecgonine (III) and *nor*ecgonine (IV) are, therefore, constituted as follows:

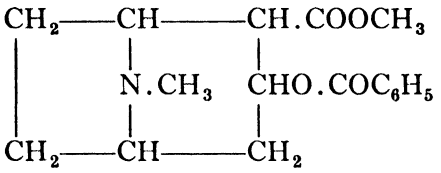


III

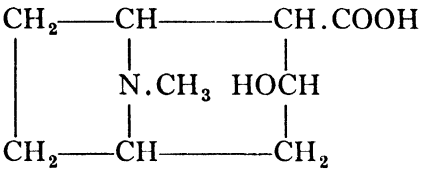


IV

Cocaine has the constitution V:

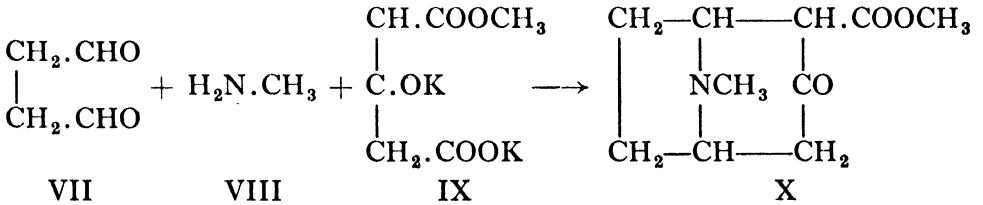


V

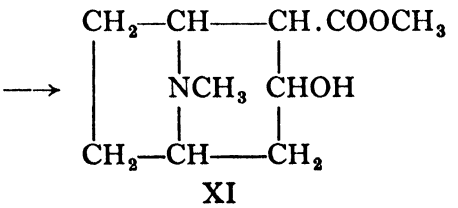


VI

Since ecgonine contains four asymmetric carbon atoms, a number of optically active stereoisomeric forms are possible. The latter may be divided into two groups, according as the hydroxyl and carboxyl groups are on the same side of the molecular nucleus (the *cis* forms) as in formula I, or on opposite sides (the *trans* forms) as in formula VI. The *cis* forms and their derivatives have been distinguished by the Greek letter ψ. Two forms of cocaine have been found in coca leaves—viz., (−)-cocaine, a derivative of the *cis* form of ecgonine, and a (+)-cocaine. Both of these forms have been synthesised (4). Methyl potassium acetone dicarboxylate (IX) is condensed with methylamine (VIII) and succindialdehyde (VII), forming the methyl ester of tropinone carboxylic acid (X):



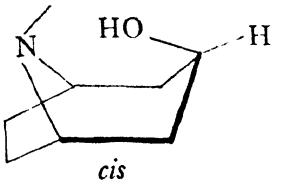
VII VIII IX X



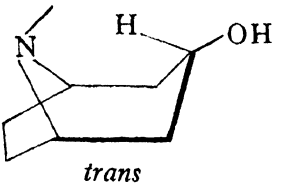
XI

By reduction a mixture of ecgonine esters (XI) is obtained. From this mixture a (±)-ecgonine ester is separated, which, on benzoylation, gives a (±)-cocaine, which may be resolved into two optically active constituents, one of which is the naturally occurring (+)-cocaine. From the residual ecgonine esters a racemic cocaine is separated which, by fractional crystallisation of the bitartrates, gives (−)-cocaine identical with the naturally occurring alkaloid. The recent work on the production of succindialdehyde (see atropine, p. 241) would therefore make the commercial synthesis of cocaine a possibility, if it were desirable.

All natural alkaloids derived from tropine have the *trans* configuration and those related to ψ-tropine the *cis* configuration (5).



cis



trans

Cocaine is therefore (−)-3α-benzoyloxy-2α-carbomethoxytropane and ψ-cocaine is the 2α : 3β-epimer. Substituents are denoted by β or α according to whether they are on the same side or on the opposite side respectively of the general plane of the ring as the >NR bridge.

Cocaine crystallises in colourless monoclinic prisms. It melts at 98°. $[\alpha]_D$ −15·8°. Cocaine is strongly alkaline, and may be titrated with acid. A solution of cocaine, when applied to the tongue, causes a numbness which lasts for a few minutes. When applied to the eye it causes mydriasis, but it is not so intense as that produced by atropine and the related alkaloids. Cocaine gives no characteristic colour reactions. When Vitali's test is applied to cocaine (evaporation with strong nitric acid followed by the addition of alcoholic potassium hydroxide), no colour is produced, but an odour variously described as resembling citronella or peppermint is given off. When cocaine hydrochloride is warmed with alcoholic potash, an odour of ethyl benzoate is observed. Cocaine forms characteristic crystals of cocaine permanganate when treated with potassium permanganate. The permanganate is not reduced, as is the case with cinnamyl cocaine and other impurities. Cocaine forms an aurichloride, which is thrown down as a crystalline precipitate from dilute solutions. Under the microscope, the crystals appear as delicate feathery rosettes. Platinic chloride also forms crystals in dilutions up to 1 : 4,000.

Cocaine hydrochloride. $C_{17}H_{21}O_4N.HCl$. This is the most commonly used salt of cocaine. When pure, cocaine hydrochloride melts at 191°. When 0·1 g of cocaine hydrochloride is dissolved in 85 ml of water and 0·2 ml of 10 per cent ammonia solution are added, on rubbing the sides of the vessel with a glass rod a crystalline precipitate of cocaine is thrown down, leaving the supernatant liquid clear. If the solution becomes milky, the presence of amorphous alkaloids is indicated.

The nitrate and sulphate of cocaine are also used in medicine.

Cocaine was formerly a most valuable local anaesthetic but has now been

almost entirely displaced by synthetic compounds. Owing to its action on the central nervous system cocaine is a habit-forming drug, and numerous synthetic compounds have been prepared, with the intention of preserving the local anaesthetic effect and eliminating the other undesirable actions (see Part I, Chapter IV). The action of cocaine has been shown to be essentially dependent on the fact that it is an aminoalkyl ester. If the $-COOCH_3$ group is removed we have tropacocaine which is still active. Benzoylecgonine, however, is inactive. It appears that the bridged nitrogen ring is not necessary to the activity of cocaine, nor is even the presence of a simple ring an essential. Norcocaine, in which the methyl group attached to the nitrogen atom is replaced by hydrogen, is even more active than cocaine. It has been found that (±)-ψ-cocaine is a more powerful anaesthetic than (±)-cocaine. The (+)- forms are more active and less toxic than the (−)- forms, and the ψ- forms are less toxic than the ordinary forms.

Tropacocaine, $C_{15}H_{19}O_2N$, found by Giesel in 1891 in coca leaves is benzoyl-ψ-tropeine. Tropacocaine melts at 49°, is very slightly soluble in water, but soluble in alcohol and ether. It is optically inactive. Tropacocaine hydrochloride forms white needles or rhombic crystals, easily soluble in water, melting at 271°. The aurichloride melts at 208°.

In the fact that it is a ψ-tropine, and not an ecgonine derivative, tropacocaine forms a link between the coca alkaloids and the solanaceous alkaloids, since ψ-tropine may be converted into tropine with which it is isomeric. The action of tropacocaine is similar to that of cocaine, and it has been used in medicine to some extent.

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CHAPTER X

Colchicum Alkaloids

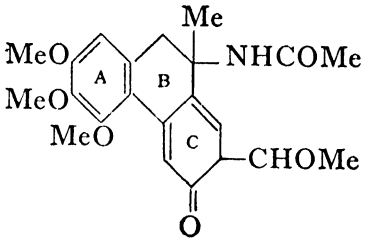
THE seeds and corms of *Colchicum autumnale* contain about 0·3 per cent of the alkaloid *colchicine*. Colchiceine, which has been stated to occur in colchicine, is probably formed in the process of extraction; it is easily formed by heating colchicine with dilute sulphuric acid.

Colchicine, $C_{22}H_{25}O_6N$, (IIa). This alkaloid is prepared from colchicum seeds by exhausting with ethanol; the extract is evaporated and diluted with water; fat and resinous matter are thrown out and, after filtration, the solution is extracted with chloroform. The chloroform solution is evaporated until a syrupy residue remains. While warm, small amounts of ethanol are added until the whitish masses, which at first separate, redissolve. The liquid is then kept at 0° until crystals of the chloroform compound of colchicine separate; these are suspended in a small quantity of water and the chloroform removed by steam. The water is evaporated *in vacuo*, leaving a residue of colchicine in the form of a yellow varnish which softens at 142° and melts at 147°. It has been prepared by Clewer, Green and Tutin (1) by crystallisation from ethyl acetate as pale yellow needles melting at 155° to 157°; $[\alpha]_D^{16\cdot5}$ −120·6° (0·88 per cent in chloroform) or −429° (in water). Colchicine can also be crystallised from water as a trihydrate. It may also be purified by chromatography (2).

Colchicine is a very feeble base and can be extracted from an acid solution by chloroform; it forms no crystalline salts with the common acids, but the aurichloride may be obtained crystalline with some difficulty; it melts at 209°. Colchicine dissolves in sulphuric acid to a yellow solution, which, on adding a drop of nitric acid becomes green, violet and finally red. Colchiceine gives an intense green colour with ferric chloride solution which is not shown by colchicine.

Structure. When colchicine is warmed with dilute sulphuric acid colchiceine and methanol are formed. More vigorous treatment with hydrochloric acid gives methanol, acetic acid and trimethylcolchicinic acid; colchiceine is therefore acetyltrimethylcolchicinic acid. The further action of hydrochloric acid is the production of three molecules of methyl chloride and colchicinic acid. Fusion with potassium hydroxide followed by oxidation with permanganate gives terephthalic and benzene-1 : 2 : 3-tricarboxylic acid; direct oxidation with alkaline permanganate yields 3 : 4 : 5-trimethoxy-*o*-phthalic acid.

For many years the structure of colchicine (I) proposed by Windaus (3) appeared to be the most satisfactory explanation of its properties though it had several unsatisfactory features as pointed out by Cook and his colleagues (4, 5, 6). On the basis of this work Cook (7) suggested that ring B of colchicine is seven-membered and Dewar (8) proposed the structure (II) in which ring C is also seven-membered. This suggestion was strongly supported by Arnstein and his



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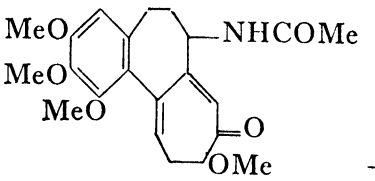
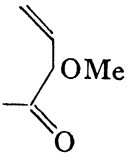
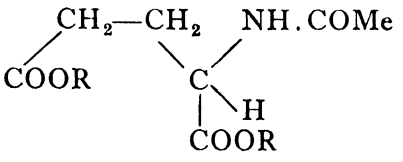


II



IIa



III

colleagues (9) and infra-red studies by Scott and Tarbell (10) and by Kemp and Tarbell (11) were also in its favour. Horowitz *et al.* (12) have produced further evidence in favour of the seven-membered B ring so that the nature of both the B and C rings seems to be firmly established. The evidence for the relative positions of the carbonyl and methoxy groups in the C ring adduced by King, de Vries and Pepinsky (13) was in favour of Dewar's formula (II) but Muller and Velluz have produced evidence for a reversal of this arrangement (IIa) (14) so that (II) becomes *iso*colchicine. Corrodi and Hardegger (15) by successive ozonolysis and oxidation of colchicine have obtained N-acetyl-L-glutamic acid (III) which is a further confirmation of Muller and Velluz's formula (IIa).

The complete synthesis of colchicine has not yet been accomplished (January 1958) though some approaches have been explored, notably in the preparation of compounds embodying the B-ring structure (16, 17).

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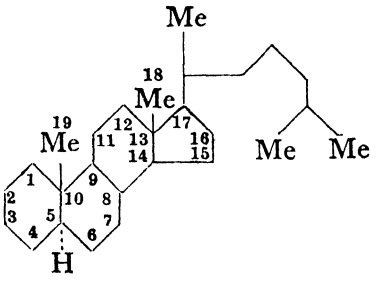
CHAPTER XI

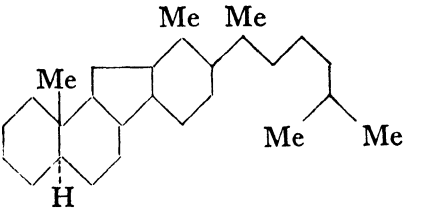
Steroidal Alkaloids

SEVERAL groups of alkaloids are now recognised as possessing the characteristic steroidal carbon skeleton. These may be divided into three groups, (a) solanum alkaloids from the potato (*S. tuberosum*), the tomato (*S. lycopersicum*) and other species; (b) veratrum alkaloids from *V. album* (white hellebore) and *V. viride* (green hellebore) and from sabadilla (*Asagraea officinalis*); (c) kurchi or holarrhena alkaloids from *Holarrhena antidysenterica* and other species of *Holarrhena.*

The carbon skeleton is either that of cholestane (I) or the modified cholestane skeleton (II).



I

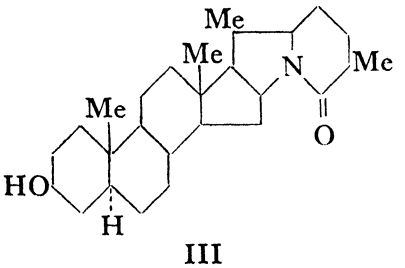


II

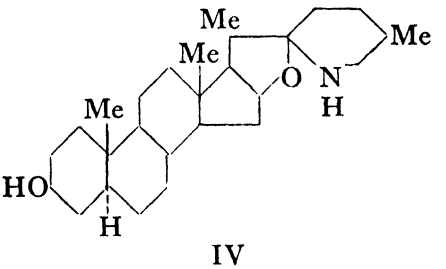
Many veratrum and solanum alkaloids contain the 3β-hydroxy group and the 5 : 6- double bond and are precipitated by digitonin.

Solanum alkaloids. The most important of these alkaloids, which are contained in the potato plant, is *solanine*, $C_{45}H_{73}O_{15}N$, which is a glycoalkaloid formed from *solanidine*, $C_{27}H_{43}ON$, and a glucosylgalactosyl rhamnose. Solanine is not hydrolysed by alkalis but acids convert it to solanidine and sugars. The formula III for solanidine was proposed by Prelog and Szpilfogel (1) and has been generally accepted.

Tomatidine, $C_{27}H_{45}O_2N$, is combined in tomato plants as tomatine with glucose (2 molecules), xylose (1 molecule) and galactose (1 molecule). It has the structure IV, (2).



III



IV

These alkaloids have not been used in medicine to any extent, though tomatidine has a hypertensive action, but the veratrum alkaloids have been widely used in the treatment of hypertension.

Veratrum alkaloids. These alkaloids are obtained from *Veratrum album* L. and *V. viride* Ait. The hypotensive activity of this group of alkaloids has long been recognised, but the therapeutic applications have been limited by the frequency of disturbing side-effects and inconsistent action, but the development of new methods of extraction and isolation has aroused a new interest.

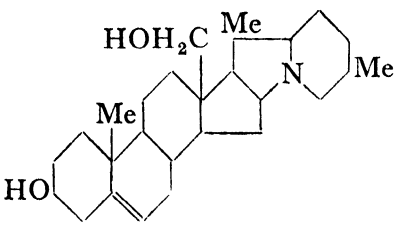
The active principles of these alkaloids have been shown to be esters of polyhydroxylated alkamines and hypotensive potency is closely associated with the presence of ester groups. In general, maximum activity is found in alkaloids containing three acyl groups, although diesters and tetraesters are also very active (3, 4). The esterifying acids are most commonly veratric, acetic, angelic, tiglic, methylethylacetic, methylethylglycollic and $\alpha\beta$-dihydroxy-α-methylbutyric acids. The esterified polyhydroxylated amines include cevine, germine and protoverine. The first occurs in sabadilla seeds (*q.v.*), but esters of germine and protoverine predominate in *V. viride* and *V. album* respectively. The tertiary bases rubijervine and *iso*rubijervine are devoid of hypotensive activity, as also are the secondary bases jervine and veratramine.

The presence of labile ester groups in the hypotensive veratrine alkaloids necessitates the use of extraction procedures which minimise loss of potency through hydrolysis. Such methods for the preparation of concentrates of alkaloidal esters from commercial *V. viride* and *V. album* based on the work of Jacobs and Craig are described in the literature (5, 6, 7).

Concentrates of the alkaloidal esters from *V. viride* have been resolved by Craig counter-current distribution into esters of both germine and protoverine. Various workers (8) have reported the isolation of the following ester alkaloids: germbudine, *iso*germidine, germerine, germidine, germitrine, *neo*germitrine, *neo*protoveratrine, veratetrine and protoveratrine. The last is probably the dominant hypotensive alkaloid in this drug and structural investigations have indicated that it is an ester of protoverine with acetic, α-methylbutyric and methylethylglycollic acids. In *V. album* the chief ester alkaloids are protoveratridine, germerine and protoveratrine.

Rubijervine and ***iso*rubijervine**, $C_{27}H_{43}O_2N$, are isomeric tertiary bases but are not interconvertible epimers. The structure of *iso*rubijervine has been established as V; rubijervine probably has the structure VI. Structure V has been confirmed by converting *iso*rubijervine to solanidine.

Jervine, $C_{27}H_{39}O_3N$, has the structure VII.



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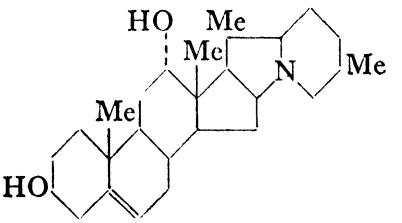

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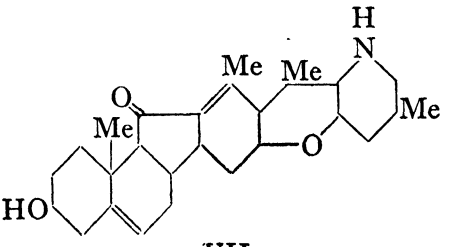
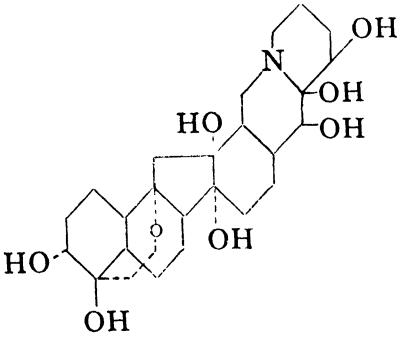


VII

Some progress has been made in the elucidation of the structure of the esterified alkaloids that possess hypotensive activity (9). *Cevine*, for example, which is esterified with angelic and tiglic acids in *cevadine*, has the structure VIII (10).



VIII

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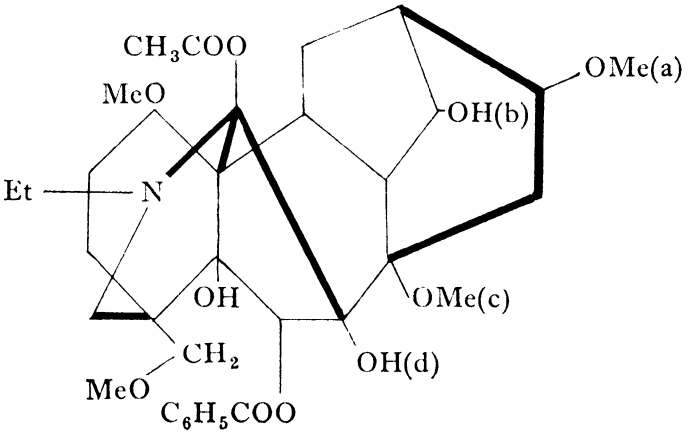
CHAPTER XII

Miscellaneous Alkaloids

Aconite alkaloids. Numerous species of *Aconitum* contain a series of toxic alkaloids known as *aconitines* which are closely related in chemical constitution but vary from species to species; a second series known as *atisines* are only slightly toxic; they are not used in medicine. The aconitines are diacyl esters of a series of polyhydric amino alcohols known as *aconines*. The constitution of aconitine has not yet been definitely established, but the structure I has been attributed to aconitine, in which the relative positions of the hydroxy and methoxy groups in positions (a), (b), (c) and (d) is uncertain (1).



I

The two most important alkaloids are *aconitine* derived from *Aconitum napellus* Linn., the common monkshood, and *japaconitine* from Japanese aconite, *A. uncinatum* Linn. var. *japonicum* Regel. It is not certain whether japaconitine is identical with aconitine, but, if not, they are certainly isomeric.

The presence of an alkaloid in aconite was reported by Geiger and Hesse (2) and aconitine was first obtained in crystalline form by Groves (3). Aconite contains about 0·5 per cent of total alkaloids of which about half is aconitine.

Aconitine, $C_{34}H_{47}O_{11}N$, occurs in many species of *Aconitum* but the source of the alkaloid is *A. napellus*. It is now little used in medicine but preparations of aconite are sometimes used in the form of liniments as anodynes.

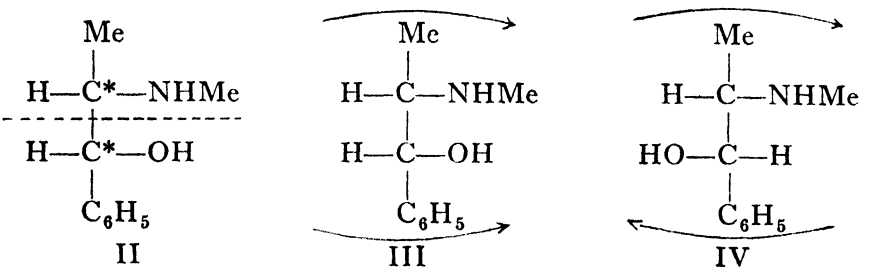
Aconitine melts at 202° to 203° and has $[\alpha]_D$ +14·6° or, according to Majima, +18·7°. The salt generally used is the hydrobromide, B.HBr.$2\frac{1}{2}H_2O$ [m.p. (anhydrous) 206° to 207°], $[\alpha]_D$ −30·8°. The aurichloride, B.HCl.$AuCl_3$.$3H_2O$

melts at 136·5° or, after drying, at 152°. The perchlorate melts at 215° to 222°. Aconitine produces a tingling sensation on the tongue in high dilution (1 in 10,000). The most characteristic test is that with potassium permanganate (4) with which in dilute acetic acid solution aconitine gives a crystalline precipitate consisting of rosettes of red prismatic crystals.

Aconitine contains four methoxyl and three hydroxyl groups. Hydrolysis yields, firstly, benzoylaconine and acetic acid, then aconine, benzoic and acetic acids. Oxidation with potassium permanganate yields acetaldehyde and oxonitine (5).

Preparation. Aconite root is thoroughly exhausted with a mixture of crude methanol and amyl alcohol (3 : 1 by volume); the methanol is distilled off and the alkaloids are extracted from the residual amyl alcohol with dilute sulphuric acid (1 per cent). The acid liquid is extracted with ether, made alkaline and again extracted with ether; this extract contains aconitine and benzaconine leaving aconine in the aqueous solution. After removal of the ether the aconitine is carefully neutralised with hydrobromic acid and crystallised as the hydrobromide. After dissolving the hydrobromide in water and making alkaline with ammonia the aconitine may be extracted with ether from which it may be crystallised.

Ephedra alkaloids. Several species of *Ephedra* contain the alkaloids (−)-ephedrine and (+)-ψ-ephedrine accompanied by smaller amounts of related alkaloids such as (−)-N-methylephedrine, *nor*-(+)-ψ-ephedrine, (+)-N-methyl-ψ-ephedrine and (−)-*nor*ephedrine. The ephedrine of commerce is mainly prepared synthetically. Ephedrine may be separated from ψ-ephedrine by extracting the mixed hydrochlorides with chloroform in which the former is almost insoluble but the latter dissolves readily (6). On boiling with 25 per cent hydrochloric acid ephedrine is partially converted to ψ-ephedrine, an equilibrium mixture of the two compounds being formed. Ephedrine and ψ-ephedrine are isomeric but they do not possess equivalent optical rotations in opposite directions and are therefore not optical antimers. The structure of ephedrine may be represented by (II) showing two asymmetric carbon atoms (*) and two unequal halves of the molecule. In (−)-ephedrine (III) the rotation of the two halves is in opposite directions, but in (+)-ψ-ephedrine (IV) the rotation of the two halves is in the same direction. Thus (+)-ψ-ephedrine is more dextrorotatory than (−)-ephedrine is laevorotatory.

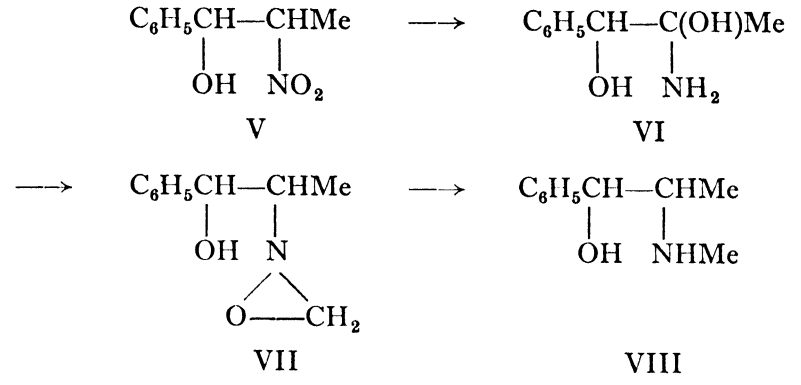


Both ephedrine and ψ-ephedrine yield methylamine and benzaldehyde with dilute potassium permanganate, both give a nitroso compound and on deamina-

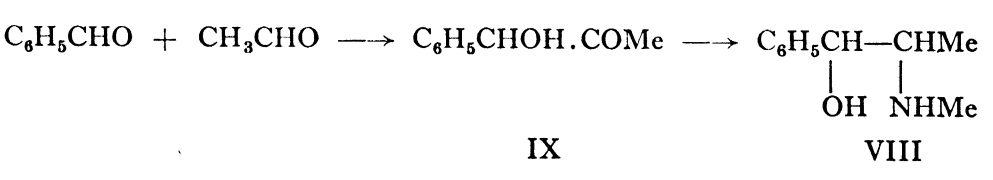
tion yield a nitrogen-free compound with the formula $C_9H_{10}O$ showing that both are secondary bases containing a methylamino group.

Ephedrine. 1-Phenyl-2-methylaminopropan-1-ol. $C_{10}H_{15}ON$. (VIII).

Synthesis. Many syntheses of ephedrine have been published (8 to 14). For example Nagai and Kanao (12) condensed benzaldehyde with nitroethane to yield 2-nitro-1-phenylpropanol (V) which, by reduction gave 2-hydroxylamino-1-phenylpropanol (VI). Treatment with formaldehyde formed a methylene-nitrone (VII) which reduced to (±)-ephedrine (VIII). This was resolved into the isomerides by crystallisation of the (+)-tartrate and the (−)-tartrate in succession, the (−)-alkaloid being identical with natural ψ-ephedrine. The mandelic acid isomers have also been used as resolving agents (10).



(−)-Ephedrine may be synthesised without the formation of the racemic compound by a method based on the discovery that (−)-phenylacetylcarbinol (IX) can be produced by the fermentation of glucose with a special yeast (13). IX can be condensed either simultaneously or subsequently with hydrogen under pressure in the presence of colloidal platinum and methylamine to give (−)-ephedrine (VIII).



This is the basis of the commercial production of ephedrine.

Properties. Ephedrine, $(C_{10}H_{15}ON)_2.H_2O$, melts at 40° to 41° when not previously dried; the anhydrous alkaloid melts at 33° to 37·5°. Ephedrine boils at 225°. The hydrated form occurs as colourless hexagonal crystals; when anhydrous it is a very deliquescent solid. Ephedrine (hydrated) is soluble in water, ethanol, ether, glycerol and fatty oils; it dissolves in chloroform or liquid paraffin with separation of water whereas the anydrous form gives a clear solution. When a chloroform solution is evaporated on a water-bath a reaction takes place which results in a conversion of the alkaloid to the hydrochloride with

decomposition of the chloroform. (—)-Ephedrine oxalate is very sparingly soluble in water in contrast to (+)-ψ-ephedrine oxalate which is soluble. Both (—)-ephedrine and (+)-ψ-ephedrine give a purple colour when 1 ml of a solution of the alkaloid is treated with 0·1 ml of a 10 per cent copper sulphate solution followed by 2 ml of 20 per cent sodium hydroxide solution (biuret test); on shaking with ether the ether layer is coloured purple and the aqueous layer is blue. The $[\alpha]_D^{20}$ of ephedrine is −6·3° (in ethanol) and +11·2° (in water.

Ephedrine is volatile in steam and may be separated from most other alkaloids and from its preparations by this property (7). (+)-ψ-Ephedrine melts at 117° to 118°.

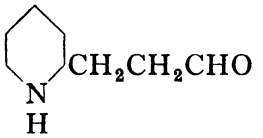
Ephedrine hydrochloride, $C_{10}H_{15}ON.HCl$, forms colourless needles melting at 217° to 219°; $[\alpha]_D^{20}$ −33° to −35·5° (c=5 in water); it is soluble in water or ethanol.

Ephedrine sulphate, $(C_{10}H_{15}ON)_2.H_2SO_4$, forms hexagonal plates melting at 235° to 236°; $[\alpha]_D^{20}$ −30°; it is soluble in water but sparingly soluble in ethanol.

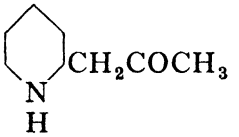
The pharmacological action of ephedrine is very similar to that of adrenaline, but the pressor and vasoconstrictor activity is slower and more persistent. In contrast to adrenaline it can be administered orally.

Pomegranate alkaloids. The alkaloids of the root bark of the pomegranate tree (*Punica granatum* L.) are used in the form of their mixed sulphates or tannates (known as 'pelletierine' sulphate or tannate) in the treatment of tapeworm. At least four alkaloids have been isolated viz. *pelletierine*, *methylpelletierine*, pseudo*pelletierine* and *methyl*iso*pelletierine*. Some doubt exists as to the identity of these alkaloids since the alkaloid formerly known as *iso*pelletierine has been shown to be identical with pelletierine (15). Pelletierine, *pseudo*pelletierine and methyl*iso*pelletierine have been identified as constituents of 'pelletierine sulphate' by paper chromatography (16).

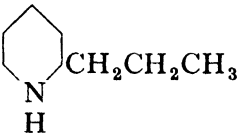
Constitution. Pelletierine was for many years regarded as 2-piperidinepropionaldehyde (X) (17), but the synthesis of this compound (18) has shown that it is not identical with pelletierine. Probably it has the structure (XI) formerly assigned to *iso*pelletierine.



X

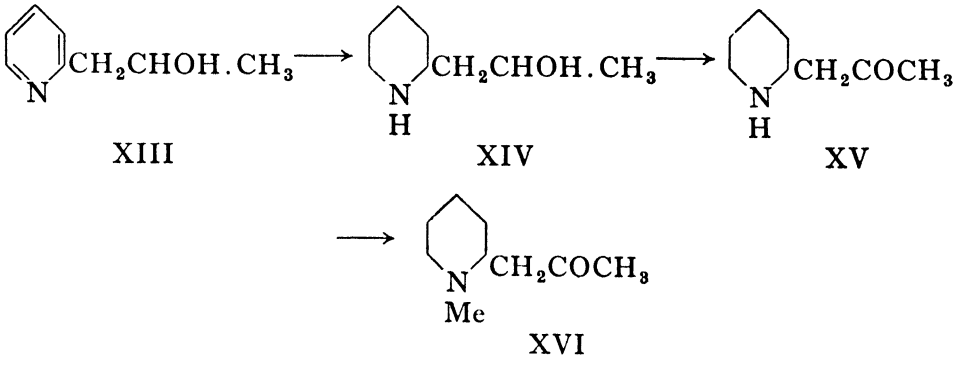


XI



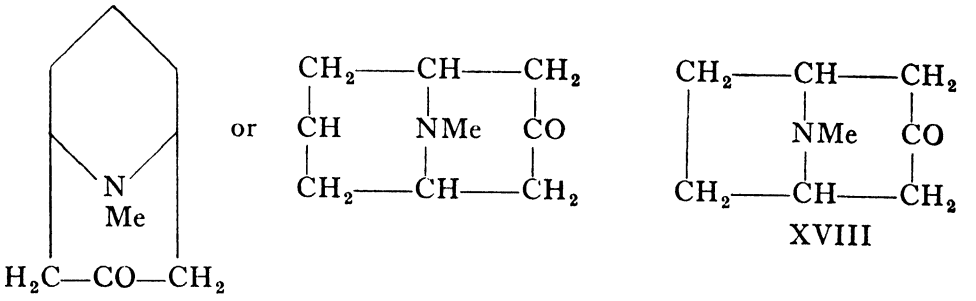
XII

Reduction of pelletierine with sodium in ethanol at 156° to 170° gives (±)-coniine (XII). Compound XI has been synthesised (19). 2-β-Hydroxy-*n*-propylpyridine (XIII) was hydrogenated to 2-β-hydroxy-*n*-propylpiperidine (XIV) which, on oxidation with chromic anhydride, gave XV; this compound, when methylated with formaldehyde yielded the N-methyl derivative of XI identical with the alkaloid known as methyl*iso*pelletierine (XVI).



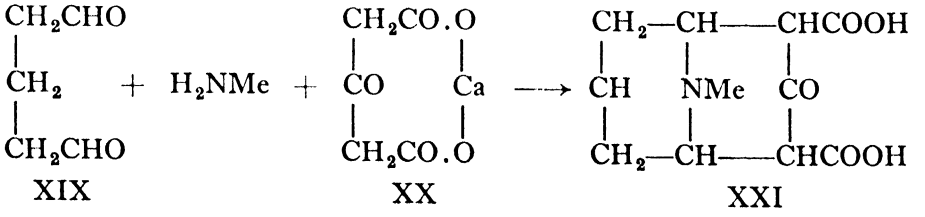
XIII XIV XV XVI

In *pseudo*pelletierine (XVII) the side-chain in the 2-position is joined to the 6-position forming a second ring. The relationship to tropinone (XVIII) is clear.



XVII XVIII

A synthesis of *pseudo*pelletierine by Menzies and Robinson (20) is interesting in that it could occur in plants under natural conditions. Glutardialdehyde (XIX), calcium acetonedicarboxylate (XX), and methylamine react in aqueous solution to form XXI which, on decarboxylation, gives *pseudo*pelletierine (XVII).



XIX XX XXI

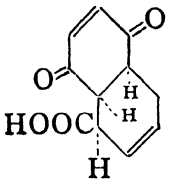
Properties.

Pelletierine. $C_8H_{15}ON$. The alkaloid is a colourless oily liquid (b.p. 106° at 21 mm.) that darkens on exposure to air. It is soluble in water, ether or chloroform. It is optically inactive but has been resolved into (+) and (−) forms (21). The salts have the following melting-points: *hydrochloride*, 143° to 144°; *picrate*, 150° to 151°; *picrolonate*, 172° to 173°; *aurichloride*, 82° to 82·5° (orange leaflets).

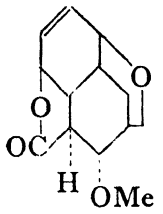
***pseudo*Pelletierine.** N-Methylgranatonine. $C_9H_{15}ON$. This alkaloid crystallises from light petroleum in prismatic tablets melting at 63° to 64°. It is

optically inactive and soluble in organic solvents. The *picrate* melts at 252° to 253° (dec.) and the aurichloride at 162° (yellow crystals).

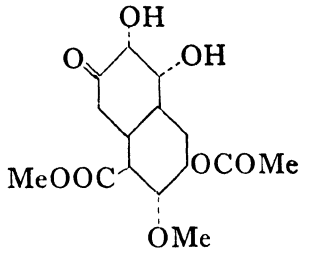
Rauwolfia alkaloids. The alkaloids derived from *Rauwolfia serpentina* Benth. have been found to be of value in the treatment of hypertensive conditions. The drug occurs in India and other Asian countries. The most important therapeutically active alkaloid is *reserpine* whose isolation was reported by Muller, Schlittler and Bein (22) in 1952, though it has been claimed by Steenhauer that it had been prepared by van Itallie and himself in 1932 (23). A number of other alkaloids have been isolated from *R. serpentina* and other species of *Rauwolfia* but so far they have not proved to be of any clinical importance. Reviews of the chemistry of these alkaloids have been published (24, 25, 26). With few exceptions the reserpine alkaloids are indole derivatives and are related to yohimbine. Reserpine has been synthesised (27).



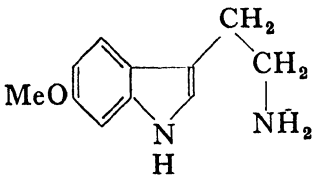
XXII



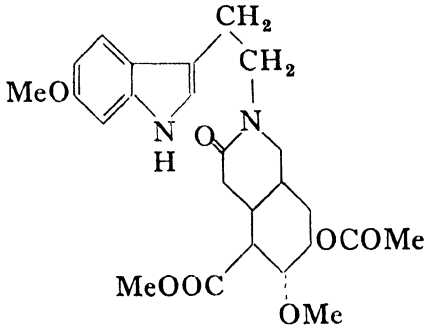
XXIII



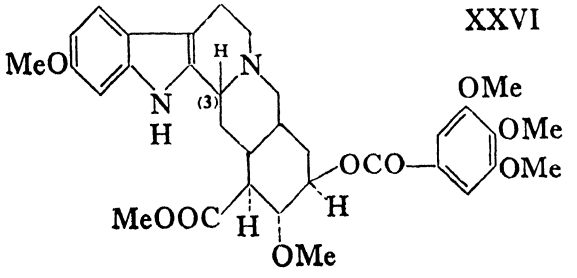
XXIV



XXV



XXVI



XXVII

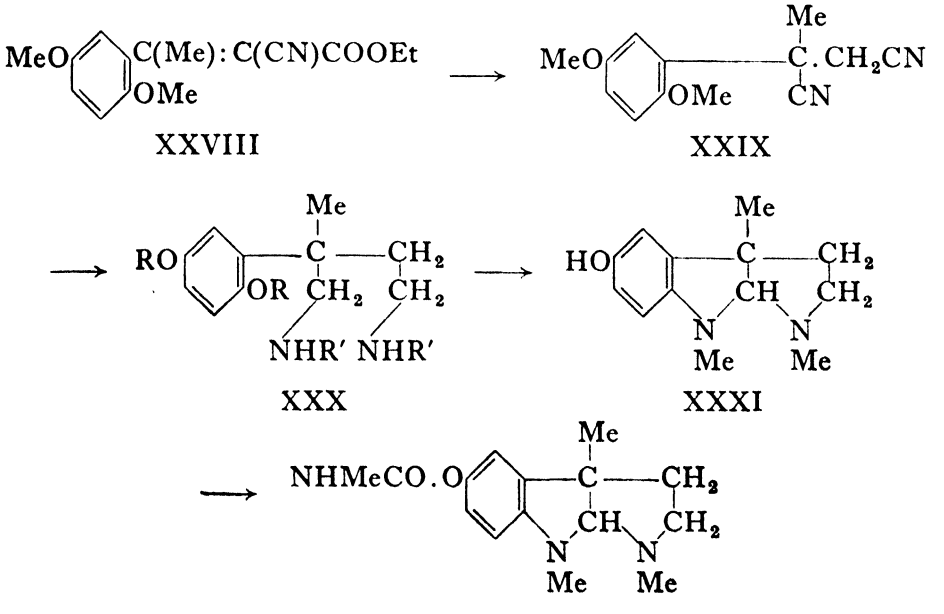
Reserpine, $C_{33}H_{40}O_9N_2$, (XXVII). The structure XXVII was originally proposed by Neuss, Boaz and Forbes (28). The alkaloid has been synthesised by Woodward *et al.* (27). By a Diels-Adler condensation of *p*-benzoquinone and

vinylacrylic acid XXII is produced in which three of the five hydrogen atoms in the E ring of reserpine are in the correct orientation. Since there are thirty-two possible arrangements this ring was the initial objective. The compound XXII was then reduced to an alcohol and converted to an oxide, lactone, ether and a methoxy ether in turn. The compound XXIII was thus formed in which the five hydrogen atoms are now all correctly orientated. Treatment with N-bromo-succinimide was followed by oxidation to the ketone and conversion to a hydroxy-acid, ester acetate and finally to the diol (XXIV). Condensation with 6-methoxy-tryptamine (XXV) yields XXVI. The ring C is now closed but this leaves the hydrogen atom at (3) on the wrong side of the molecule. Condensation with 3 : 4 : 5-trimethoxyphenol gave *iso*reserpine. This can be converted by means of a reaction with mercuric acetate to 3-dehydroreserpine which on reduction gives (±)-reserpine (XXVII).

(−)-Reserpine melts at 286° to 288° and has $[\alpha]_D^{27}$ −120° (in chloroform).

Physostigma alkaloids. These alkaloids are obtained from Calabar beans, the seeds of *Physostigma venenosum*, a plant that grows in West Africa. Calabar beans contain several alkaloids including *physostigmine* (*eserine*), *geneserine*, *eseramine* and *physovenine*, but the only one of importance in medicine is physostigmine which is used for its action in contracting the pupil of the eye.

Physostigmine. Eserine. $C_{15}H_{21}N_3O_2$. Physostigmine is the most abundant alkaloid of Calabar beans from which it is prepared by extraction of the seeds with hot ethanol; the solvent is distilled off and the residue is mixed with sodium carbonate and thoroughly extracted with ether. The extract is shaken with just sufficient dilute sulphuric acid to neutralise the alkaloid which crystallises as the sulphate on evaporating the solution; the alkaloid may also be separated as the salicylate which is less soluble than the sulphate.



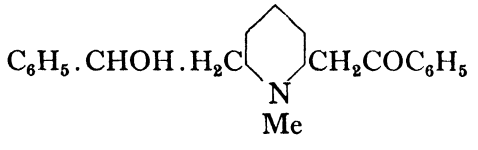
XXVIII XXIX XXX XXXI XXXII

Synthesis. Physostigmine (XXXII) is a monoacidic tertiary base. When heated *in vacuo* or with alkali eseroline, $C_{13}H_{18}N_2O$, is formed together with methylamine and carbon dioxide. Since eseroline (XXXI) is readily converted to physostigmine it is the objective of the several syntheses that have been published (29, 30). Of these the most recent is that of Harley-Mason and Jackson (31) starting with 2 : 5-dimethoxyacetophenone which was condensed with ethyl cyanoacetate to give ethyl 1-cyano-2-(2 : 5-dimethoxyphenyl)-crotonate (XXVIII) which was converted by treatment with potassium cyanide to α-(2 : 5-dimethoxyphenyl)-α-methylsuccinonitrile (XXIX). Hydrogenation over platinum oxide in the presence of hydrochloric acid gave 2-(2 : 5-dimethoxyphenyl)-2-methylbutane-1 : 4-diamine (XXX) (R=Me, R′=H). This with two molecules of benzaldehyde formed a dibenzylidene derivative which, when heated with methyl iodide in a sealed tube, gave the NN′ dimethyl derivative (XXX, R=R′=Me). This was demethylated by boiling hydrobromic acid to eseroline (XXXI) which can be converted to physostigmine (XXXII) by treatment with methylcarbimide.

Properties. Physostigmine occurs in two forms: as unstable crystals (m.p. 86° to 87°) and in a more stable form (m.p. 105° to 106°). It has $[\alpha]_D$ −75·8° to −82° (chloroform) and −120° (benzene). The aurichloride melts at 163° to 165°, the platinichloride at 180° and the picrate at 114°. The most important salts are the sulphate, $B_2.H_2SO_4$, which is a yellowish white deliquescent powder melting at 145°, very soluble in water or ethanol, and the salicylate, $B.C_7H_6O_3$, colourless or slightly yellow needles melting at 186° to 187°. When a solution of ammonia is added to a solution of physostigmine a white precipitate is formed which redissolves, the solution becoming pink.

Lobelia alkaloids. *Lobelia inflata* Linn. contains numerous alkaloids. One of these, (−)-*lobeline*, has been used in the form of the hydrochloride in the treatment of respiratory depression. Lobeline is a member of a group of alkaloids of which other members are *lobelanidine*, *lobelanine*, *norlobelanidine* and *norlobelanine*. Lobelanidine on oxidation with potassium permanganate yields lobeline and lobelanine; lobelanine on reduction gives lobeline and lobelanidine. Lobeline is converted to lobelanidine by hydrogenation and to lobelanine by oxidation.

Lobeline has the structure:



Lobelanidine has been synthesised by Sheuing and Winterhalder (32). Hebky and Kejha (33) obtained a mixture of lobeline, lobelanine and lobelanidine by catalytic hydrogenation of 2 : 6-diphenacylpyridine *p*-toluenesulphomethylate.

(−)-Lobeline melts at 130° to 131° and has $[\alpha]_D^{15}$ −42·85° (ethanol). On warming with water acetophenone is formed. (−)-Lobeline hydrochloride melts at 182° and has $[\alpha]_D^{20}$ −55·75° to −58·25° (water, c=2).

✓ XANTHINE DERIVATIVES

The compounds of this group which contains caffeine, theobromine and theophylline, are derivatives of purine (XXXIII or XXXIV) or they may be regarded as derived from xanthine (XXXV). They are not usually regarded as alkaloids, from which they differ in being only feebly basic, but they may conveniently be included here.

They are mild stimulants and diuretics and occur in a number of plants that are used for the preparation of stimulating beverages, viz. coffee, tea, cocoa, kola, maté and guarana.

Caffeine is a trimethylxanthine, while theobromine and theophylline are isomeric dimethylxanthines. All these compounds form sodium compounds, dissolving readily in caustic alkalis.

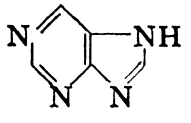
Caffeine. 1 : 3 : 7-trimethylxanthine, $C_8H_{10}O_2N_4$, was first prepared in a pure condition from coffee in 1821 by several workers almost simultaneously, viz. Runge, Pelletier, and Caventon and Robiquet. The compound prepared from tea was at first thought to be a different substance and was called *theine*, but its identity was soon established. Caffeine occurs in the following plants.

Plant	Product	Percentage of caffeine
Coffea arabica	Coffee	1 to 1·5
Camellia thea	Tea	1 to 4·8
Ilex paraguayensis	Maté	1·25 to 2
Paullinia cupana	Guarana	3·1 to 5
Sterculia acuminata	Kola	2·7 to 3·6

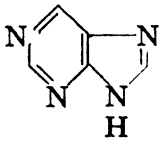
Caffeine also occurs in a small amount with theobromine in cocoa.

Caffeine is prepared commercially from damaged tea or tea-dust; the tea is exhausted with boiling water and the decoction is boiled with litharge or lead acetate. The filtrate is concentrated and the crude caffeine, which crystallises out on cooling, is purified by sublimation or by crystallisation from hot water.

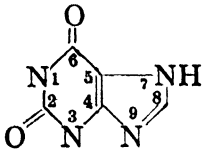
Constitution. Caffeine is formed by the methylation of theobromine or xanthine, and by demethylation can be converted to theophylline or xanthine. It may be synthesised in various ways of which the following is an example.



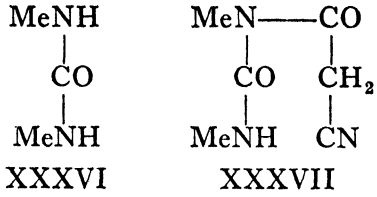
XXXIII



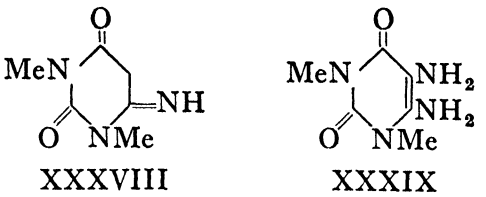
XXXIV



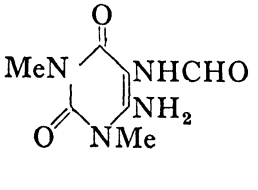
XXXV .



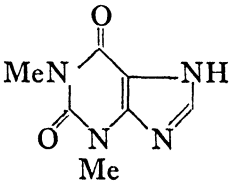
XXXVI XXXVII



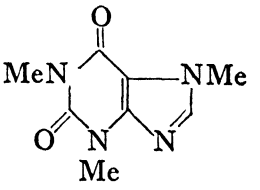
XXXVIII XXXIX



XL



XLI



XLII

Dimethylurea (XXXVI) reacts with cyanoacetic acid in the presence of phosphorus oxychloride to form cyanoacetyldimethylcarbamide (XXXVII), which, on treatment with sodium hydroxide followed by acetic acid, is converted to 4-imino-2 : 6-dioxydimethylpyrimidine (XXXVIII) and this, on reduction of its oximino derivative, gives 4 : 5-diamino-2 : 6-dioxydimethylpyrimidine (XXXIX). This compound condenses with formic acid to produce a formal derivative (XL) which, on heating, forms theophylline (XLI) which is methylated to caffeine (XLII).

Caffeine crystallises in long silky needles with one molecule of water; it sublimes at 179° and melts when anhydrous at 235° to 237°; it is a weak base and cannot be titrated with aqueous acid, but can be extracted from an acid solution with chloroform. Caffeine forms an aurichloride (m.p. 243° to 248°). Kraut's reagent (bismuth potassium iodide) gives a heavy amorphous precipitate from a 1 : 1000 solution that rapidly crystallises in small dark reddish-brown rosettes and even in a 1 : 5000 solution small crystals are formed. Mercuric chloride gives needle-shaped crystals from solutions of greater strength than 1 : 1000. Caffeine is decomposed when boiled with lime water or when warmed with sodium hydroxide. When caffeine is evaporated to dryness with bromine water or nitric acid a yellowish residue is left which is changed to a fine purple colour by ammonia (murexide reaction). Caffeine is not precipitated by a solution of iodine in potassium iodide solution in neutral solution but in the presence of acid a precipitate is formed. No precipitation occurs with Mayer's reagent.

The salts of caffeine are very unstable and are readily dissociated in solution with precipitation of caffeine. The citrate, hydrobromide, triiodide, salicylate and benzoate have been used in medicine.

Theobromine. 3 : 7-dimethylxanthine, $C_7H_8O_2N_4$, is found in cocoa beans, the fruit of *Theobroma cacao*, in which from 1 to 3 per cent is found. It is prepared by mixing the fat-free, powdered beans with lime and exhausting with 80 per cent ethanol; the solution is evaporated to dryness and the residue is extracted with chloroform.

Theobromine may be synthesised by a similar method to that for caffeine, starting from methylurea, but, since theophylline is preferred for use in medicine, the synthesis has no commercial importance and any that is required is obtained from natural sources. Theobromine is readily converted into caffeine by methylation with methyl sulphate.

Theobromine melts at 329° in a sealed tube, but sublimes at 290°. It is very slightly soluble in water (1 in 1000) but more soluble in boiling water (1 in 115); it is also very soluble in ethanol (1 in 1500) and insoluble in other organic solvents, but it dissolves in sodium hydroxide solution.

Theobromine warmed with nitric acid and bromine, heated until the bromine is removed and treated with ferrous sulphate solution and ammonia gives a blue colour; with iodine solution it behaves in the same way as caffeine and also gives a positive murexide test.

Theophylline, 1 : 3-dimethylxanthine, $C_7H_8O_2N_4$, (XLI), occurs in small quantities in tea. It may be synthesised as described under caffeine. The synthetic product is prepared commercially and is used as a diuretic in the form of aminophylline.

Theophylline crystallises with one molecule of water, which it loses at 100° and then melts at 269° to 272°; it is more soluble in water than theobromine (1 in 120) and in ethanol (1 in 80); it gives the same colour reactions as caffeine. It forms soluble compounds with alkali metals.

Aminophylline. Theophylline with ethylenediamine, is a mixture of these compounds containing from 71·5 to 78·5 per cent of anhydrous theophylline and 11·8 to 13·2 per cent of ethylenediamine. It is soluble in water (1 in 5) and is used as a diuretic and in diseases of the cardiovascular system, asthma and cardiac or renal oedema.

Choline theophyllinate. Oxtriphylline. $C_{12}H_{21}N_5O_3$. This compound, used for the treatment of bronchospasm, is prepared by the reaction between theophylline and choline hydroxide (34) or choline carbonate (35). It melts at 185°. It is very soluble in water, soluble in ethanol and slightly soluble in chloroform or ether.

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CHAPTER XIII

Glycosidal Drugs

IN this chapter are included naturally occurring drugs which depend for their pharmacological action on the presence of glycosides and the active principles derived therefrom that are used in medicine. Certain compounds which are glycosidal in character, such as tannins and certain alkaloids, are included in other chapters. The purgative drugs containing anthraquinone derivatives which are probably active in the form of glycosides are included in Part II, Chapter XIX.

The term 'glycoside' is applied to all compounds containing a sugar group attached to an organic group which may be simple in character, such as a methyl group, or complex, such as a steroid grouping. The most commonly occurring sugar group is D-glucose, compounds containing it being termed glucosides, but many other sugars such as rhamnose, galactose, fructose or arabinose are found. In addition, a number of sugars including digitoxose, cymarose, sarmentose and digitalose occur exclusively in the cardiac glycosides. No glucoside of L-glucose is known. Some glycosides contain complex sugar groups such as bioses or trioses which may be hydrolysed in stages. For example, amygdalin, a compound of mandelonitrile with gentiobiose, can be hydrolysed to one molecule of glucose and one molecule of mandelonitrile glucoside which can be further hydrolysed to mandelonitrile and glucose; this frequently happens also in the cardiotonic group.

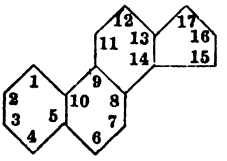
The sugar-free product of the hydrolysis of glycosides is known as the 'aglycone or aglucone'. Most aglycones have names ending in '-genin', e.g. digitoxigenin for the aglycone of digitoxin.

Glycosides are accompanied in the plant by enzymes which hydrolyse them and when the structure of the plant is broken up by grinding, or otherwise, destruction of the glycosides may occur unless the enzyme is destroyed by heat or inhibited by a chemical agent.

Glycosides are usually colourless crystalline substances with a bitter taste. They are, with some exceptions, soluble in water or dilute alcohol. Methods of extraction vary according to the substance, but a common method is extraction of the plant material with dilute alcohol, precipitation of impurities with lead acetate or basic lead acetate, followed by removal of the excess of lead, concentration of the solution containing the glycoside, salting out with ammonium sulphate and crystallisation from a suitable solvent, or the glycoside may be precipitated from alcoholic solution by chloroform. The preparation of glycosides in a state of purity is often a difficult matter as they do not, as a rule, form insoluble derivatives. Where several glycosides occur together it is often difficult or impossible to separate them by crystallisation, but the application of chromatography usually leads to successful results.

THE CARDIOACTIVE GLYCOSIDES

By far the most important group of glycosides medicinally is that of the 'cardioactive' glycosides or 'heart poisons'. These contain the hydrogenated cyclopentenophenanthrene ring system I



I

and are closely related to the steroids. They contain hydroxyl groups and a lactone ring attached at C_{17}. The sugar group is always attached at the 3-position and may be made up of one or more hexose groups. When more than one group is present, they are linked as a chain. Hydrolysis may break the chain at different points according to the method used, e.g. k-strophanthoside contains the sugar chain:

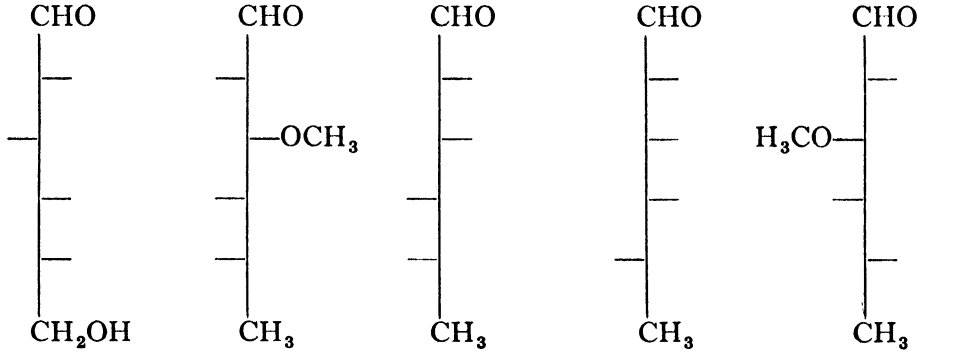
strophanthotriose

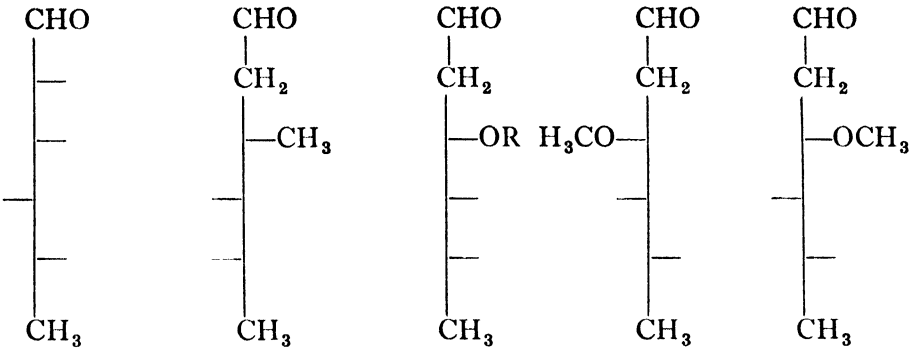
cymarose-β, D-glucose-α, D-glucose

strophanthobiose

The terminal glucose may be split off by enzymatic hydrolysis yielding k-strophanthin-β; a further molecule of glucose is removed by the enzyme strophanthobiase. By acid hydrolysis of k-strophanthoside the aglycone and a triose strophanthotriose is obtained and by acid hydrolysis of k-strophanthin-β a biose strophanthobiose can be separated.

Except for D-glucose the sugars combined with the aglycones are all deoxyhexoses, i.e. they contain one or two oxygen atoms fewer than the corresponding hexose. The following sugars have so far been found in the cardiac glycosides.





D-Gulomethylose L-Oleandrose D-Digitoxose (R=H) D-Cymarose (R=CH_3) D-Diginose D-Sarmentose

The aglycones are usually insoluble compounds, and for that reason have slight physiological activity, the function of the sugar group being to increase the solubility.

By far the most extensively used in medicine are the glycosides of digitalis digoxin, digitoxin and lanatoside-C (digilanide-C): the leaf itself, in a powdered form as tablets or as the tincture, is still used to some extent. The glycosides of strophanthus are used much less often and the glycoside of squill, scillaren A, is occasionally administered.

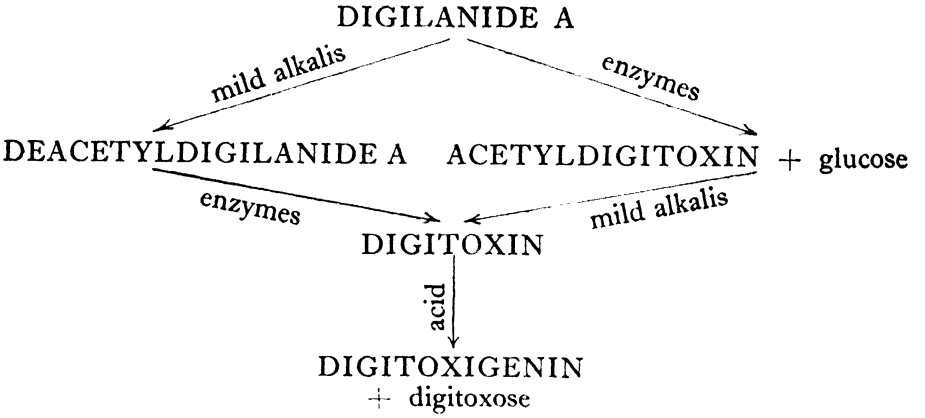
Digitalis glycosides. Two species of digitalis are important in medicine, *Digitalis purpurea*, the common foxglove, and *D. lanata*, which is indigenous to the Balkans. The leaves of *D. purpurea* are official in the B.P. and are used in the form of the dried biologically standardised powder or as the tincture. The most important glycosides occurring in the leaves are *deacetyldigilanides A and B* which correspond with digilanides A and B found in *D. lanata* but contain no acetyl group in the sugar chain; no glycoside corresponding to digilanide C has been found. Partial hydrolysis of digilanides A and B gives *digitoxin* and *gitoxin* respectively. The water-soluble glycoside known as *digitalin* is also present in small amount in the leaves but the main source of this glycoside is the seeds. Confusion is likely to arise in the nomenclature of digitoxin and digitalin; the official name for digitoxin in the French Codex is *digitaline crystallisée* and the name digitalin is sometimes used, especially in foreign literature, to denote digitoxin. In order to avoid this confusion digitalin is sometimes called *digitalinum verum* or amorphous digitalin. The glycosides *gitalin* and *digitalein*, which have been stated to occur in the leaves, are probably mixtures. *Digitonin* and *gitonin* are saponins and of no medicinal importance.

D. lanata leaves are much richer in glycosides than those of *D. purpurea*. The three most abundant glycosides are *digilanides A*, *B* and *C* (also known as *lanatosides*). The aglycones and the order of attachment of the sugar groups are as follows:

Digilanide A digitoxigenin—digitoxose—digotoxose—acetyldigitoxose-β—D-glucose.

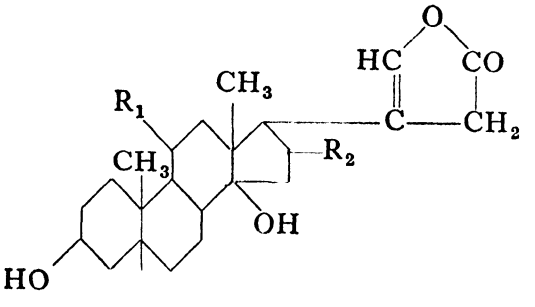
Digilanide B	gitoxigenin—digitoxose—digitoxose—acetyldigitoxose-β—D-glucose.
Digilanide C	digoxigenin—digitoxose—digitoxose—acetyldigitoxose-β—D-glucose.

Enzymes occurring in the plant readily split off the glucose group of the digilanides; e.g. digilanide A yields acetyldigitoxin and glucose. Mild alkaline hydrolysis removes the acetyl group from the next sugar group giving deacetyldigilanide A which occurs in *D. purpurea*. Further action of enzymes forms digitoxin and digitoxose; the action of mild alkalies on acetyldigitoxin also forms digitoxin. This series of reactions may be illustrated in the following scheme.



The acetyl glycosides exist in two forms known as α- and β-. *D. purpurea* leaves contain in addition *gitalin* which has not been obtained in a form corresponding to the digilanides. Gitalin, on acid hydrolysis, gives gitaligenin and two molecules of digitoxose. Stoll obtained yields of digitoxin from *D. purpurea* varying from 0·01 per cent or less to 0·06 per cent. Samples giving a low yield of digitoxin usually showed a higher gitoxin content.

The aglycones of the digitalis glycosides may be represented by the following structural formula:



Digitoxigenin	$R_1=R_2=H$
Gitoxigenin	$R_1=H$, $R_2=OH$
Digoxigenin	$R_1=OH$, $R_2=H$

The isolation of the glycosides of digitalis leaves is due to the work of Stoll and Kreis (1). The leaves were ground at a low temperature with a solution of ammonium sulphate. The glycosides are precipitated with the inactivated enzymes. The residue is thoroughly extracted with ethyl acetate, which removes the glycosides. The ethyl acetate is removed and the residue is thoroughly extracted with ether which removes many impurities. The residue of glycosides in combination with tannic acid is dissolved in ethanol and treated with lead hydroxide which precipitates the tannic acid leaving the glycosides in solution; on evaporation these separate out and can be recrystallised from dilute methanol. After repeated recrystallisation a mixture of digilanides was obtained. These can be separated by a long series of extractions with chloroform from aqueous methanol or by chromatography.

A number of other glycosides have been isolated from *Digitalis* species among which are *strospeside*, *gitorin*, *digiproside*, *digicorin* and *odoroside H*.

Colour tests. Numerous colour tests have been described for digitalis glycosides; some of these are due to the sugar portion of the molecule, e.g. the well-known Keller-Killiani reaction is due to digitoxose. It is carried out by the addition of sulphuric acid so as to form a layer below a solution of the glycoside in glacial acetic acid containing a trace of ferric chloride: a blue colour is formed in the acetic acid layer. Among the colour reactions due to the aglycone part of the molecule are:

Baljet's reaction: a deep orange-red colour is formed with alkaline picrate solution (2); this has been studied by Bell and Krantz (3).

Kedde's reaction. This depends on the production of a brown colour with 3 : 5-dinitrobenzoic acid in alkaline solution (4).

Raymond's test. A blue colour is produced with *m*-dinitrobenzene in strongly alkaline solution (5).

Reviews of colorimetric tests have been published by Canbäck (6) and by Rowson (7).

Chromatography. The separation of digitalis glycosides can most satisfactorily be accomplished by chromatography. A number of methods have been published by which the glycosides have been effectively separated by paper chromatography (8–18).

Digitoxin. Digitaline crystallisée. $C_{41}H_{64}O_{14}$. The digitoxin used in medicine contains varying amounts of gitoxin which cannot be separated economically. It is a white crystalline powder, almost insoluble in water or petroleum spirit, slightly soluble in ether but soluble in ethanol or chloroform. It melts at about 250° (dec.). U.v. absorption: E(1 per cent, 1 cm) at max. λ—200 to 226. $[\alpha]_{5461}^{20}$ +18·5° to +20°. Digitoxin may be prepared from either *Digitalis purpurea* or *D. lanata* leaves by extraction with hot 90 per cent ethanol, precipitation of impurities with basic lead acetate, concentration of the filtrate and extraction with chloroform; the chloroform solution is shaken with sodium sulphide solution to remove traces of lead, dried and precipitated with light petroleum. The precipitate of crude digitoxin is crystallised from dilute ethanol. Pure digitoxin may be prepared by chromatographic separation.

Digoxin. $C_{41}H_{64}O_{14}$. Digoxin is prepared by extracting the total glycosides

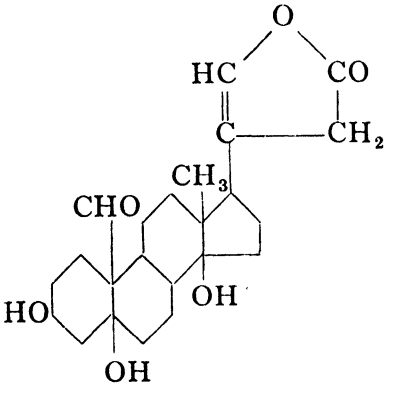
of *D. lanata* with acetone, fractionating by precipitation from aqueous acetone, discarding the less soluble fractions and crystallising the residue from aqueous methanol (19). M.p. 265° (dec.); $[\alpha]^{20}_{5461}$ (c=2·0 in pyridine), +13·3° to +13·9°.

Digilanide C. Lanatoside C. $C_{49}H_{76}O_{20}$). Digilanide C is prepared by the method described above for the separation of the digilanides from *D. lanata*. It is a white crystalline powder melting with decomposition at about 250°. It is soluble in water (0·005 g in 100 ml) and in ethanol (0·55 g in 100 ml). $[\alpha]^{20}_{5461}$ (c=2·0 in ethanol) +33·4° to +33·7°.

Digitalin. Digitalinum verum. $C_{36}H_{56}O_{14}$. This glycoside occurs in the seeds of *D. purpurea* and *D. lanata*. It is a compound of the aglucone digitaligenin which is probably identical with gitoxigenin, and the sugars digitalose and D-glucose. K. Mohr and T. Reichstein (20) have described a method of isolation from the seeds of either species. After defatting with light petroleum the seeds are extracted with 50 per cent ethanol; treatment with lead hydroxide follows and the filtrate is evaporated until the ethanol is removed. The aqueous solution is extracted with ether and chloroform to remove impurities and then with chloroform-ethanol (2 : 1). The glycoside so obtained contains an appreciable amount of digitonin which can be removed by precipitation with cholesterol. The glycoside is then acetylated to form the hexa-acetate which is recrystallised from benzene. The hexa-acetate may be hydrolysed by potassium bicarbonate in aqueous methanol giving digitalin which may be recrystallised from aqueous methanol. Digitalin melts at about 245°. It is optically inactive.

Strophanthus glycosides. Many species of *Strophanthus* contain cardioactive glycosides but the most important in medicine are *S. kombé* which yields strophanthin-K and *S. gratus* yielding ouabain. Other species and the glycosides obtained from them are: *S. glabra* (ouabain), *S. emini* (cymarin, emicymarin), *S. courmontii* (cymarin, strophanthin-Kα), *S. hispidus* (cymarin) *S. sarmentosus* (sarmentocymarin).

Strophanthin-K is obtained from the seeds of *S. kombé*. It is a mixture of glycosides formed from the aglycone strophanthidin by combination with the sugar cymarose to which D-glucose groups may be attached. Two crystalline



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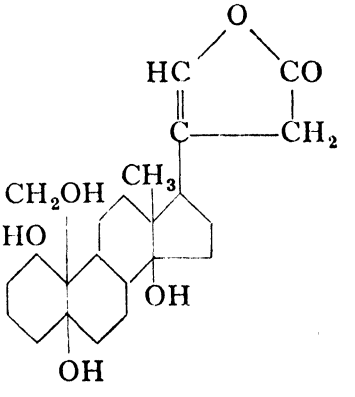

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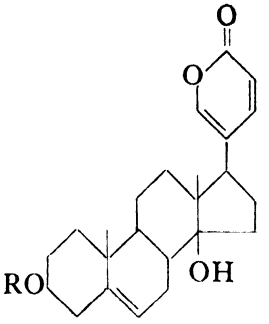

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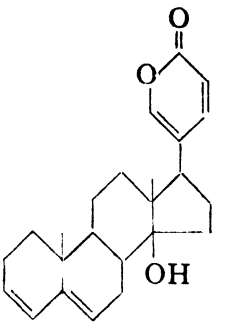

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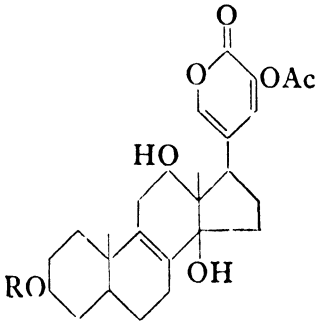


VI

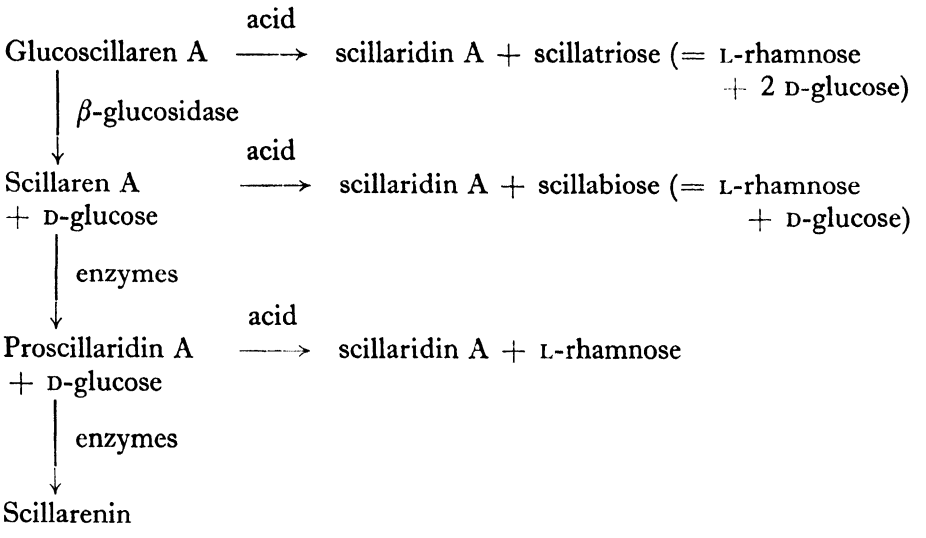
glycosides have been separated, *cymarin* (*strophanthin-Kα*) and *strophanthin-Kβ*. The sugar group in cymarin is cymarose only; k-strophanthin contains in addition one molecule of D-glucose. Stoll, Renz and Kreis (21) have isolated a glycoside *strophanthoside-K* containing yet another molecule of D-glucose. Strophanthidin has the structure II. Cymarin melts at 142° to 150° and has $[\alpha]_{5461}^{20}$ +45·0° (in ethanol).

Strophanthin-K gives a green colour when dissolved in a cold mixture of four volumes sulphuric acid and one volume of water.

Ouabain. Strophanthin-G, $C_{29}H_{44}O_{12}.8H_2O$, is a crystalline glycoside which occurs in the seeds of *Strophanthus gratus* and in the wood of *Acokanthera Schimperi*. It is much more soluble in water (1 in 100) than other glycosides of this type. It is also soluble in alcohol but almost insoluble in ether or chloroform. It gives a pink colour with the sulphuric acid test described above for strophanthin-K. Ouabain melts when anhydrous at about 240° after sintering at about 185°. $[\alpha]_D^{20}$ −39·8° to −40·8° (c=2·5 w/v in methyl alcohol) calculated to the anhydrous substance. Ouabain is a combination of the aglycone ouabagenin (III) with a single molecule of rhamnose. Ouabain is easily prepared from *S. gratus* seeds by defatting with petroleum spirit, mixing the residue with calcium carbonate and extracting with 95 per cent alcohol. On concentration and standing, crude ouabain crystallises and may be recrystallised from dilute alcohol.

Squill glycosides. Squill is the bulb of *Urginea maritima* (Linn.) Baker. The variety known in commerce as white squill is official in the B.P.C. but there is also a variety known as red squill which is used as a rat poison. The pharmacological action of squill is similar to that of digitalis but is much weaker; it is rarely used for its cardiac effect, but in small doses is a constituent of many cough mixtures.

Stoll and his colleagues have isolated eight glycosides from white squill (22). The most important of these is *glucoscillaren A* which is a compound of the aglycone *scillarenin* and a chain of sugar groups which can be split off in stages according to the following scheme (23).



Scillarenin has a high cardiac activity; it has the constitution IV (R=H) and is the true aglycone. In glucoscillaren A, R=L-rhamnose+2 D-glucose; in scillaren A, R=L-rhamnose + D-glucose and in proscillaridin A, R =L-rhamnose. Scillaridin A (V) has lost H_2O during hydrolysis with acid with the formation of the 3 : 4 double bond.

Red squill contains the glycoside *scillaroside* (VI) (24).

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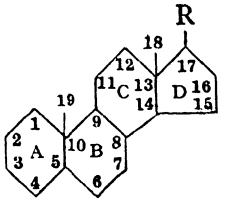
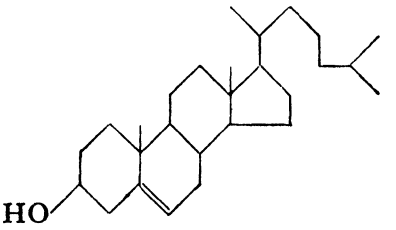
CHAPTER XIV

Steroid Hormones

Introduction. The steroid hormones include the male and female sex hormones and the hormones of the adrenal cortex. The steroids form a group of chemical compounds with a common structure based on the *cyclo*pentane-perhydrophenanthrene system. This structural skeleton consists of four fused rings A, B, C and D with the carbon atoms numbered as indicated (I).



I



II

The group R at carbon-17 is termed the side-chain and the rest of the molecule is the nucleus. Methyl groups are attached at carbon-10 and -13 and by convention are shown as single lines.

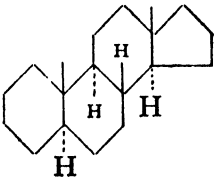
The stereochemistry of the steroid nucleus is complex; in the molecule of cholesterol (II) for example there are asymmetric carbon atoms at positions 3, 8, 9, 10, 13, 14, 17 and 20. Thus there are 2^8 or 256 possible isomers.

Cortisone has 6 asymmetric centres and 64 possible isomers, oestrone has 4 asymmetric centres and 16 possible isomers, whilst equilenin with its 2 aromatic rings has only 2 asymmetric carbon atoms and thus 4 possible isomers.

This isomerism is shown in the graphic formulae by the use of heavy or dotted lines for the bonds joining the peripheral groups to the nucleus, which is assumed to lie in the plane of the paper. A heavy line shows that the bond and the group attached to it project upwards and outwards from the paper, whilst a dotted line indicates the reverse. This method of representation indicates the relative configuration of the groups and shows whether a ring junction is *cis* or *trans*. Amongst the natural steroids the following configurations of the groups at the ring junctions are found.

	A/B	B/C	C/D
Cholestane	Trans	Trans	Trans
Coprostane	Cis	Trans	Trans
Cardiac aglycones	Trans	Trans	Cis

Androstane, 5-allopregnene and 5-allocholane have the same type of ring junctions as cholestane whilst 5-*iso*androstane, pregnane, aetiocholane and cholane are similar to coprostane. Among natural steroids only the cardiac aglycones have a *cis* C/D junction. Cholestane is represented by the full graphic formula III and coprostane by IV.



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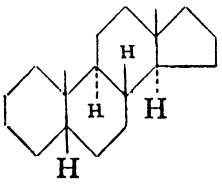
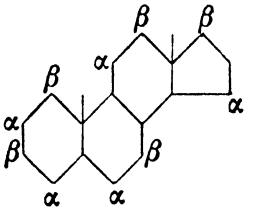


IV

In addition the hydrogen atoms at C-3 and C-17 are usually substituted and the groups at these positions increase the number of isomers. Where the group is *trans* relative to the methyl group at C-10 it is termed an α-orientated group and where it is *cis* it is termed a β group; e.g. the hydroxyl group in *epi*cholesterol is α and in cholesterol is β. Thus in formula II for cholesterol the OH group is shown attached to carbon at position 3 by a heavy continuous line because, like the methyl group at C-10, it projects above the plane of the paper.

This question of the isomerism of the steroid nucleus has been carried a stage further by the work of Hassel (1) and Barton (2) on the chemistry of *cyclo*hexane derivatives. It has been shown for the stable-chair form of *cyclo*hexane that at each carbon atom one of the hydrogen bonds is parallel to the axis of the molecule and is termed an axial bond; the other is directed away from the axis and is termed an equatorial bond. If the steroid nucleus is drawn as a spatial formula with the three *cyclo*hexane rings fused in the chair forms, then the above αβ type of notation which refers to the configuration of a group relative to the Me group at C-10 can be correlated with the axial or equatorial character of the bond. In the cholestane type of compound, for example, the configurations of the stable epimeric secondary alcohols at positions round the nucleus are shown below.



At each position, however, it is found by inspection of the spatial formula that the stable configuration is that occupied by an equatorial bond.

SEX HORMONES

Introduction. There are two kinds of female sex hormones, called the oestrogens and the gestogens. *Oestradiol* is the primary natural oestrogen and the other

oestrogens described below are metabolic transformation products formed from this compound. *Ethinyloestradiol*, which is used clinically, is a synthetic derivative of oestradiol. *Progesterone* is the sole natural gestogen but *ethisterone*, a synthetic compound, has similar therapeutic properties and is used clinically.

Testosterone is the primary male sex hormone or androgen and *androsterone* is a secondary naturally occurring compound. *Methyltestosterone* is a synthetically produced compound used clinically and, as its name implies, a methyl derivative of testosterone.

In the first quarter of this century a great deal of research work was carried out on extracts of male and female sexual-organ tissues and it was shown that hormonal substances were present. The isolation of pure hormones from these active extracts proved to be an extremely difficult task, but in 1927 Zondek (3) reported the presence of an oestrogen in the urine of pregnant women and this important discovery of an alternative source of active compounds led directly, in the period 1927 to 1935, to the isolation of all the major sex hormones.

Oestrone, extracted in 1929 (4, 5) from pregnancy urine, was the first steroid hormone to be obtained in a pure state. Oestriol was isolated from the same source in 1930 (6) and oestradiol from ovarian tissue in 1935 (7). The latter compound was then already known, for it had been prepared by the chemical reduction of oestrone. Progesterone was first isolated by Butenandt in 1934 (8). His source of the hormone was the corpus luteum tissue of sows' ovaries; the difficulties inherent in this type of work may be appreciated from the fact that the ovaries of 50,000 sows yielded 20 mg of pure progesterone. Human male urine was found in 1928 (9) to contain small amounts of an androgenic substance and androsterone was obtained from this source in 1931 (10). Testosterone, the primary androgen, was isolated in 1935 (11) by the extraction of bull testicular tissue.

For a description of these compounds see (12).

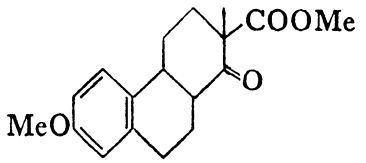
FEMALE SEX HORMONES

Oestrone. Estrone. 3-Hydroxy-1 : 3 : 5(10)-oestratriene-17-one. $C_{18}H_{22}O_2$. (IX).

Preparation. Zondek in 1930 (13) found mare's pregnancy urine to be a better source of oestrone than human urine and this led to a commercial process for the extraction of the hormone from this source.

The correct formula for oestrone was put forward by Butenandt (14) and independently by Marrian and Haslewood (15). The extraction of oestrone from urine is a costly procedure and the total synthesis of the hormone was a problem which many investigators endeavoured to solve. It is complicated by the fact that oestrone is one of 16 possible stereoisomers. Equilenin, a related natural oestrogen, which has two aromatic rings in its nucleus, is one of only four isomers and it was the first natural oestrogen to be synthesised (16). A synthetic compound identical with natural oestrone was prepared by Anner and Miescher in

1948 (17). The total synthesis used by these workers was based on experience gained in the preparation of the synthetic oestrogens known as doisynolic acids. Anner and Miescher used as starting material the keto-ester (V) which had been previously made by Bachmann and by Robinson. This compound can exist as four racemates and Anner and Miescher used one particular crystalline racemate for the preparation of oestrone. The keto-ester was reacted with methyl bromoacetate by the Reformatsky procedure and the compound (VI) was obtained. This was dehydrated by means of phosphoryl chloride and pyridine and then catalytically hydrogenated to yield a mixture of two racemates (VII). This diester was half hydrolysed and the acid ester was subjected to the Arndt-Eistert method of chain lengthening with the formation of VIII. Cyclisation and decarboxylation yielded racemic oestrone (IX) and its C-14 epimer. The oestrone was resolved through its phenolic ester with (—)-menthoxyacetic acid.



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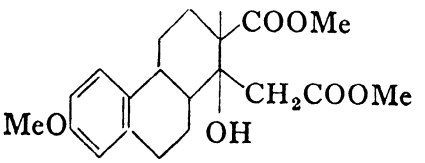

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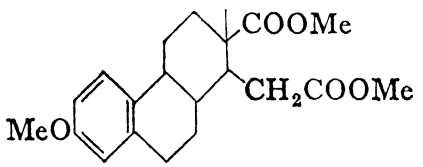

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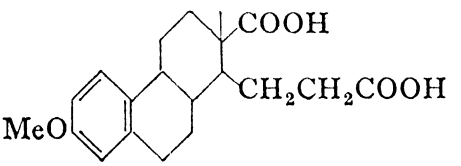

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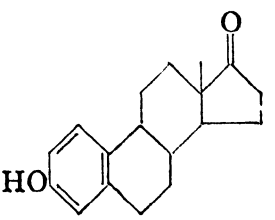
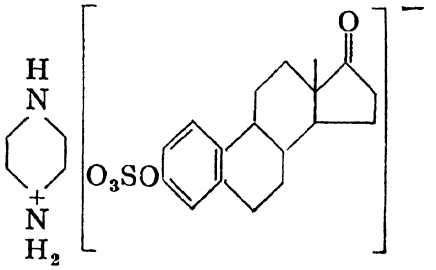


IX

Recently Johnson and his associates (18) have, by a total synthesis, prepared oestrone and some of its isomers; all eight of the possible racemates are now known.

Properties. Oestrone forms colourless crystals melting at 262°; $[\alpha]_D^{20}$ +163° (dioxan). It is almost insoluble in water (2·1 mg per litre at 18°); soluble in 200 parts of acetone and in 400 parts of ethanol. Oestrone propionate melts at 134° to 135°. A compound of oestrone acid sulphate with piperazine called piperazine oestrone sulphate (X) has been introduced into therapy (19). It is a white

crystalline powder which melts at 185° to 195° to a syrup that solidifies and remelts at 240° to 250°. It is slightly soluble in water and ethanol.

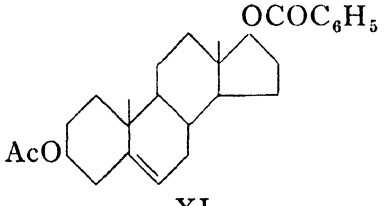


X

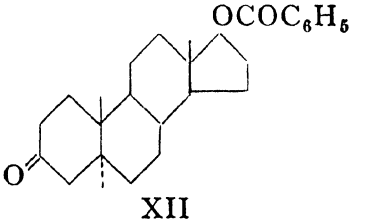
Oestradiol. Estradiol. 1 : 3 : 5(10)-Oestratriene-3 : 17β-diol. $C_{18}H_{24}O_2$. (XIV).

Preparation. Oestradiol may be obtained by the reduction of oestrone, by which method it was first prepared as a mixture of the epimers at C-17 (20). Later workers have carried out this reduction by the use of lithium aluminium hydride (21) and sodium borohydride (22). The mixture of isomers can be separated through the dipropionates (23).

Inhoffen prepared oestradiol by partial synthesis from cholesterol. Previous workers had obtained androstenediol-3-acetate-17-benzoate (XI) as an intermediate in the manufacture of testosterone from cholesterol. The main problem in its use for the synthesis of oestradiol is the removal of the angular methyl group at C-10 and the consequent aromatisation of ring A. Inhoffen first saturated the 5 : 6 double bond and then removed the 3-acetate group by hydrolysis. The resulting 3-hydroxyl group was oxidised to yield androstanolone-17-benzoate (XII). Two successive brominations allowed the introduction of double bonds at the 1 : 2 and 4 : 5 positions and hydrolysis of the benzoate led to XIII. The angular methyl group at C-10 was then removed (24). This



XI



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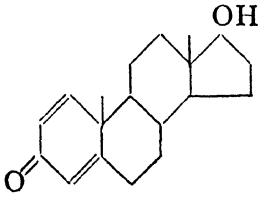
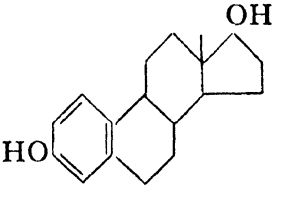


XIII



XIV

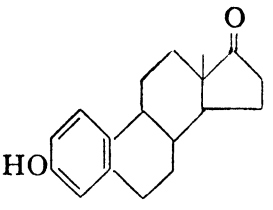
remarkable aromatisation step was carried out in a special apparatus consisting of a quartz tube packed with quartz and heated to 600° by means of a spiral electrical heater; a spray of the intermediate steroid (XIII) in tetralin was blown through the tube by nitrogen. The oestradiol which formed was isolated as a crystalline complex with tetralin which decomposed on steam distillation and the oestradiol (XIV) was recrystallised from methanol.

Properties. Oestradiol is a white crystalline powder melting at 177° with $[\alpha]_D^{20}$ +78° (dioxan). It is almost insoluble in water but soluble in ethanol, acetone and aqueous solutions of alkali hydroxides.

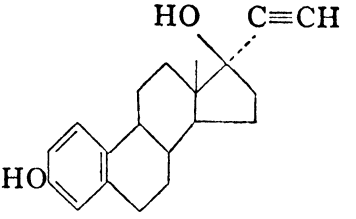
Many esters of oestradiol have been introduced into therapy mainly because of their more prolonged action. The dipropionate (26, 27) melts at 104° to 106° and has $[\alpha]_D^{20}$ +36° to +40° (dioxan); the monobenzoate (28) melts at 190° to 195° and the 17-*cyclo*pentylpropionate (29) at 151° to 152°; $[\alpha]_D^{25}$ +45° (chloroform).

Ethinyloestradiol. 17-Ethynyl-1 : 3 : 5(10)-oestratriene-3 : 17-diol. $C_{20}H_{24}O_2$. (XV).

Preparation. The Nef reaction is used in which oestrone (IX) is dissolved in a mixture of dioxan and ether and added to a solution of potassium in liquid ammonia saturated with acetylene. Theoretically two isomers may be formed but one predominates (30, 31).



IX



XV

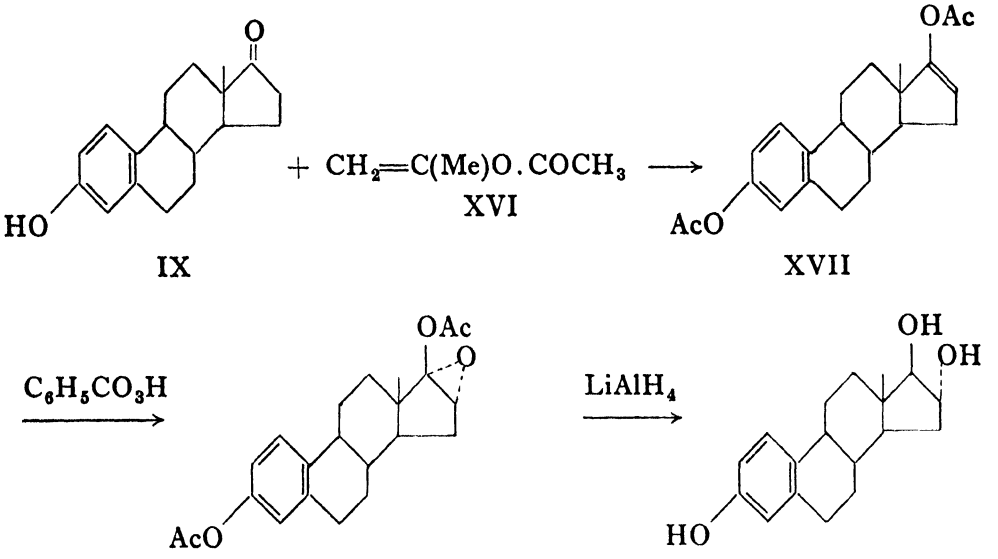
Properties. Ethinyloestradiol is dimorphic; it melts at 146°, solidifies at 150° to 160° and then remelts at 186°. It is almost insoluble in water but soluble in acetone, chloroform, ether, ethanol and dioxan; it also dissolves in aqueous solutions of alkali hydroxides. The benzoate melts at 200° to 202°.

Oestriol. Estriol. 3 : 16 : 17-Trihydroxy-1 : 3 : 5-oestratriene. $C_{18}H_{24}O_3$. (XIX).

Preparation. Oestriol was made in 1948 by a partial synthesis from oestrone methyl ether (32). A recent paper claims an improved method (33). In this synthesis oestrone (IX) was first converted to the enol diacetate (XVII) by reaction with *iso*propenyl acetate (XVI) in the presence of sulphuric acid. This interesting reagent, which is used for mild acetylations and especially for enol acetylations, decomposes under acid conditions to ketene, $H_2C{=}C{=}O$ and acetone (34). The ketene acetylates the hydroxyl group and the acetone is distilled off during the reaction.

The diacetate is then reacted with excess of perbenzoic acid to yield the

epoxide (XVIII) which on reduction with lithium aluminium hydride leads to oestriol (XIX).

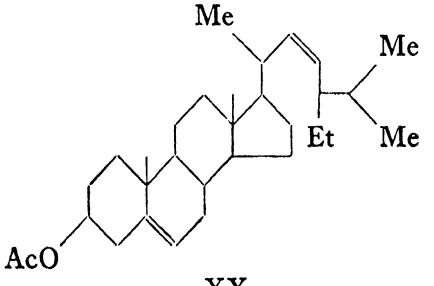


Properties. Oestriol is a white powder exhibiting a reddish fluorescence under ultra-violet light. When heated on a hot-stage microscope it melts sharply at 282°, after a phase change at 270° to 275°. The $[\alpha]_D^{20}$ is +61° (ethanol). It is insoluble in water but soluble in ethanol and dioxan.

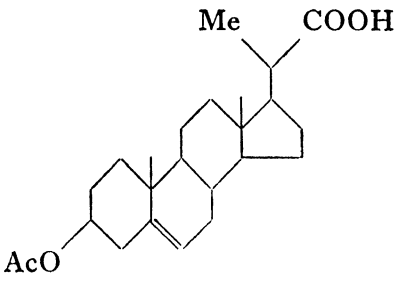
Progesterone. 4-Pregnene-3 : 20-dione. $C_{21}H_{30}O_2$. (XXIV).

Preparation. A number of syntheses of progesterone have been reported and those published prior to 1949 have been reviewed by Fieser (12). The subject became of greater importance with the publication in 1952 of the microbiological oxidation of progesterone to 11-hydroxyprogesterone, a compound which is convertible to cortisone.

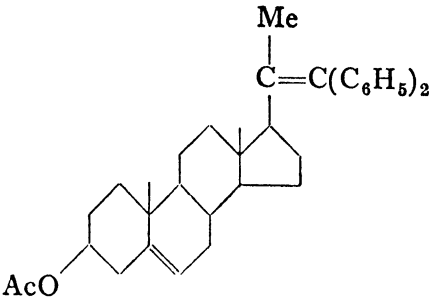
Progesterone was prepared by partial synthesis from stigmasterol (XX) in 1934 by Butenandt (35) and Fernholz (25, 36). Stigmasterol acetate was brominated at the double bond, ozonised and debrominated to the acetate of hydroxybis*nor*cholenic acid (XXI); this was converted via the ester and the diphenyl carbinol into the unsaturated compound XXII. Further bromination, oxidation and debromination led to pregnenolone acetate (XXIII). The double bond



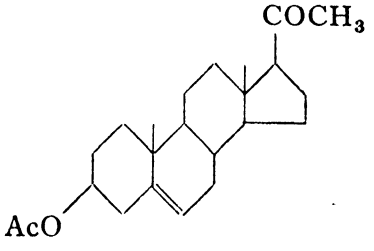
XX



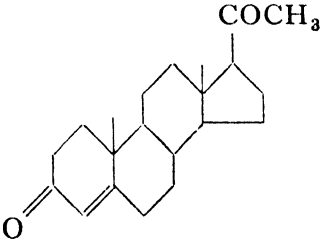
XXI



XXII



XXIII



XXIV

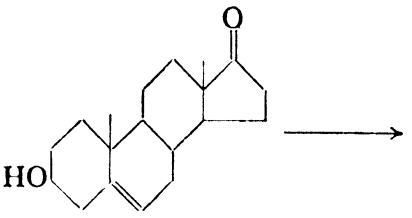
was brominated and, after hydrolysis, the hydroxyl group was oxidised to a ketone; debromination gave progesterone (XXIV).

A recent variation of this synthesis from stigmasterol has been published (37).

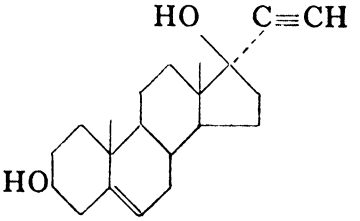
Properties. Progesterone occurs as a white crystalline powder melting at 128° to 133° with an isomorphic form melting at 121°. It has $[\alpha]_D$ +175° to 183° (dioxan) and E (1 per cent, 1 cm) 525 to 545 at 241 mμ. It is insoluble in water, but soluble in ethanol, ether, benzene, acetone, dioxan and chloroform.

Ethisterone. 17-Ethinyltesterone. $C_{21}H_{28}O_2$. (XXVII).

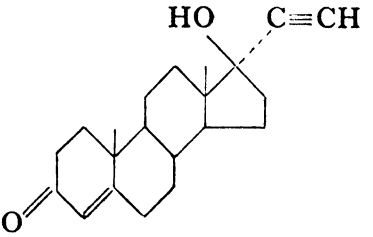
Preparation. Acetylene is added to dehydro*epi*androsterone (XXV) in the



XXV



XXVI



XXVII

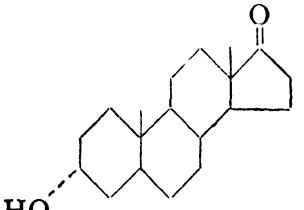
presence of potassium *tert.*-butoxide forming XXVI. The 3-hydroxyl group is converted to a ketone group by the Oppenauer oxidation (38, 39, 40) to yield ethisterone (XXVII).

Properties. Ethisterone is a white tasteless microcrystalline powder melting at 269° to 275°; it is stable in air, but is affected by light. It is insoluble in water and sparingly soluble in ethanol, acetone, chloroform and vegetable oils.

Ethisterone has a similar pharmacological action to that of progesterone but is active orally.

MALE SEX HORMONES

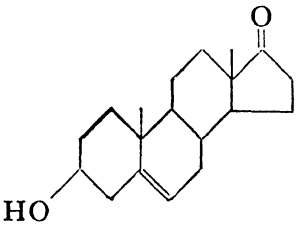
Androsterone (XXVIII) was the first male sex hormone to be obtained in a pure state. Butenandt (10) isolated it but obtained only 15 mg of crystalline material from 15,000 litres of normal male urine; on the basis of a total quantity of only 25 mg he proposed a formula which was later shown to be correct (41). The later discovery of testosterone, which is a more potent androgen, has reduced androsterone to secondary importance.



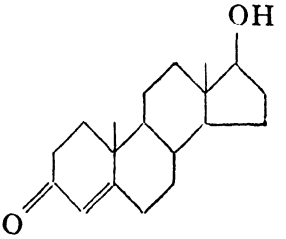
XXVIII

Testosterone. 17-Hydroxy-4-androstene-3-one. $C_{19}H_{28}O_2$. (XXX).

Preparation. Ten mg of the pure hormone were obtained by Laqueur and his colleagues (11) from 100 kg of bull's testicular tissue. The fact that it had the absorption spectrum of an $\alpha\beta$ unsaturated ketone and that it yielded the known 4-androstene-3 : 17-dione on oxidation suggested the formula (XXX) for testosterone. This was verified by Butenandt (42) when he converted dehydro-*epi*androsterone (XXIX) to testosterone.



XXIX

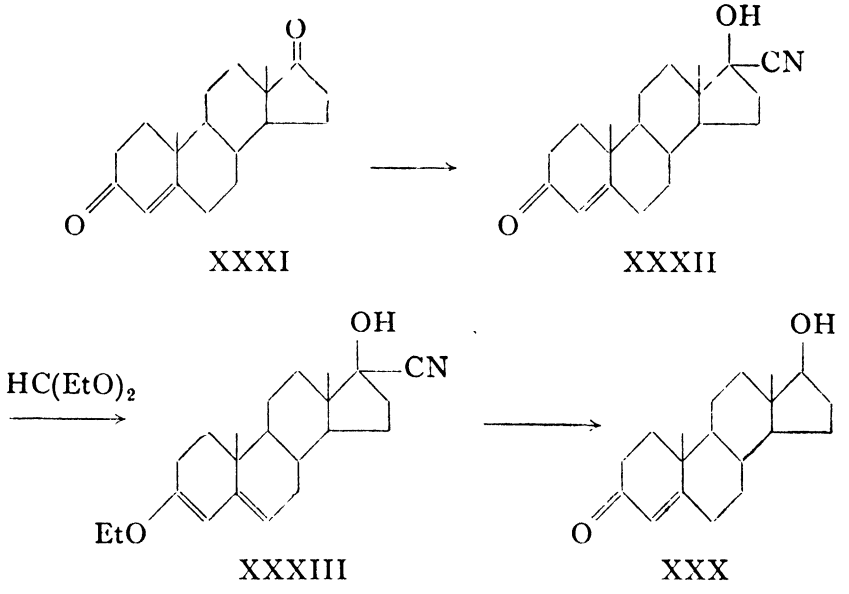


XXX

This conversion is most simply and efficiently carried out by a two-step method discovered by Mamoli (43). Dehydro*epi*androsterone is shaken for two days with oxidising yeast in a phosphate buffer when the 3-hydroxyl group is

oxidised to a 3-keto group. Simultaneously the double bond shifts from the 5 : 6 to the 4 : 5 position. The solid matter in the reaction vessel is collected and extracted with ethanol which removes the dione. The solution after concentration is added slowly to actively fermenting yeast in a sugar medium and the 17-keto group is reduced to a hydroxyl group.

Recent routes to testosterone (44, 45) have been via the enol ethyl ether. 4-Androstene-3 : 17-dione (XXXI) is reacted with acetone cyanohydrin to yield the steroid cyanohydrin (XXXII); this on treatment with excess of ethyl orthoformate in benzene in the presence of hydrogen chloride gives the 3-enol ethyl ether of the cyanohydrin (XXXIII) and reduction with either sodium in propanol or lithium aluminium hydride leads to testosterone enol ethyl ether, which, on mild acid hydrolysis, gives testosterone (XXX).



XXXI XXXII XXXIII XXX

Properties. Testosterone is a white crystalline powder melting at 155° to 156° with $[\alpha]_D^{20}$ +109° (ethanol) and E (1 per cent, 1 cm) 520 to 560 at 241 mμ. It is insoluble in water; 1 g dissolves in 6 ml of anhydrous ethanol, 2 ml of chloroform or 100 ml of ether; it is also soluble in dioxan.

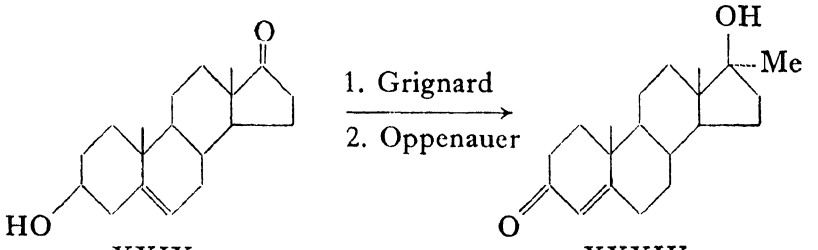
The propionate (44, 46) is a white powder melting at 121°; it is insoluble in water, but soluble at 15·5° in 30 parts of ethanol or of propylene glycol; it is also soluble in ether and acetone.

The *cyclo*propionate (44, 47) melts at 101° to 102° with $[\alpha]_D^{25}$ +76·4° (chloroform). Testosterone acetate is dimorphic: there is a transition point at 80° and the acetate then melts at 141°.

Methyltestosterone. 17α-methylandrost-4-ene-17β-ol-3-one. $C_{20}H_{30}O_2$. (XXXIV).

Preparation. Methyltestosterone is a synthetic derivative of testosterone. It is

readily prepared by the reaction of dehydro*epi*androsterone (XXIX) with an excess of methyl magnesium iodide; the 3-hydroxyl group is then oxidised by the Oppenauer method with acetone and aluminium *iso*propoxide (48).

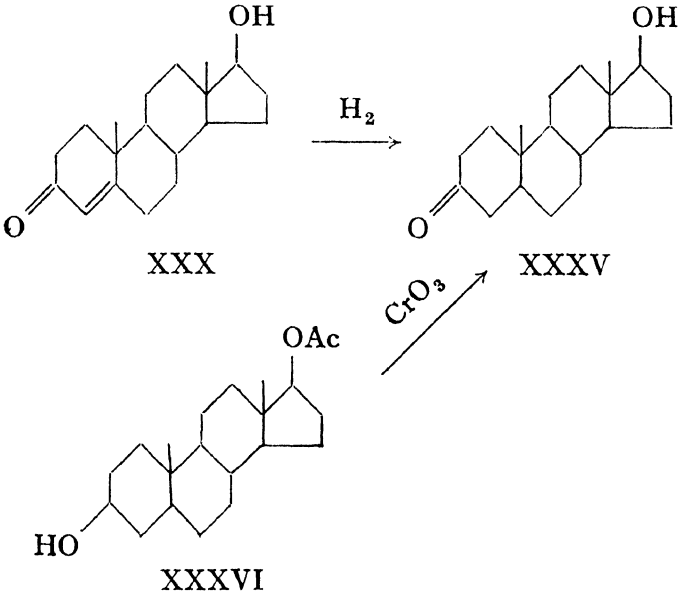


XXIX XXXIV

Properties. Methyltestosterone is a white crystalline powder melting at 166° with $[\alpha]_D$ +76° (ethanol); it is insoluble in water but soluble in ether, ethanol and acetone. It is affected by light.

Stanolone. Androstane-17β-ol-3-one. $C_{19}H_{30}O_2$. (XXXV).

Preparation. Since stanolone is 4-dihydrotestosterone it may be prepared from testosterone (XXX) by hydrogenation (49) or from *epi*androsterone (XXXVI) by oxidation (50). In addition a method similar to that used for testosterone via the cyanohydrin has been used (44).



XXX XXXV XXXVI

Properties. Stanolone melts at 181° and has $[\alpha]_D$ +32°; it is insoluble in water, but soluble in ethanol (6 g in 100 ml of solution) and in ether (1·5 g in 100 ml of solution).

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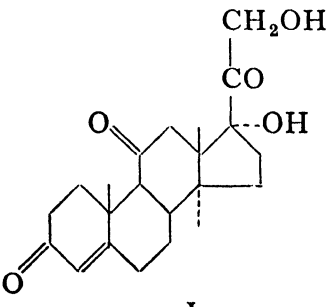
CHAPTER XV

Hormones of the Adrenal Cortex

ADRENALECTOMY invariably results in death in a few days; this is due to the loss of hormones produced by the *cortex* or outer tissues of the gland. The *medulla*, or central part of the gland, is responsible for the production of adrenaline. In 1930 Swingle and Pfiffner (1) first prepared active cortical extracts, which, on continued administration to moribund adrenalectomised animals, prolonged life for an indefinite period. Later workers isolated a number of crystalline substances from the extracts and thirty steroid compounds have been identified. These substances possess certain features in common. When saturated they are derivatives of allopregnane. Position 3 is occupied by a hydroxyl group or by an $\alpha\beta$ unsaturated ketone group whilst the carbon at position 17 carries a carbon chain of two atoms and often in addition an α-hydroxyl group. Carbon-11 may or may not be linked to an oxygen atom.

Certain of the adrenocortical hormones have a controlling influence on carbohydrate metabolism; these are known as *glucocorticoids*. To this category belong cortisone and hydrocortisone; others such as deoxycortone and aldosterone control the electrolyte balance and are called *mineralocorticoids*.

Cortisone. 17α-Hydroxy-11-dehydrocorticosterone. 17α : 21-Dihydroxypregn-4-ene-3 : 11 : 20-trione. $C_{21}H_{28}O_5$. (I). Cortisone was isolated in 1936 by three groups of workers (1a, 2, 3) and its structure was elucidated by Reichstein (4) by whom it was called Compound F. For some time its importance was not realised. From experience with purified cortical extracts it was hoped that compounds might be found having curative properties in Addison's disease and useful in the treatment of wound and surgical shock. In 1941 research work began in various American laboratories on the problem of the partial synthesis of 11-oxy steroids; in 1945 dehydrocortisone (a substance which has the cortisone structure but lacks the 17α-hydroxy group) was synthesised, tested but found to be of little value. In 1946 Sarett (5, 6) obtained 29 mg of cortisone by the first partial synthesis of the compound. There was no indication then that it



I

would become important and its later applications in the field of rheumatoid arthritis are due entirely to the work of Hench and his colleagues.

It had been known for 50 years that jaundice exercises a beneficial effect on the syndrome of rheumatoid arthritis and in 1938 Hench (7) attempted to relieve the condition by the injection of bile salts, but was only partially successful. In 1948, however, he suggested that, since certain conditions such as jaundice, pregnancy, surgery and starvation, which favoured remission of rheumatoid arthritis, also stimulated the adrenal cortex, cortical hormones should be tested for activity. In 1948 he was supplied with a few grams of cortisone by Kendall and in 1949 he published an account (8) of its dramatic effect in certain cases of rheumatoid arthritis; a large demand for cortisone consequently arose and stimulated work in many laboratories on a commercial synthetic process. It was clear from previous work that the synthesis would be a long and difficult matter and that not the least difficulty would be supplies of a suitable starting-material. Consequently a great many papers have been published on the chemistry of cortisone; a number of excellent reviews of this work have appeared (9 to 13).

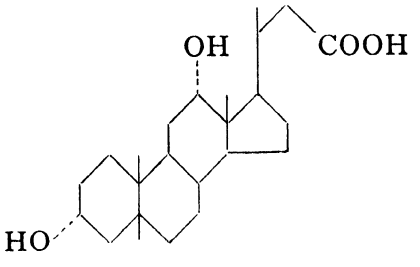
Preparation. Cortisone (I) may be obtained either by partial or total synthesis. The compounds shown on p. 298 have been used as starting-materials for partial syntheses.

Progesterone is of particular interest since it is an intermediate in the process in which biological methods are employed.

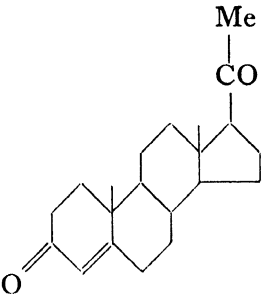
The chemical approaches to the synthesis of cortisone involve three main stages: (*a*) the introduction of the 4 : 5 double bond and the 3-keto group; (*b*) the formation of the 2-carbon side-chain and introduction of the 17-hydroxyl group; and (*c*) oxygenation at position 11. This last step presents the principal difficulty and it is here that the microbiological approach has been extremely useful.

Sarett's original synthesis of cortisone began with deoxycholic acid. This has the advantage that rings A and B have a *cis* junction which facilitates the introduction of a 4 : 5 double bond. In addition the hydroxyl at position 12 can be used to introduce the required oxygen atom at position 11. This synthesis after intensive development was used as a commercial process for the production of cortisone. Deoxycholic acid, however, is derived from ox bile and is in limited supply; 100 kg of ox bile yield only 0·7 kg of deoxycholic acid and therefore intensive efforts were made to find starting-materials that were naturally abundant. Marker (14) in 1940 had shown that it was possible to oxidise rings E and F of the natural sapogenins to a pregnane side-chain and this resulted in the consideration of such compounds as diosgenin, hecogenin and sarmentogenin as possible starting-materials. Of these sarmentogenin had several points in its favour; the A/B junction is *cis* and it has an 11-hydroxyl group that could be easily oxidised to an 11-keto group. Unfortunately no suitable source capable of supplying the quantities required has been found in spite of widespread searches in different parts of the world.

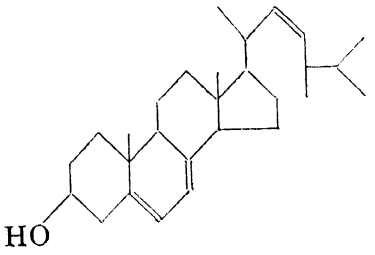
Hecogenin is potentially abundant as it can be extracted from the juice of the sisal plant (*Agave sisalana*) (15). The conversion to cortisone has been



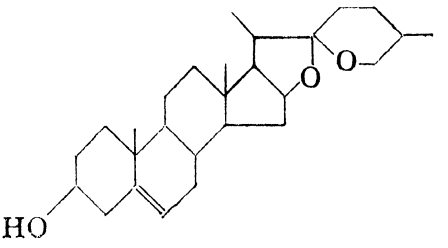
Deoxycholic acid



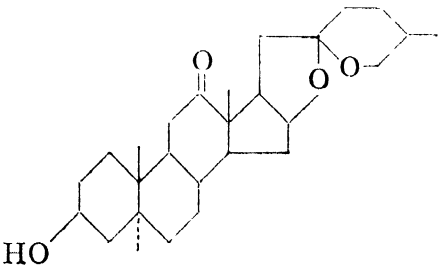
Progesterone



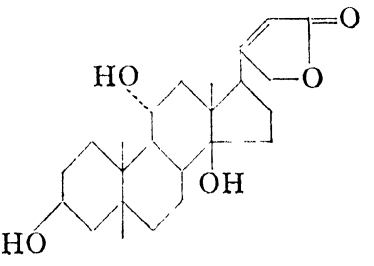
Ergosterol



Diosgenin



Hecogenin



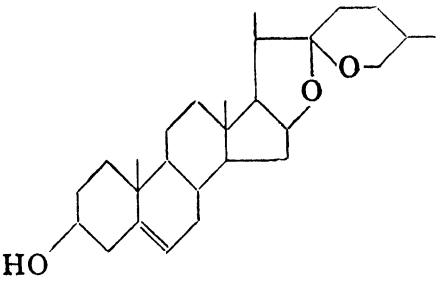
Sarmentogenin

accomplished (16) but it has disadvantages in that the A/B ring junction is *trans* and the introduction of the 4 : 5 double bond is not simple.

Diosgenin is extractable from plants of the yam family and one of these, *Testidinaria sylvatica*, is used as the commercial source of supply of the sapogenin, which is the starting-point in a manufacturing process for the production of cortisone. Progesterone is first prepared and this is then oxidised biologically at position 11 to 11-hydroxyprogesterone which is converted to cortisone. This process involves 14 stages from diosgenin to cortisone while the Sarett synthesis requires 35 stages.

Diosgenin (II) is first acetylated (17) in the presence of aluminium chloride to give *pseudo*diosgenin acetate (III) which, on oxidation (18) leads to pregnadienolone acetate (IV) reduced and hydrolysed to pregnenolone (V). The side-chain of progesterone has now been formed from rings E and F of the genin. The 3-hydroxyl group is now oxidised to a keto group and the 5 : 6 double bond shifts

to the required 4 : 5 position with the formation of progesterone (VI). Microbiological oxidation at position-11 by the mould *Rhizopus nigracans* produces 11α-hydroxyprogesterone (VII) in remarkably high yield. This procedure for



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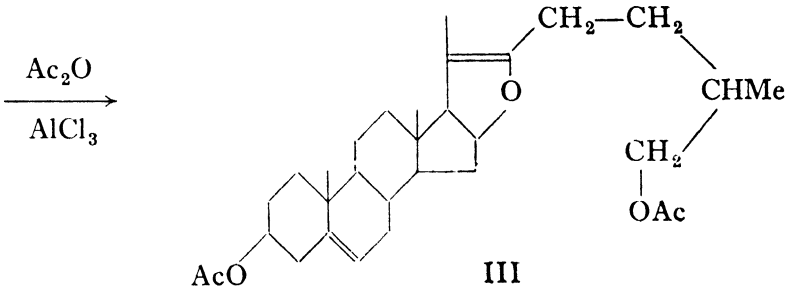

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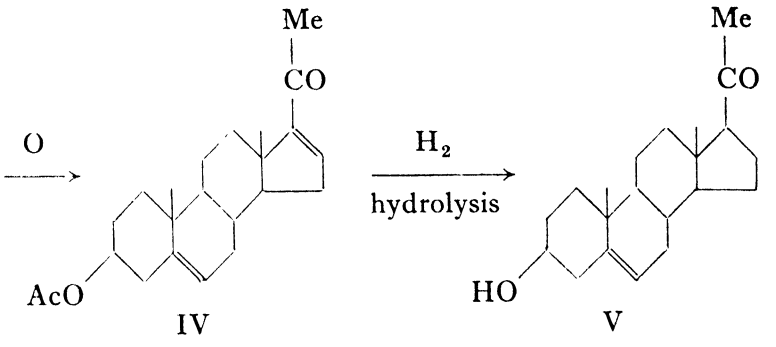
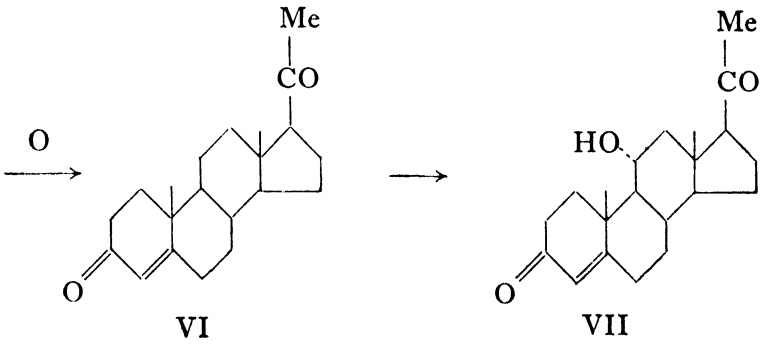
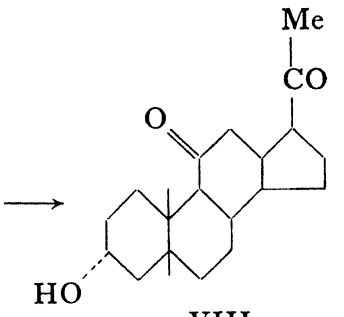


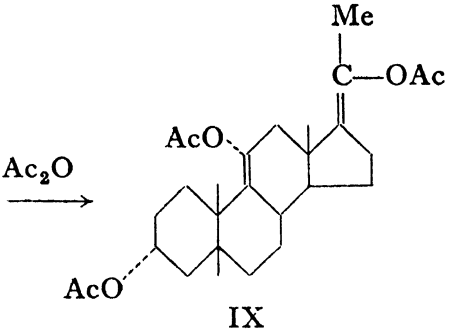
IV V



VI VII



VIII



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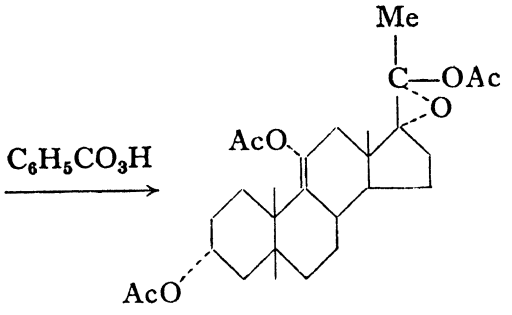

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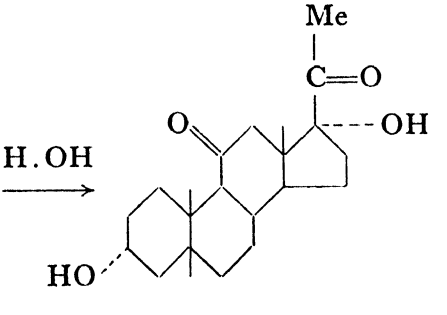

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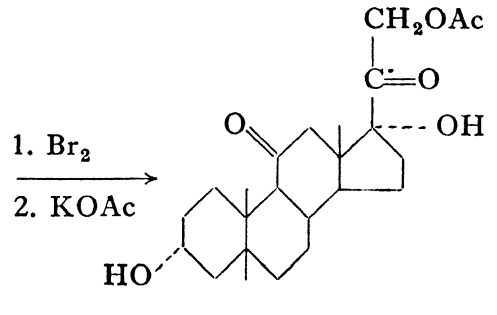

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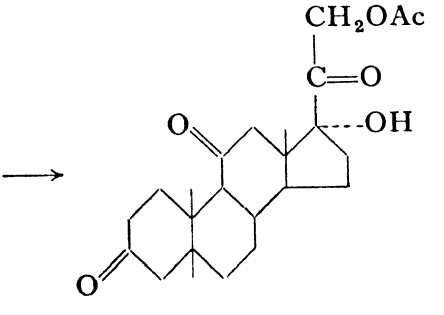

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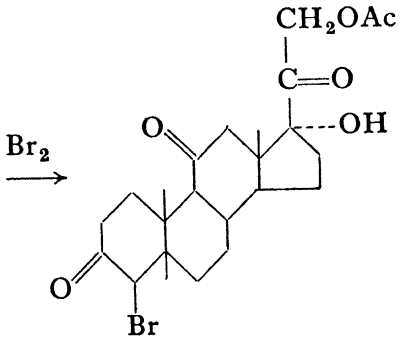

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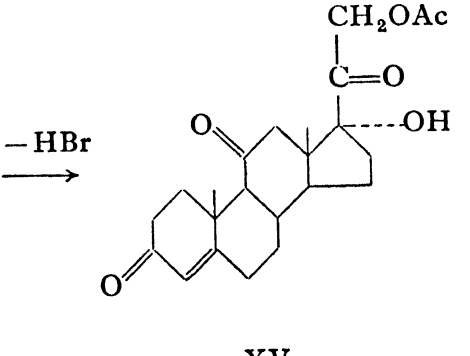


XV

the preparation of 11-oxy steroids was announced by Peterson and his colleagues in 1952 (19). It is of considerable importance since only steroids unsubstituted in ring C are abundant in nature and the chemical methods for the introduction of an 11-oxy group are not single-stage processes; thus the bio-oxygenation procedure represents a major advance in steroid chemistry. Reviews in this field have been published (20, 21, 22).

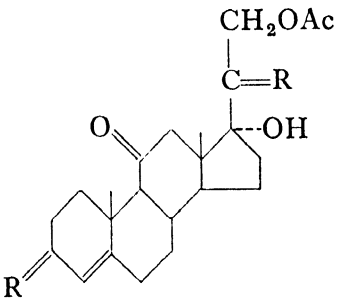
The 11α-hydroxyprogesterone (VII) prepared from progesterone by microbiological oxidation is then reacted with hydrogen with a palladised charcoal catalyst in the presence of alkali. The 11α-hydroxy-3 : 20-dione formed is fortunately a normal pregnene derivative with the A/B *cis* ring junction; hence a simple partial synthesis of cortisone is possible (23). The 11α-hydroxyprogesterone is first reduced at the double bond, then the 11α-hydroxy group is oxidised by chromium trioxide to a ketone and finally reduction of the 3-keto group is effected by sodium borohydride in pyridine leading to 3α-hydroxypregnane-11 : 20-dione (VIII). The 11-keto group characteristic of cortisone is now present and the 17 side-chain requires to be built; the dione is therefore acetylated in its enol form giving 3α : 11 : 20-triacetoxypregn-9(11) : 17(20)-dione (IX). This is epoxidised by the use of perbenzoic acid; only one double bond [at 17(20)] is attacked and X is obtained. Hydrolysis leads to XI and at this stage the 17 α-hydroxyl group is present. The side-chain methyl group is now brominated and the bromo compound acetylated to XII. Oxidation of the hydroxyl group at position 3 by N-bromo-acetamide in *tert.*-butanol gives 21-acetoxy-17α-hydroxypregnan-3 : 11 : 20-trione (XIII). The side-chain is now complete (24) and the 4 : 5 double bond must be reconstituted; the modified Mattox-Kendall procedure is used (25). The nucleus is brominated at position 4 by bromine in acetic acid giving XIV. Normal dehydrobromination with collidine or pyridine affords reasonable yields of a 4 : 5 ketone only if the 17 side-chain is quite simple. Cortisone acetate (XV) is therefore obtained by the following method (26). The bromoketone is first converted to its semicarbazone; by this means the 4-bromo atom is rendered labile. Hydrolysis with aqueous acetic acid yields cortisone acetate. Cortisone is obtained by reaction with methanolic hydrogen chloride (27).

The total synthesis of cortisone and other steroids is not economic compared with the partial synthesis depending on bio-oxidation techniques; their importance lies in the increased command of the chemistry of these biologically important compounds that is now possessed by workers in this field. In addition a very useful body of knowledge of selective reaction procedures has been built up: the theory of stereoisomerism has also been enriched by many examples encountered during the work. There are now four total synthetic routes to 11-oxygenated steroids (28 to 32). Reviews have been published (33, 34).

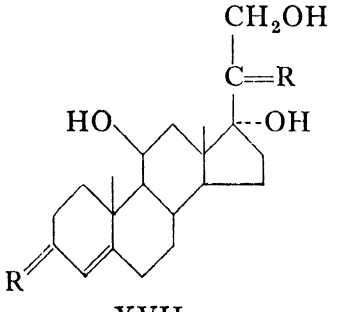
Properties. Cortisone is a white crystalline powder melting at 227° to 229°. The acetate is commonly used in medicine; it is a white powder melting at 248° to 249° (dec.) with $[\alpha]_D$ +208° to +219° (dioxan); it is almost insoluble in water (1 in 5,000), slightly soluble in ethanol (1 in 300), more soluble in chloroform (1 in 4).

Hydrocortisone. Cortisol. 11β : 17α : 21-Trihydroxypregn-4-ene-3 : 20-dione. $C_{21}H_{30}O_5$. (XVIII).

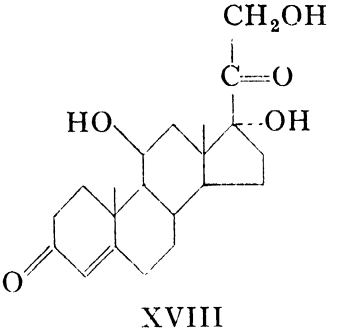
Preparation. Hydrocortisone was isolated by Kendall in 1937; since that date many chemical syntheses of this compound have been published (35 to 39). A recent method (40) in which cortisone acetate is the initial material is as follows.



XVI



XVII

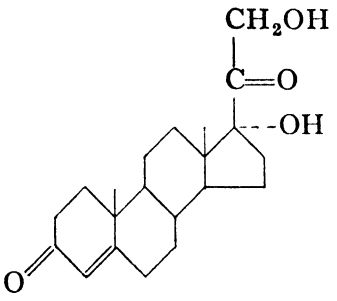


XVIII

The 3 : 20 dione groups are first converted to the 3 : 20-disemicarbazone (XVI) (R= : N·NH·$CONH_2$); they are thus protected during the subsequent reduction of the 11-keto group to 11β-hydroxyl with simultaneous removal of the acetyl group with the formation of hydrocortisone 3 : 20-disemicarbazone (XVII). Potassium borohydride in aqueous tetrahydrofuran is used as the reducing agent; the semicarbazone groups are then split off by the use of nitrous acid giving hydrocortisone (XVIII).

Hydrocortisone has also been prepared by a variation of the synthesis of cortisone from 11α-hydroxyprogesterone described above (41, 42). Micro-organisms have been found with enzyme systems capable of introducing a 11β-hydroxyl group into the steroid nucleus and these have been used in the preparation of hydrocortisone; in one method (43) only a token yield was obtained, but later modifications led to increased yields (44, 45). The starting material was 17α : 21-dihydroxypregn-4-ene-3 : 20-dione (Reichstein's Compound S) (XIX) which is readily available as the result of efficient chemical procedures. Hydroxylation converts it in one step to hydrocortisone by the action of certain moulds.

Properties. Hydrocortisone is a white powder melting at 218° to 221° (dec.) and having $[\alpha]_D$ +163° (ethanol); it is freely soluble in dioxan and methanol, but slightly soluble in water or ether. The acetate is a white solid melting at



XIX

218° to 223° with $[\alpha]_D$ +156° (chloroform). It is almost insoluble in water, slightly soluble in ether, chloroform (0·73 g in 100 ml) or ethanol (0·45 g in 100 ml).

Hydrocortisone has the same qualitative effects as cortisone but differs from it in possessing a powerful local action.

Deoxycortone acetate. 21-Hydroxyprogesterone acetate. 21-Hydroxypregn-4-ene-3 : 20-dione. acetate. $C_{23}H_{32}O_4$. (XXIV).

Preparation. Deoxycortone was synthesised in 1937 (46) before it was known to exist in the adrenal glands, from which it was isolated by Reichstein in 1938 (47). This early synthesis of deoxycortone has been adapted for large scale production of the hormone (48). A more recent route (48, 49) is as follows.

Pregnenolone (XX) is condensed with ethyl oxalate and the resultant ester (XXI) is first hydrolysed to the acid which is treated with iodine in alkaline solution to give the 21-iodo compound (XXII); reaction with potassium acetate in acetone leads to the 21-acetate (XXIII). The 3-hydroxyl group is then oxidised by the Oppenauer method with *cyclo*hexanone as the hydrogen acceptor; deoxycortone is thus obtained (XXIV). Other methods of synthesis have been used (50, 51).

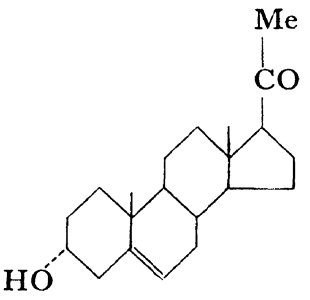
Properties. Deoxycortone melts at 141° to 142° and has $[\alpha]_D$ +178°. The acetate is a colourless tasteless powder melting at 159° to 161°, insoluble in water but soluble in ethanol, acetone or propylene glycol (1 in 50) or in arachis oil (1 in 100).

Deoxycortone has no 11-hydroxy group; it is a mineralocorticoid, i.e. it controls retention of sodium and excretion of potassium in the body. It has been used in the treatment of Addison's disease.

Aldosterone. 11β : 21-Dihydroxypregn-4-en-18-al-3 : 20-dione.

$C_{21}H_{28}O_5 \cdot H_2O$. (XXV).

Preparation. The amorphous residue left after the crystallisation of all the identifiable compounds from adrenal extracts was found still to have a high biological potency. In 1953 three groups of workers (52, 53, 54) isolated a further



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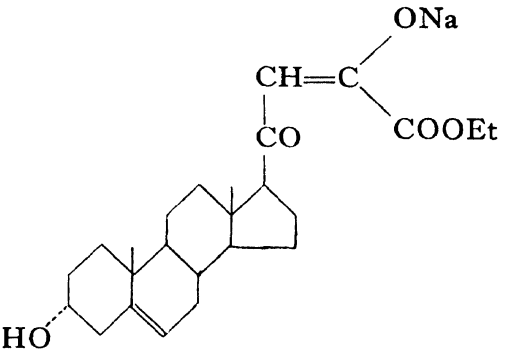
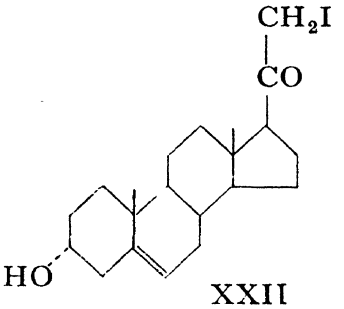


XXI



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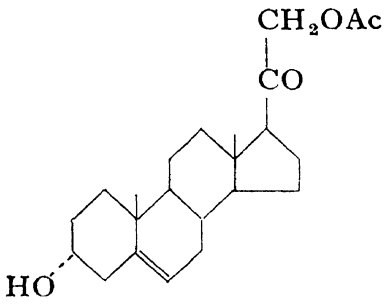

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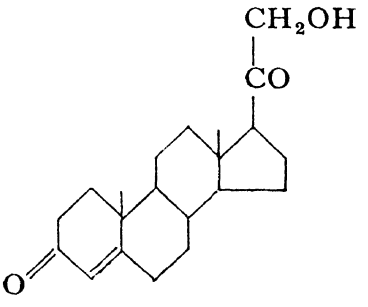

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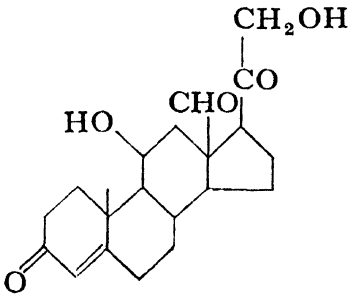
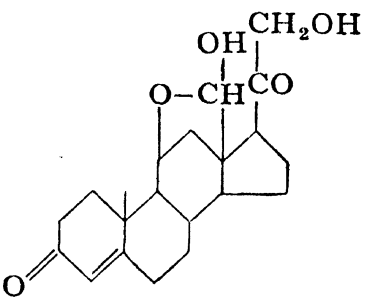


XXV



XXVI

crystalline compound that has been named aldosterone. Certain features of its structure were suggested by the above workers and degradation studies carried out in 1954 (55) led to the formula XXV. It has been suggested that the aldehyde (XXV) exists in equilibrium with the hemiacetal (XXVI). The total synthesis of aldosterone has been announced (56). The compound melts at 154° and again at 183° to 185°.

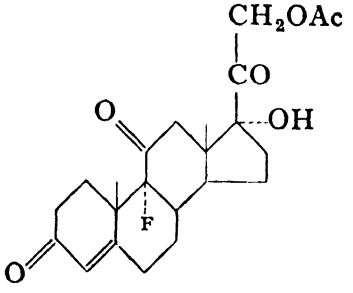
MODIFIED STEROIDS WITH HORMONAL ACTIVITY

Since the successful introduction into therapy of the natural hormones, cortisone and hydrocortisone, synthetic chemical studies have led to modifications in the steroid structure with the production of compounds possessing enhanced activity. Three main modifications have been reported on, viz. halo-compounds, compounds containing a 1 : 2 double bond and 2-methyl steroids.

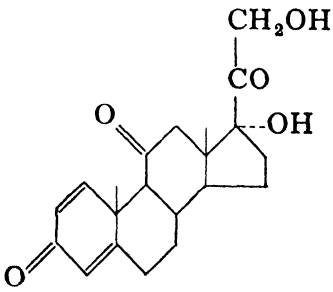
9-Halogenated steroids were first prepared in 1953 (57); of these 9α-fluoro-17-hydroxycorticosterone-21-acetate (XXVII) is known as *fludrocortisone acetate*; it melts at 233° to 234° and has $[\alpha]_D$ +123° (chloroform).

In 1955 Herzog (58) prepared cortisone derivatives with a double bond in the 1 : 2 position; these have been named *prednisone* (XXVIII) and *prednisolone* (XXIX). These compounds have increased anti-inflammatory activity compared with cortisone but, in contrast to the halogenated compounds, the sodium-retaining capacity is unaltered.

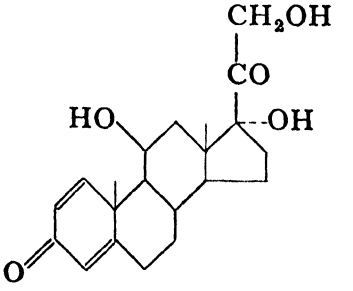
The development of the 2-methyl steroids (59, 60) has resulted in compounds having enhanced sodium-retaining properties especially 2-methylhydrocortisone (XXX).



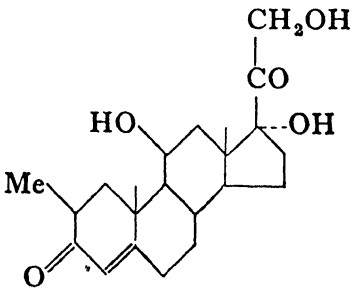
XXVII



XXVIII



XXIX



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CHAPTER XVI

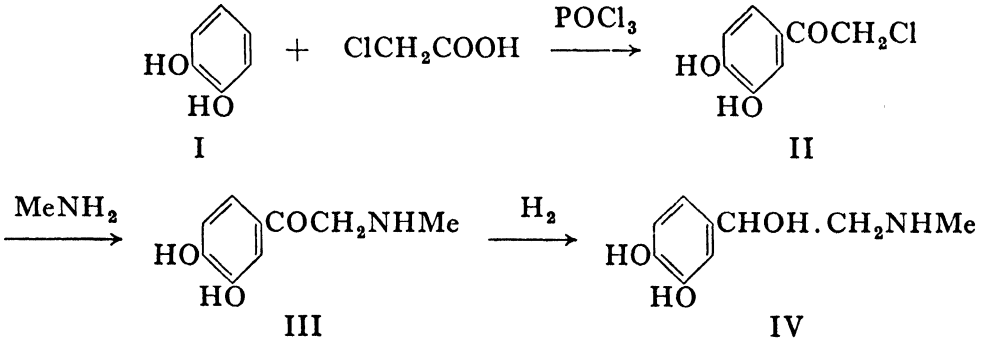
Non-Steroid Hormones

THE non-steroid hormones are derived from the thyroid, parathyroid, pancreas and pituitary glands and from the adrenal medulla. The hormones of the parathyroid are protein-like substances and our knowledge of their structure is far from complete. The substances described below, whose structure is known, are adrenaline and the allied compound, noradrenaline, thyroxine, insulin, oxytocin and vasopressin.

(—)-**Adrenaline.** (—)-Epinephrine. (—)-1-(3 : 4-Dihydroxyphenyl)-2-methylaminoethanol. $C_9H_{13}O_3N$. (IV).

Preparation. Adrenaline and noradrenaline are produced by the adrenal medulla. Adrenaline was the first hormone to be isolated and chemically identified (1, 2). It can be readily obtained from adrenal glands. According to Abel's method the glands are extracted with a solution of trichloroacetic acid in ethanol. The mixture is filtered after 24 hours and extracted twice more with the menstruum. Adrenaline is readily oxidised and therefore the process must be carried out in the presence of a reducing agent (3). The mixed filtrates are concentrated to low bulk and, after again filtering, a slight excess of ammonia is added. The crude adrenaline is filtered off and washed with water, ethanol and ether. The crude adrenaline is extracted with ethanolic oxalic acid solution, inorganic impurities remaining behind. After filtration and dilution with water, ammonia is added to precipitate the base which is freed from ammonium oxalate by thorough washing.

Adrenaline was synthesised in 1904 by the following method (4, 5, 6). Catechol (I) is reacted with chloroacetic acid in phosphorus oxychloride and the substituted acetophenone (II) obtained is condensed with methylamine in aqueous ethanol. The product, 3 : 4-dihydroxymethylaminoacetophenone (III) is converted by reduction to (±)-adrenaline (IV). The reduction may be carried out by the use of aluminium amalgam, catalytic methods (7, 8), metal hydrides



I II III IV

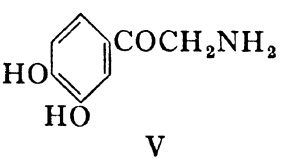
or aluminium *iso*propoxide in *iso*propanol (9). Racemic adrenaline can be resolved with (+)-tartaric acid; the (−)-adrenaline (+)-tartrate obtained is made alkaline with ammonium hydroxide solution to yield the required (−)-adrenaline (10, 11). The residual (+) isomer is racemised and the process repeated. The acid oxalate has been used for the purification of adrenaline (12).

Alternative syntheses of adrenaline have been published (13 to 17).

Properties. (−)-Adrenaline is a white crystalline powder. M.p. 211°. It is slightly soluble in water but insoluble in ethanol, ether and chloroform; the aqueous solution is alkaline to litmus. Neutral or alkaline solutions are unstable and become red on exposure to air. It is soluble in mineral acids, in tartaric acid and in caustic alkalis, but not in aqueous ammonia or alkali carbonates. Adrenaline is mainly injected in the form of the acid tartrate. Solutions may be protected from oxidation by the addition of a reducing agent such as ascorbic acid or sodium metabisulphite. (−)-Adrenaline (+)-hydrogen tartrate melts at 154° to 155°. The specific rotation of (−)-adrenaline is −53° (in dilute hydrochloric acid).

(−)-Noradrenaline. (−)-Norepinephrine. (−)-Arterenol. (−)-1-(3 : 4-Dihydroxyphenyl)-2-aminoethanol. $C_8H_{11}O_3N$. (VII).

Preparation. (−)-Noradrenaline was shown to be present in the adrenal medulla in 1949 (18) and it may be separated from adrenaline extracted from the glands (19). Racemic noradrenaline was synthesised many years ago by the reduction (20) of amino-3 : 4-dihydroxyacetophenone (V), the corresponding



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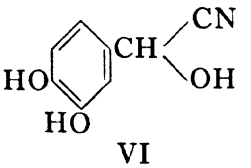
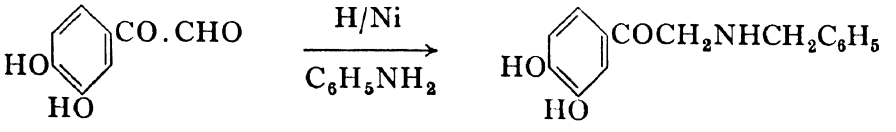
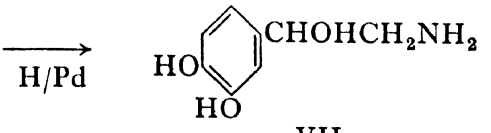


VI

nitro compound or of protocatechuic aldehyde cyanhydrin (VI). In a more recent method (21) the following route was followed:





VII

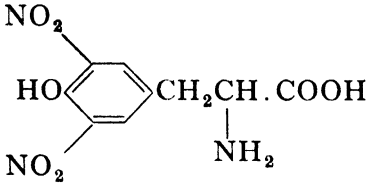
Racemic noradrenaline can be resolved in the same way as adrenaline (22).

Properties. M.p. 216·5° to 218° (dec.); $[\alpha]_D^{25}$ −37·3° (c=5 per cent in water with one equivalent of HCl). The hydrochloride melts at 145° to 146°; $[\alpha]_D^{25}$ −40° (c=6 per cent). (−)-Noradrenaline (+)-hydrogen tartrate monohydrate melts at 102° to 104°; $[\alpha]_D^{25}$ −11° (c=1·6 per cent in water).

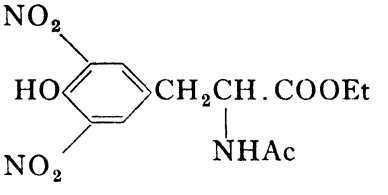
(—)-**Thyroxine.** $C_{15}H_{11}O_4NI_4$. (XII). It was found in the late nineteenth century that removal of the thyroid glands of experimental animals caused the appearance of myxoedema. Oral administration of thyroid extract was found to abolish the condition in human beings. Kendall isolated the active principle from thyroid gland tissue in 1919 (23) and named it thyroxine; this substance was the first material to be isolated from the tissues of higher animals and shown to contain iodine. Harington improved the method of extraction (24) and established the constitution of thyroxine (25).

Preparation. Thyroxine is present in the thyroid gland in a bound condition; it forms part of a protein and is freed by hydrolysis with baryta. The barium salt of thyroxine so obtained is suspended in dilute aqueous sodium hydroxide and the barium ion is removed as barium sulphate. The filtrate is treated with 50 per cent sulphuric acid while boiling until just acid to Congo red. The precipitate is dissolved in *N* sodium hydroxide, ethanol is added to 80 per cent concentration, filtered and the boiling filtrate is acidified with acetic acid. Thyroxine separates in a partly crystalline condition. It may be purified by dissolving in boiling 0·5 per cent sodium carbonate solution; on cooling, the sodium salt separates out and may be converted into thyroxine by dissolving in ethanol and again precipitating with acetic acid (24). Improvements in this method have been patented (26).

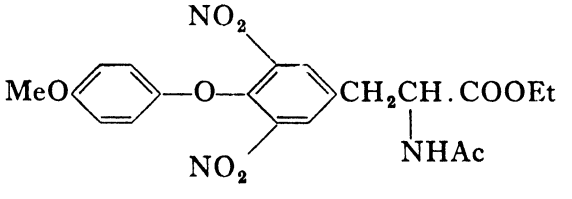
Synthesis. (—)-Thyroxine was synthesised by Harington in 1927 (25) but a more convenient synthesis has been published by Hems *et al.* (27). The starting material is (—)-tyrosine and there is no appreciable loss of optical activity during the synthesis so that (—)-thyroxine is obtained as the final product. (—)-Tyrosine in sulphuric acid is converted by nitric acid to 3 : 5-dinitrotyrosine (VIII). This is acetylated and the acetate is esterified by ethanol and 4-toluenesulphonic acid in chloroform. The product IX is then condensed in pyridine with 4-methoxyphenol to yield the substituted diphenyl ether, viz. ethyl 3 : 5-dinitro-4(4-methoxyphenyl)-N-acetylphenylalaninate (X). This is hydrogenated to the



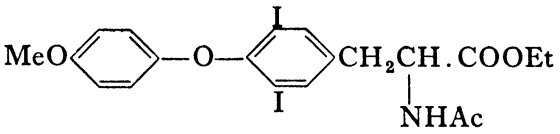
VIII



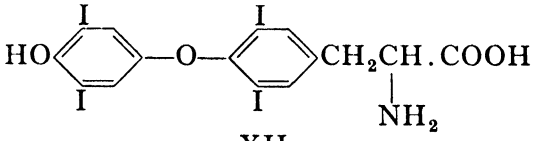
IX



X



XI



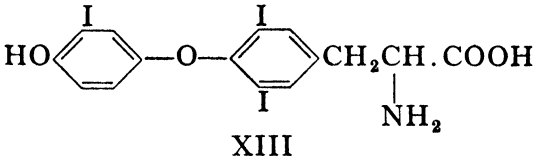
XII

corresponding diamine. The Sandmeyer reaction by which this diamine is converted to the diiodo derivative (XI) is of special interest; the diazotisation reaction is carried out under anhydrous conditions and, instead of the usual aqueous sodium nitrite solution, nitrosylsulphuric acid is used. This is a useful reaction when the amine is only weakly basic and often succeeds when the normal diazotisation technique is inadequate (28). The diiodo compound (XI) is first demethylated with hydriodic acid in glacial acetic acid and then the phenolic ring is iodinated by iodine and potassium iodide in aqueous triethylamine; on hydrolysis (—)-thyroxine (XII) is obtained. The important steps in the synthesis have been patented (29).

Racemic thyroxine can be resolved by enzymatic hydrolysis (30).

Properties. (—)-Thyroxine has a m.p. 233° to 235° (dec.) and $[\alpha]_D$ —5·7° (in *N* ethanolic NaOH); the sodium salt has $[\alpha]_{5461}$ —3·8° (60 per cent ethanol). The sodium salt, which is a pentahydrate, is used in the treatment of myxoedema.

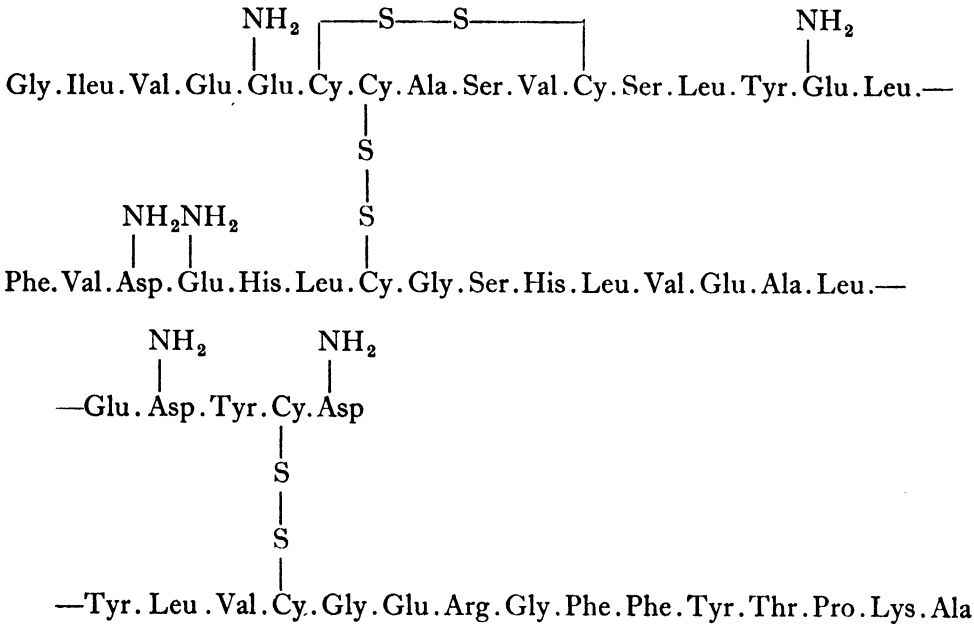
Triiodothyronine, (XIII), has been isolated from the thyroid gland and from the blood. It has been suggested (31) that triiodothyronine is formed from thyroxine by deiodination in the extrathyroidal tissues and is in fact the active hormone.



XIII

Insulin. Mol. wt., 5733. (XIV). Insulin is secreted by the Islets of Langerhans, groups of cells situated in the pancreas. It is an essential hormone for the metabolism of carbohydrates in animals and is an important therapeutic agent for the treatment of diabetes mellitus, a disease in which there occurs a disturbance of carbohydrate metabolism due to an impairment of the natural secretion of insulin from the pancreas. In 1922 it had been known for some time that symptoms characteristic of diabetes mellitus in man appeared when the pancreas was removed from experimental animals and in that year Banting and Best (32) obtained an extract of pancreatic tissues that was successful in clinical trials; insulin in the form of an acid aqueous purified extract was soon manufactured

on a large scale. It was first obtained in crystalline form by Abel in 1927 (33) and improvements in its manufacture have since been described (34, 35). Insulin is a protein composed of 51 amino acids; there are appreciable differences in the composition of insulin obtained from different species but the complete formula XIV for ox insulin has been elucidated by Sanger (36).



XIV

Extraction. Banting and his co-workers stated the basic problems of insulin extraction, the most important of which is the avoidance of the destructive action of proteolytic enzymes; this is effected by the use of ethanol to precipitate most of the enzymes without loss of insulin and by the use of sufficient acid to give a pH below 3·5, at which the enzymes are inactivated. The other problems are the purification of the insulin from inactive protein and lipoid material. Details of the method used by the British manufacturers have not been published (37) but it is based on these essential principles; the yield and quality of the product depend largely on careful attention to details at each stage of the process. The following description of the extraction procedure is based on that of Romans (34). The usual source of insulin in this country is ox pancreas, but pig glands are also used. The glands are frozen as soon as possible after the death of the animal and maintained in that condition until extracted; they are then minced into acidified ethanol of such a strength that the final extract contains about 70 per cent of ethanol. The acidifying agent may be a mineral acid but organic acids have been used (38); the extract is centrifuged to remove protein and fatty material from which the proteolytic enzymes may be recovered (39). The filtrate is adjusted to pH 8 by the addition of ammonia (40) and again filtered; the filtrate is acidified and evaporated under vacuum to remove the ethanol,

when fat separates and is removed. The insulin may then be purified by precipitation as the picrate or it may be salted out and crystallised by careful adjustment of the pH (41).

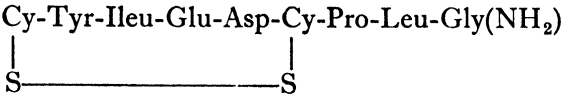
Properties. Insulin is almost insoluble in water at the isoelectric point at pH 5·2, but it is readily soluble in more acid or alkaline media; it may be precipitated by half saturation with ammonium sulphate or sodium chloride; it is insoluble in absolute ethanol. Insulin is precipitated by picric, phosphotungstic and trichloroacetic acids; it is stable for a considerable time in slightly acid solution but the activity disappears in alkaline conditions.

Long-acting insulins. Ordinary insulin is soluble at the pH of the blood (pH 7·3) and therefore, although on injection it has an almost immediate effect, this is transient and the diabetic patient needs frequent doses to maintain his blood sugar at the normal level. Numerous attempts have been made to overcome this difficulty and to prepare an insulin compound having a more prolonged action. Hagedorn in 1935 (42) introduced protamine insulin in which the insulin is combined with a protein, protamine, obtained from salmon roes. Scott (43) showed that the addition of zinc formed protamine zinc insulin, an insoluble compound, that could be injected as a suspension and for the first time brought a single daily injection within reach (44). N.P.H. insulin (Neutral Protamine Hagedorn), also known as Isophane Insulin, was later introduced. It differs from ordinary protamine zinc insulin in not containing an excess of protamine and in being miscible with unmodified zinc insulin (45). Other complexes of insulin that have been suggested are: Surfen insulin (46) in which 1 : 3-bis-(2-methyl-4-amino-6-quinolyl)urea is used; globin insulin (47) containing globin, a protein obtained from beef haemoglobin; and polylysine insulin (48) in which insulin is combined with a polypeptide have also been used.

In 1952 Hallas-Møller and his co-workers reported on a new long-acting insulin (49 to 51). They have confirmed and extended the work of Sahyun (52) who showed in 1939 that insulin could be precipitated as a zinc complex by zinc chloride in the presence of sodium acetate as the buffering agent. They suggest that, when the preparation is buffered by phosphate or citrate as in the earlier products, the zinc combines preferentially with the buffer and the insulin is rendered soluble. The new long-acting insulin is as insoluble as protamine zinc insulin at the pH of the blood and thus protamine and other similar compounds are unnecessary. The method of preparation is as follows. Zinc insulin is made from thrice crystallised insulin by the addition of 2 mg of zinc for each 1000 units of insulin in the presence of sodium acetate; when the pH is between 5 and 6 the insulin compound is crystalline and, once formed, it is soluble over a wide range of pH; outside this range of pH the compound is an amorphous solid. The length of action of the insulin compound varies in proportion to the particle size. This amorphous material has been named Insulin Zinc Suspension (amorphous). It exerts a hypoglycaemic action in man for about 12 hours; the crystalline material is named Insulin Zinc Suspension (crystalline) and exerts its effect over 24 to 36 hours; a stable mixture of 3 parts of amorphous to 7 parts of crystalline material is called simply Insulin Zinc Suspension and has an effect lasting for 24 hours; this is due to the early action of the amorphous insulin

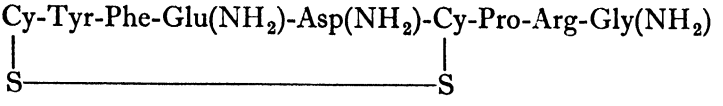
followed by the more prolonged effect of the crystalline material. The absence of foreign proteins from these newer insulin preparations lessens the possibility of allergic reactions after injection. Soluble insulin is still used in severe diabetic ketosis.

Oxytocin. (XV). This hormone causes contraction of the uterus and has, together with vasopressin, been isolated from the posterior lobe of the pituitary gland. Purified oxytocin has been obtained by the use of the Craig countercurrent technique (53). Oxytocin is a protein composed of 9 amino acids; the structural formula was proposed independently by Tuppy (54) and Du Vigneaud and his colleagues (55, 56); it has been synthesised by the latter workers and by Boissonass (57). All the amino acids shown in the formula for oxytocin have the (—) configuration. The chemistry of the hormones of the posterior pituitary gland has been reviewed by Pincus and Thimann (58).



XV

Vasopressin. Hypophamine. (XVI). This compound, which causes a rise in blood pressure on injection and also has diuretic properties, has been isolated from the posterior pituitary gland (59). Vasopressins from the ox and the pig are similar but not identical compounds; an arginine residue in the former hormone is replaced by lysine in the latter. Both compounds have been synthesised by Du Vigneaud and his colleagues (60). The formula of bovine vasopressin is shown below.



XVI

Vasopressin tannate has been introduced as a compound with a long duration of action (61).

Corticotropin. Adrenocorticotrophic hormone. ACTH. This hormone stimulates the adrenal cortex to secrete its series of hormones. It is extracted from the anterior lobe of the pituitary gland (62, 63). Little is yet known of its structure except that it is a polypeptide composed of amino acid residues.

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CHAPTER XVII

Antibiotics

Introduction. The antibiotics covered in this chapter are penicillin, streptomycin, chloramphenicol, the tetracycline group, erythromycin, neomycin and polymyxin B.

To Pasteur and Joubert goes the honour of having published the first account of microbiological antagonism. In 1877 (1) they discovered that an unidentified air-borne bacillus was able to check the growth of *Bacillus anthracis*, and they envisaged the use of this activity for therapeutic purposes. For many years before the discovery of penicillin, numerous workers showed that bacteria, yeasts and moulds were able to inhibit the growth of other micro-organisms. In some cases metabolic antibacterial products were isolated from the culture fluids. Products of this type are now known as antibiotics. The clinical use of these early antibiotics was limited by their high toxicity and they were therefore comparable with the known antiseptics such as formaldehyde and mercuric chloride. In September 1928 came the discovery of penicillin. Air-borne spores of the mould *Penicillium notatum* landed on a bacterial culture plate in Fleming's laboratory in London. The mould grew on the surface of the culture medium and in its vicinity the bacterial growth was suppressed. Fleming was at that time interested in the problem of natural bacterial inhibitors, and so he grew a pure culture of the mould and then determined which of the main groups of bacteria were sensitive to the culture fluid. He suggested that since the culture fluid was neither toxic nor irritant, it might well be an effective antibacterial agent for injection into areas infected with penicillin-sensitive organisms (2).

At this time, six years before the introduction of the sulphonamides, the attitude of most people towards bacterial chemotherapy was entirely negative and Fleming's suggestion was not acted upon. In 1930, Raistrick and his colleagues (3) attempted to isolate and purify the antibacterial agent present in the culture fluid, but they had little success. They did, however, contribute several new facts. They found that the mould could be grown upon a synthetic medium, and that it produced besides penicillin, a yellow pigment which they named chrysogenin. They found that, although on extraction of the acidified culture fluid with ether the antibacterial activity passed into the solvent, evaporation of the ether destroyed this activity.

There the matter rested until 1938. In that year a background of successful research upon the natural antibacterial substance lysozyme led Florey and Chain at Oxford to consider the extension of their work to other antibacterial substances. A review of the literature by Chain showed that in common with a few other antibacterial agents, Fleming's penicillin was worthy of further attention. Chain has stated (4) that the work upon penicillin was undertaken purely for the purpose

of establishing its chemical nature and was not motivated by the belief that penicillin was a new antibiotic of great potential therapeutic value. The Oxford workers soon discovered the essential property for the concentration of penicillin to be the relative solubility of the substance under acid conditions in certain organic solvents, and the solubility of its sodium and barium salts in water. By taking advantage of this reversal of solubility a weak solution of crude penicillin was obtained. In 1940, trials upon mice infected with pathogenic bacteria demonstrated that penicillin had therapeutic value (5) and in 1941 the first clinical trials were carried out (6). British pharmaceutical houses were extremely interested in the future of penicillin as a therapeutic agent, but England in 1941 was a country at war, and there was at first a lack of official support for any plans for the commercial production of penicillin.

Florey and Heatley visited the U.S.A. in June 1941 to seek aid from American manufacturers. As a result, American workers investigated and solved the formidable problem of the submerged culture method for the manufacture of penicillin. The mould used was *Penicillium chrysogenum* since it was found to be more suitable for deep culture than *P. notatum.* Another notable advance in manufacturing technique was the use of a culture medium containing corn steep liquor as a source of nitrogen. This liquor is a by-product of the starch industry in the maize-producing areas of the U.S.A. Maize is soaked in water containing sulphur dioxide during one stage in starch manufacture and it is this liquor which is used in antibiotic production. The deep-culture method of production of penicillin has been universally adopted, and it forms the basis for the production of the other antibiotics.

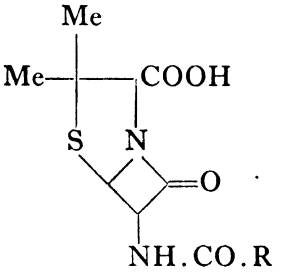
The discovery of penicillin was due to the fortuitous growth of *Penicillium notatum* upon Fleming's culture plate. Florey (7) has described this as 'quite one of the luckiest accidents that have occurred in medicine, for, without exception, all the other mould antibiotics so far examined are poisonous'. The discovery of the other antibiotics now in use has been the result of an immense amount of planned research beginning with the preliminary screening of thousands of micro-organisms and their metabolic products. *Actinomycetes* (or *Streptomycetes* as they have been called) are micro-organisms found in the soil. At one end of this ill-defined group are bacteria-like organisms and at the other the *Streptomyces* which are much-branched elongated rods related to the moulds. In 1939 a team of workers in the U.S.A. began a systematic investigation of the antibacterial substances produced by the actinomycetes. In 1944 (8) Waksman crowned a life-time of research upon actinomycetes by the isolation of streptomycin from cultures of *Streptomyces griseus.* Clinical trials (9) established its usefulness and later it was shown to be a powerful tuberculostat (10). Streptomycin was soon in commercial production by the deep-culture method.

The isolation of chloramphenicol from a culture of *Streptomyces venezuelae* was announced in 1947 (11). The micro-organism used was isolated from a soil sample taken from a mulched field in Venezuela. The same antibiotic substance was later obtained independently from another soil culture (12). Chloramphenicol was originally prepared by the fermentation technique, but it was soon synthesised and is now produced commercially by chemical methods.

Chlortetracycline was isolated from cultures of *Streptomyces aureofaciens* in 1948 (13) and oxytetracycline from cultures of *Streptomyces rimosus* in 1950 (14). Tetracycline was prepared in 1953 (15). Other useful antibiotics obtained from cultures of *Streptomyces* are erythromycin isolated from cultures of *S. erythreus* in 1952 (16) and neomycin first obtained by Waksman and his colleagues in 1949 (17) from cultures of *S. fradiae.*

All the above antibiotics are produced by *Penicillium* or *Streptomyces.* Polymyxin, which was isolated from the culture fluid of *Bacillus polymyxa* by independent groups of workers in 1947 (18, 19, 20), is an antibiotic produced by a bacillus.

Penicillin. There exists a family of penicillins in which the individual members differ only in the nature of the side-chain R in formula I.



I

The most noteworthy penicillins are listed below:

Name	Side-Chain R.	Formula
Penicillin F	Pent-2-enyl	$C_{14}H_{20}N_2O_4S$.
Penicillin G	Benzyl	$C_{16}H_{18}N_2O_4S$.
Penicillin K	Heptyl	$C_{16}H_{26}N_2O_4S$.
Penicillin V	Phenoxymethyl	$C_{16}H_{18}N_2O_5S$.
Penicillin X	4-Hydroxybenzyl	$C_{16}H_{18}N_2O_5S$.

The type of penicillin that will be formed in a particular fermentation depends upon the mould strain and culture method used. Penicillin F was found to be the main product obtained by British workers when *Penicillium notatum* was grown by the surface-culture method. American workers using *Penicillium chrysogenum* and the submerged-culture technique obtained mainly penicillin G (benzylpenicillin). Studies on the relative stability, ease of production and efficacy of the different penicillins have led to the general use of penicillin G in medical practice. The production by the mould of penicillin G at the expense of other forms is due to the presence in the medium of certain constituents, derived from proteins, that are termed precursors. These chemical compounds influence the course of the synthesis by the mould. Phenylethylamine, for example, has been detected in corn-steep liquor and aids the mould to synthesise benzylpenicillin by supplying it with the preformed benzyl group. Coghill (21)

in 1943 found that the addition of phenylacetic acid to the medium stimulated the formation of benzylpenicillin and it is now common practice (22) to add 0·05 per cent of precursor to influence the course of the fermentation. Many hitherto unknown penicillins have been obtained by the use of this technique (23).

The mould strains now used for industrial fermentation have been obtained by careful selection (24). High-yielding strains have been obtained by mould mutations brought about by X-rays, ultra-violet rays and nitrogen mustards. By these means strains yielding 3,000 units per ml have been produced. In contrast the penicillin solutions used by the Oxford workers contained only 50 units per ml.

Benzylpenicillin. $C_{16}H_{18}N_2O_4S$. (I).

Preparation. All the benzylpenicillin produced commercially is obtained by the fermentation process. A chemical synthesis has been evolved, but it is not competitive with the fermentation method, as the yield is very poor.

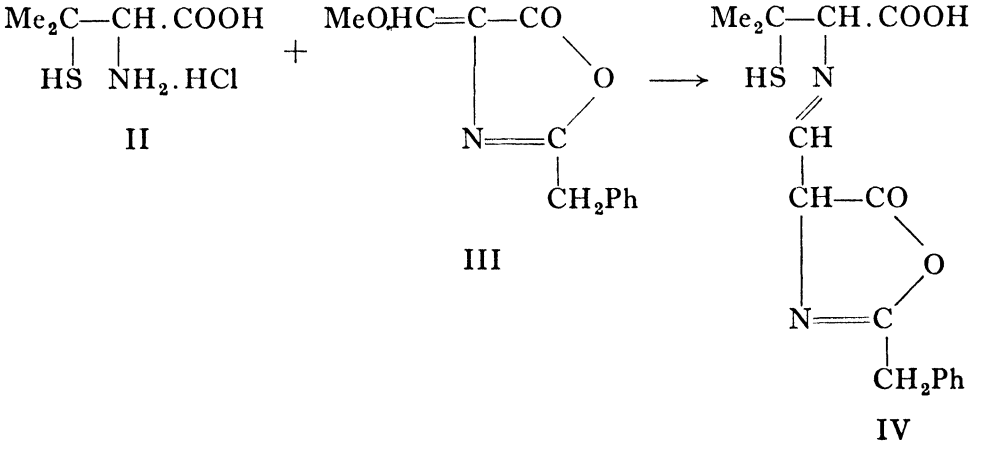
Penicillin is a metabolic product of the mould fermentation of an aqueous nutrient solution. The master culture, which in recent years has often been *Penicillium chrysogenum* Wis.Q.176, is used to seed a flask of nutrient broth and the mould obtained is moved successively to a 10-gallon, thence to a 100-gallon, to a 1,000-gallon and finally to a 10,000-gallon vessel. This final fermentation vessel contains the culture medium which has been heat-sterilised. A typical culture medium (25) contains the following parts by weight of solids in 1,000 parts by volume of aqueous solution: lactose 20, corn-steep solids 20, sodium nitrate 3, dipotassium phosphate 0·05, magnesium sulphate 0·125, calcium carbonate 1·8, phenylacetic acid 0·5.

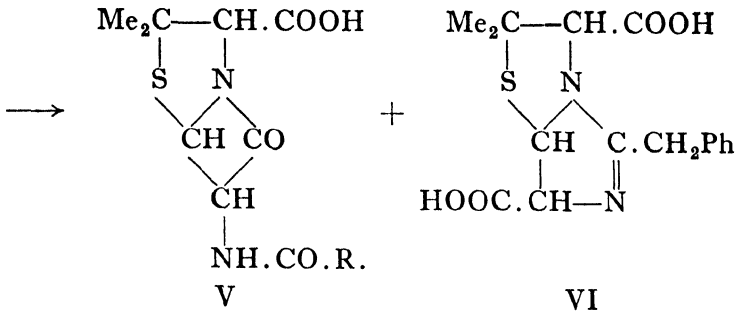
The fermentation is carried on for two to three days at a controlled temperature of 24° C., and during this period sterile air is blown through the medium at the rate of 0·5 to 1 volume of air to 1 volume of medium per minute. The fermentation vessel is sealed, and a small positive air pressure is kept inside the vessel to prevent the entry of harmful material from the outside air. Some bacteria, notably strains of *Escherichia coli*, secrete the enzyme penicillinase which ruptures the basic penicillin structure. These organisms must therefore be rigorously excluded from the working area. This problem of sterility is the most important single factor in penicillin manufacture. The air used is sterilised by filtration through slag wool or charcoal and all pipe-work and valves serving the fermenter are steam jacketed. The even distribution of air through the medium is aided by high power stirring which breaks down the mycelium mass and prevents coalescence of the air bubbles (26). The combination of air and cellular material present in a fermenter is ideal for foam formation and therefore periodically during the fermentation a charge of sterile anti-foam agent is added. A 3 per cent solution of octadecanol in lard oil has been used for this purpose and it has been suggested that the lard oil also acts as a source of energy and helps to increase yields.

After fermentation, the vessel contents are cooled rapidly and the mycelium is filtered on a sterile rotary filter. The cooled filtrate is acidified with phosphoric acid and butyl or amyl acetate is added. The mixture is passed through a high-speed, counter-current extraction machine and then centrifuged. Emulsions are

commonly formed and are broken with the aid of a wetting agent (27). The solvent solution of penicillin is then shaken with chilled sodium carbonate solution and an aqueous solution of crude sodium benzylpenicillin is obtained. The transfer to a solvent and back to aqueous alkali is repeated and the weak solution of sodium benzylpenicillin is the starting-point for the purification stage. Manufacturers have claimed a bewildering number of methods by which the purification may be effected. The following examples are therefore not completely representative of the published techniques. The penicillin may be precipitated from the solution in a solvent such as chloroform by the addition of an organic base such as N-ethyl hexamethyleneimine (28), N-ethylpiperidine (29) or triethylamine. The amine salt so obtained is filtered and converted to sodium penicillin. The triethylammonium salt, for example, is reacted with sodium iodide in anhydrous ethanol. Sodium benzylpenicillin crystallises out and is filtered and dried (30). Alternatively, an aqueous solution of sodium benzylpenicillin can be treated with procaine hydrochloride and the precipitated procaine penicillin converted to the sodium salt of benzylpenicillin (31). Where the sodium benzylpenicillin is present as a concentrated aqueous solution, it may be salted out by the addition of ammonium sulphate (32).

Chemical synthesis of benzylpenicillin. The synthesis of benzylpenicillin was achieved by du Vigneaud and his colleagues in 1946 (33, 34). The low yield obtained, however, renders the method impractical for commercial use. (+)-Penicillamine hydrochloride (II) in water was added to an ice-cold solution of 2-benzyl-4-methoxymethylene-5-oxazolone (III) in pyridine containing triethylamine. Crude benzylpenicillenic acid (IV) was obtained from this conversion and it was dissolved in pyridine to which hydrogen chloride and triethylamine had been added. The mixture was heated at 130° for 7 minutes and the solvent evaporated at 50°. The residual solid was dissolved in chloroform and extracted first into an aqueous buffer and then into ether. The solid residue obtained on evaporation of the ether was subjected to an intensive separation, using the counter-current distribution technique. Material so obtained was converted to the triethylammonium salt. This compound was found to be identical with that





V VI

made from natural benzylpenicillin. The overall yield of benzylpenicillin (V) was 0·14 per cent of theoretical. A 19 per cent yield of benzylpenillic acid (VI) was obtained as a by-product. The chemistry of penicillin synthesis has been reviewed by Ohle (35).

Preparation of other penicillins. As mentioned above (23) a standard method is used for the biosynthesis of new penicillins. The type of penicillin obtained is determined largely by the precursor present in the nutrient liquor. Phenoxymethylpenicillin (penicillin V), for example, is obtained when 2-phenoxyethanol or phenoxyacetic acid are used as precursors (36, 37). Penicillin V would appear to be more stable under acid conditions than benzylpenicillin and it can therefore be administered orally, since it is only slowly attacked by stomach acids. Penicillin V has been synthesised (37a).

Properties of the penicillins. All the penicillins are fairly strong acids with a pK value of approximately 2·7. They are soluble in most organic solvents except for the aliphatic hydrocarbons. 4-Hydroxybenzylpenicillin is exceptional, being comparatively insoluble in chloroform. The penicillins are only sparingly soluble in water and are rapidly deactivated by aqueous acids to give penillic acids.

Clinically, the penicillins are often employed in the form of their sodium or potassium salts or as compounds with amines. Sodium benzylpenicillin has a m.p. of 215° and an $[\alpha]_D^{22}$ of +302°. It is soluble in water and fairly soluble in methanol, but only sparingly soluble in ethanol. It is almost insoluble in *iso*-propanol, normal and tertiary butanol, acetone, ethyl acetate and pyridine. Pure sodium benzylpenicillin is used as a standard for penicillin potency. One penicillin unit is equivalent to 0·000006 g of sodium benzylpenicillin. The potassium salt melts at 214° to 217° and has an $[\alpha]_D^{22}$ of +310°. The ammonium salt melts at 137° to 138°. Triethylammonium benzylpenicillin melts at 145° to 147° (dec.) and has an $[\alpha]_D^{23}$ of +236° and the N-ethylpiperidinium salt melts at 167° to 168° (dec.).

Sodium 2-pentenylpenicillin forms a trihydrate with a melting-point of 204° to 205° and has an $[\alpha]_D^{21}$ of +316°. The benzylammonium salt melts at 126° to 127°. Sodium 4-hydroxybenzylpenicillin melts at 228° to 235° and has a comparatively low rotation at $[\alpha]_D$ +267°. The benzylammonium compound melts at 134° to 135°. It is a monohydrate.

The potassium salt of penicillin V has a m.p. of 263° (dec.) and $[\alpha]_D^{25}$ +223° (c=0·2 in water).

Long-acting penicillin compounds. The procaine salt of penicillin was the

first successful long-acting penicillin compound; many other similar compounds have been introduced. The method of preparation is normally that in which an amine salt is caused to react with sodium benzylpenicillin. Procaine penicillin, for example, is made by the reaction of procaine hydrochloride with sodium benzylpenicillin (38). The product has a molecular formula of $C_{29}H_{38}N_4O_5S$ and a m.p. of 129° to 130°.

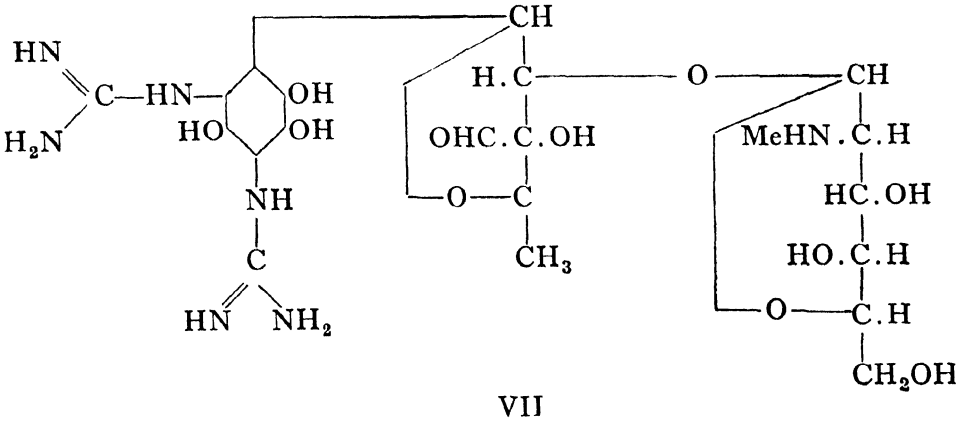
In 1951 Szabo and his colleagues introduced NN-dibenzylethylenediamine dipenicillin G (benzathine penicillin G) (39). The molecular formula is $C_{48}H_{56}N_6O_8S_2$ and the m.p. 123° to 124°. The compound is soluble in dimethylformamide, moderately soluble in ethanol, sparingly soluble in acetone and almost insoluble in water. Dibenzylamine forms a salt with penicillin (40), as also does 2-phenylethylbenzylamine (41).

Recently, several antihistamines have been combined with penicillin to give salts that on hydrolysis in the body liberate penicillin and the antihistamine which it is claimed reduces the incidence of allergic reactions (42, 43). Penethamate is the name for the hydriodide of the 2-diethylaminoethyl ester of benzylpenicillin (44). It is prepared by reacting potassium benzylpenicillin in *iso*propanol with diethylaminoethyl chloride (45). Potassium chloride is formed and is filtered. A solution of citric acid is added to the filtrate and the citrate which separates can be converted to the hydriodide by reaction with potassium iodide.

Penicillin has also been administered in conjunction with 4-(dipropylsulphamyl)benzoic acid (46). The latter compound renders the penicillin long-acting by inhibiting its excretion by the kidneys.

Streptomycin. $C_{21}H_{39}N_7O_{12}$. (VII).

Preparation. The announcement of the discovery of streptomycin was made in 1944 (8). Its formula was finally elucidated in 1948 (47). Streptomycin was originally prepared by the surface-culture technique but commercial exploitation of the process followed quickly, and now streptomycin is produced by a deep-culture process, similar to that used for penicillin.



VII

Spores of *Streptomyces griseus* are produced on agar and a spore suspension is then used to inoculate the nutrient medium in small conical flasks. The mycelium

so produced is transferred first to a small tank and then to a layer tank and finally to a 15,000-gallon fermenter. The strains of *S. griseus* that produce streptomycin are rare in nature and an active strain may gradually deteriorate. It is therefore necessary continuously to select active strains from the mother culture. The usual methods of inducing mutants in *Penicillia* have been used also for *Streptomyces* (48). The culture medium used may have soya-bean or cotton-seed meal in place of the more usual corn-steep liquor as a source of nitrogen. The fermentation is carried out at 25° for about three days. An anti-foaming agent is added to the medium and sterile aeration is employed. In the early stages of growth *Streptomyces griseus* is susceptible to attack by a virus-like agent termed an actinophage and so sterility during the fermentation is essential. The reaction of the medium during the fermentation changes first to acid and then to alkaline. The point of highest alkalinity, i.e. pH 8·2 to 8·6, corresponds to the highest streptomycin production. The mycelium is filtered and the filtrate is ready for extraction of the streptomycin. The penicillin method of solvent extraction of the aqueous solution is apparently not applicable to streptomycin and adsorption upon charcoal (49, 50) and upon a cationic exchange resin has been employed. The latter method is more efficient (51). Alternatively, tungstophosphoric acid may be added to the aqueous streptomycin liquor and the precipitated tungstophosphate converted to the sulphate (52, 53).

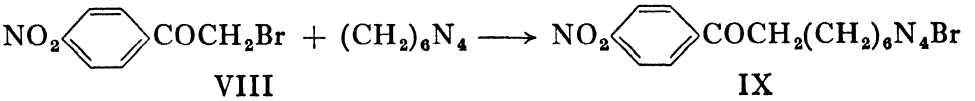
Properties. Streptomycin is a water-soluble base that is stable at or under 28° and between pH 3 and 7. It forms a trihydrochloride of $[\alpha]_D^{26}$ −86·1°. This compound combines with calcium chloride to form a complex (54). Streptomycin has been of great use as a tuberculostat.

Dihydrostreptomycin. $C_{21}H_{41}N_7O_{12}$.

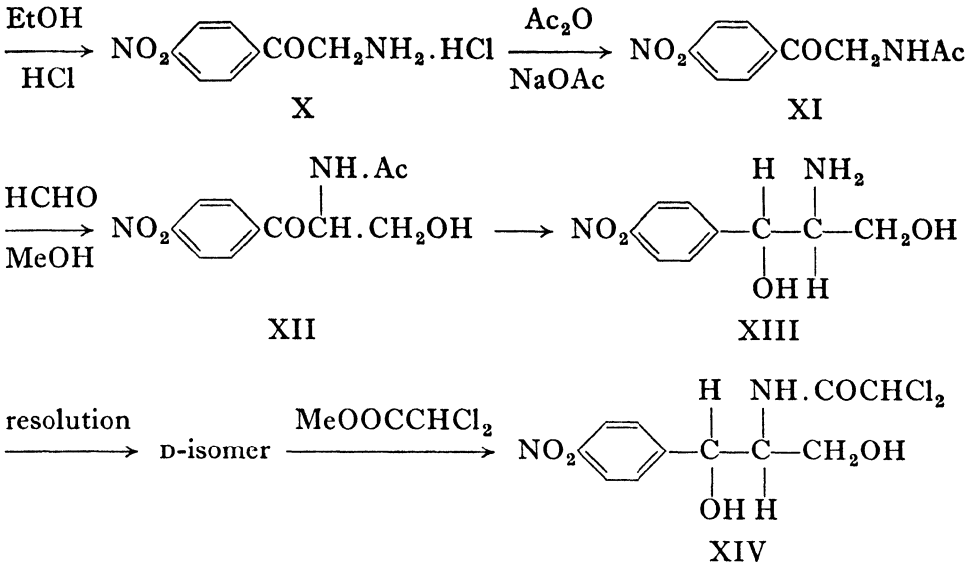
Preparation and properties. Streptomycin trihydrochloride can be reduced by hydrogen in the presence of Raney nickel or by aluminium amalgam to give dihydrostreptomycin (55, 56). It differs from the parent compound in that the aldehyde group in streptomycin has in dihydrostreptomycin been converted to a primary alcohol group. Dihydrostreptomycin has been prepared crystalline (57). It has no m.p. up to 300°. It forms a trihydrochloride $[\alpha]_D^{25}$ −95° and a trisulphate $[\alpha]_D^{25}$ −88°. The latter has a m.p. of 255° to 265° (dec.).

Chloramphenicol. D-(−)-*threo*-N-(1 : 1′-Dihydroxy-1-*p*-nitrophenyl*iso*-propyl)dichloracetamide. D-(−)-*threo*-1-(4-Nitrophenyl)-2-dichloroacetamido-1 : 3-propanediol. $C_{11}H_{12}Cl_2N_2O_5$. (XIV).

Preparation. The clinical success of penicillin and streptomycin led to an intensive search for other useful antibiotics. The discovery of chloramphenicol was announced in 1947 (11, 12). It was originally prepared by fermentation and was obtained as a pure crystalline substance in 1948 (58). Chemical synthesis followed rapidly and all chloramphenicol now produced commercially is made by the synthetic route (59, 60). The method used is as follows (61, 62):



VIII IX

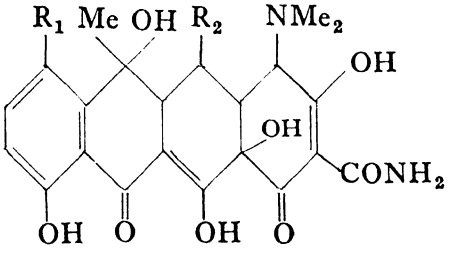


4-Nitrobromoacetophenone (VIII) is reacted with hexamine to yield the complex (IX). Chloroform or chlorobenzene may be used as solvents for the reaction. The complex is hydrolysed by means of concentrated hydrochloric acid in methanol or ethanol at room temperature. The product is washed with a small volume of cold water to remove the unwanted ammonium chloride and 4-nitro-aminoacetophenone hydrochloride (X) is obtained. The amino group is next acetylated with acetic anhydride. The amine hydrochloride is used and is converted to the free amine by means of sodium acetate. 4-Nitroacetamido-acetophenone (XI) is so obtained. This compound is hydroxymethylated in the next step. It is reacted in methanol with formaldehyde in the presence of a basic material such as sodium bicarbonate to give 4-nitro-(1-acetamido-2-hydroxy)-propiophenone (XII). This is subjected to a Meerwein-Ponndorf reduction, and the ketonic group is thus converted to a secondary alcohol (63). The usual Meerwein-Ponndorf technique is employed, i.e. the ketone is dissolved in *iso*-propanol containing aluminium *iso*propoxide and the reaction mixture is slowly distilled until no more acetone is present. Cold hydrochloric acid is added to destroy the *iso*propoxide and the reaction product is extracted with ethyl acetate. Racemic *threo*-1-(4-nitrophenyl)-2-amino-1 : 3-propanediol (XIII) is obtained. It is contaminated with a small amount of the *erythro* isomer, i.e. the compound in which the 1-hydroxy and 2-amino groupings are *cis* instead of *trans* to each other. The racemic mixture is now separated into its component optical isomers. It may be resolved by means of an optically active acid such as tartaric acid (64). The D-(—)-*threo* isomer on reaction with methyl dichloroacetate (65) then yields chloramphenicol (XIV).

Properties. Chloramphenicol forms white crystals with a m.p. of 150·1°. It is soluble in ethyl acetate, propylene glycol, acetone and ether. One part dissolves in 400 parts of water. The solution in ethyl acetate is laevorotatory with $[\alpha]_D^{25}$ —25·5 and that in ethanol is dextrorotatory.

Chloramphenicol palmitate is an ester of the parent substance that has none of the disagreeable bitter taste possessed by chloramphenicol. It is prepared by the reaction between palmitoyl chloride and chloramphenicol in boiling benzene (66, 67) and it melts at 95°.

The tetracycline group of antibiotics. This group comprises chlortetracycline (XV), oxytetracycline (XVI) and tetracycline (XVII). The latter substance has the simplest structure of the three, but was in fact discovered last.



XV R_1=Cl, R_2=H
XVI R_1=H, R_2=OH
XVII R_1=H, R_2=H

Chlortetracycline. $C_{22}H_{23}ClN_2O_8$. (XV).

Preparation. Chlortetracycline was isolated by Duggar in 1948 (13) and the structural formula now used was proposed in 1954 (68). A fermentation method is used for the production of this antibiotic. The organism used is *Streptomyces aureofaciens* and mutants have been introduced (69). The usual antibiotic fermentation technique is employed (70, 71). After filtration from insoluble material, the liquor containing crude chlortetracycline can be treated with an organic acid to give a water insoluble salt that is then dissolved in amyl alcohol. The solution is basified with caustic soda solution and the solvent phase separated and made acid with dilute sulphuric acid. Chlortetracycline crystallises and can be converted to the hydrochloride. Other methods have been used (72).

Properties. Chlortetracycline has a specific rotation in 0·1 *N* hydrochloric acid of −240°. The hydrochloride is a yellow crystalline powder that possesses a bitter taste. 1 g dissolves in 75 ml water and in 560 ml of ethanol. It is soluble in solutions of alkali hydroxides and carbonates and insoluble in acetone, dioxane, chloroform and ether.

Oxytetracycline. $C_{22}H_{24}N_2O_9.2H_2O$. (XVI).

Preparation. Oxytetracycline was discovered in 1950 (14) and the formula now used was proved to be correct in 1952 (73). The submerged culture method of production is used and the micro-organism that elaborates oxytetracycline is *Streptomyces rimosus* (74). The fermentation broth after filtration may be basified and the oxytetracycline extracted with butanol (75). Alternatively, oxytetracycline hydrochloride can be salted out from the acidified aqueous phase into a solvent from which it crystallises (76). More recent patents describe water-insoluble complexes formed by oxytetracycline with barium and mag-

nesium chlorides (77), with dyes (78) and with quaternary ammonium salts (79). These complexes can be filtered and converted to oxytetracycline hydrochloride.

Properties. Oxytetracycline is a yellow crystalline powder, with a specific rotation of approximately −212° in 0·1 N HCl. It loses its activity in solutions of pH under 2 and in alkali hydroxide solutions. 1 g dissolves in 100 ml of ethanol and 2 litres of water. It is readily soluble in dilute hydrochloric acid. Oxytetracycline hydrochloride is a yellow crystalline material that possesses a bitter taste. It is hygroscopic and has a m.p. of approximately 180° (dec.). 1 g dissolves in 2 ml of water, but hydrolysis occurs and the solution becomes opaque due to liberation of the base. 1 g dissolves in 45 ml of methanol and 35 ml of ethanol. It is insoluble in chloroform and ether.

Tetracycline. $C_{22}H_{24}N_2O_8 . 3H_2O$. (XVII).

Preparation. Tetracycline may be prepared biosynthetically by the fermentation technique (80), but it was first obtained by the catalytic reductive dehalogenation of chlortetracycline (81, 82).

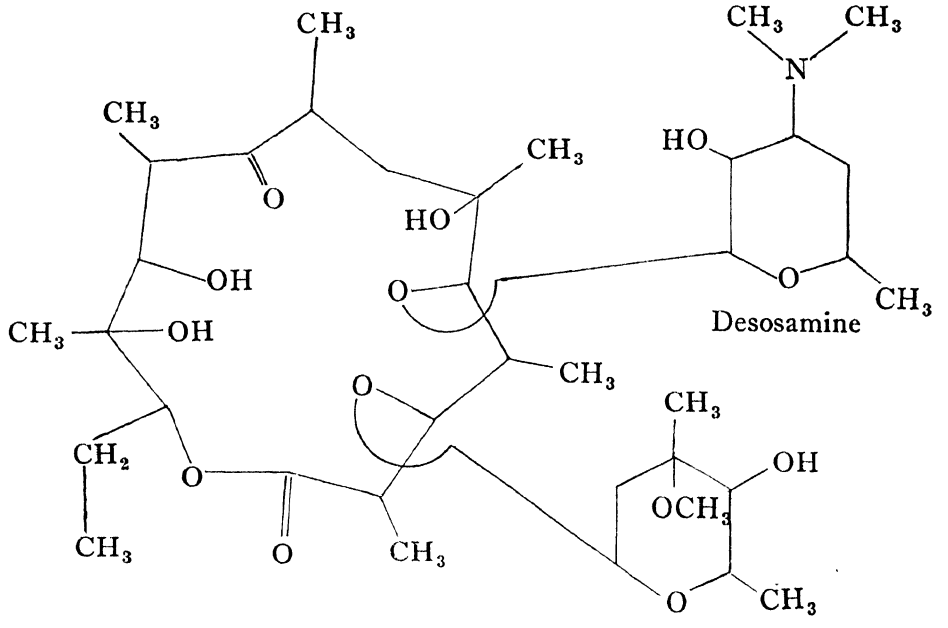
Properties. As prepared chemically tetracycline is obtained as the trihydrate which melts at 170° to 173° (dec.). It has pK values of 8·3 and 10·2 in 50 per cent aqueous dimethylformamide. The specific rotation is −257° in 0·1 N HCl. It becomes inactivated in alkali hydroxides and in solutions of pH below 2. 1 g dissolves in 50 ml of ethanol and 2·5 litres of water. It is soluble in dilute hydrochloric acid. The hydrochloride melts at 214° (dec.). It dissolves in water to the extent of 1 g in 10 ml, but hydrolysis occurs and the base is liberated. 1 g dissolves in 100 ml of ethanol. It is insoluble in ether or chloroform.

Erythromycin. (XVIII).

Preparation. The isolation of erythromycin from the culture fluid in which *Streptomyces erythreus* had been grown was reported in 1952 (16). This antibiotic has now been manufactured on a large scale (83). The method follows the usual pattern described above for penicillin. The nutrient broth which is sterilised before use contains the following parts by weight of constituents: starch 3, soya-bean meal 3, corn-steep solids 1, calcium carbonate 0·7, sodium chloride 1, water 240. An inoculant culture of *S. erythreus* is added aseptically and is grown in the broth for 4 days at 26°. During this period the medium is stirred and aerated with sterile air. The broth is then brought to pH 9·5 by addition of sodium hydroxide solution and the liquor is filtered. The filtrate is extracted with amyl acetate, and the latter solvent is then shaken with two portions of dilute sulphuric acid. This aqueous solution is made alkaline and concentrated until crystallisation of erythromycin occurs. It may be purified by recrystallisation from aqueous acetone. The structure is represented by XVIII (83a).

It has been shown that *Streptomyces erythreus* can also produce a second antibiotic called erythromycin B (84).

Properties. Erythromycin is a monobasic compound possessing a pK of 8·8 (in dimethylformamide). It crystallises as white needles of m.p. 136° to 140° and possesses a bitter taste; $[\alpha]_D^{25}$ −78°. It is very soluble in ethanol, acetone, ethyl acetate and chloroform. The solubility in water is 0·002 g per ml. Erythromycin is rapidly deactivated in solutions with pH below 4. It forms



XVIII

water-soluble salts with acids. The hydrochloride which forms white needles of m.p. 170° to 173° is very soluble in water and the lower alcohols. It is slightly soluble in ethyl acetate and insoluble in ether, amyl acetate and chloroform.

Several compounds of erythromycin have been introduced for clinical use. These include the ethyl carbonate, the glucoheptonate, the lactobionate and the stearate.

Neomycin.

Preparation. The isolation of neomycin from cultures of *Streptomyces fradiae* was announced in 1949 (17). The fermentation procedure follows normal practice (85). After filtration the liquor may be acidified and the neomycin adsorbed upon charcoal or upon a cationic resin (86). Alternatively, an aqueous solution of neomycin may be rendered acid and reacted with sodium 2-anthraquinonesulphonate to give a precipitate of the neomycin anthraquinonesulphonate. This may be converted to the sulphate by addition of sulphuric acid and this latter salt on passage through an anion exchange column yields neomycin (87).

Properties. Neomycin sulphate, the salt which is used clinically, occurs as white crystals soluble in water (1 g per ml) and slightly soluble in ethanol. It is insoluble in acetone, chloroform and ether. Its solutions are dextrorotatory. It differs from other antibacterial agents in being active in alkaline solution.

Polymyxin B sulphate.

Preparation. Polymyxin is a mixture of polypeptides produced by *Bacillus*

polymyxa (*B. aerosporus*). It was first described in 1947 (18, 19, 20). The mixture has been separated into five components named A, B, C, D and E, and the amino acid content of the different polymyxins has been investigated (88). Polymyxin B sulphate has been used clinically but it appears that this substance is not a single entity (89).

Polymyxin is made by submerged cultivation of the bacillus for a few days at 25° in a neutral medium (90). The medium contains, for example, lactose, corn-steep liquor or soya-bean meal, ammonium chloride, magnesium sulphate, potassium dihydrogen phosphate and sodium chloride. It is aerated during the fermentation and anti-foaming agents are added periodically. When fermentation is complete, diatomaceous earth is added and the insoluble material is filtered. The filtrate may be rendered alkaline, extracted with butanol which is then extracted with dilute hydrochloric acid. In this way, a weak aqueous solution of polymyxin hydrochloride is obtained. It can be reacted with naphthalenesulphonic acid and the polymyxin naphthalenesulphonate that precipitates can be converted to polymyxin by addition of ammonia (91). After further purification the polymyxin is suspended in ethanol and reacted with concentrated sulphuric acid to yield polymyxin B sulphate. Structural formulae have been proposed for polymyxin B (92, 93).

Properties. Polymyxin B is a laevorotatory material. It forms salts with mineral acids and also derivatives such as the picrate, the flavianate and the helianthate. Polymyxin B sulphate is a white powder that is freely soluble in water and slightly soluble in ethanol.

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CHAPTER XVIII

Vitamins

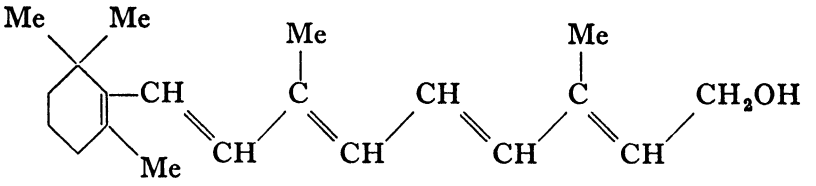
Vitamin A. Vitamin A alcohol. Axerophthol. In the early years of this century it was first observed that the absence of a certain fat-soluble factor from the diet of experimental animals led to lack of growth and ultimately to death (1, 2, 3). This growth-promoting substance was later named Vitamin A. It was found to be present in cod-liver oil, which had been used medicinally for many years for its nutrient properties; later other fish-liver oils were found to be much richer sources of the vitamin, particularly halibut- and tunny-liver oils and the liver oils of certain sharks. In these oils vitamin A is accompanied by vitamin D in which halibut- and tunny-liver oils are particularly rich. Vitamin A also occurs in mammalian livers in which the amount of vitamin D is small; whale livers are a very rich source of vitamin A and are an important commercial material for the production of concentrates of natural vitamin A. When these oils are saponified the vitamin is concentrated in the unsaponifiable matter; further concentration may be effected by molecular distillation.

The structure of vitamin A was established in 1931 (4) and it was first isolated in pure form in 1942 (5).

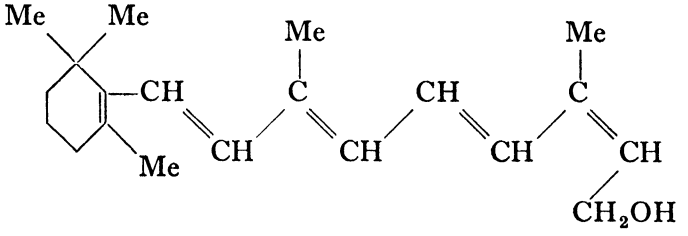
Vitamin A is present in fish-liver oils as a mixture of geometrical isomers; the all-*trans* form is the most abundant and is known as vitamin A_1 (I); the *trans-cis* isomer is called *neo*vitamin A (II); synthetic vitamin A is the all-*trans* isomer. These two forms are present in marine fish-liver oils in the approximate ratio of 65 per cent vitamin A_1 and 35 per cent *neo*vitamin A (6). A third form of vitamin A called Vitamin A_2 is found in the liver oils of fresh-water fish and in small amounts in marine fish-liver oils; it has the structure III and has recently been synthesised (7). Vitamin A occurs in nature almost entirely in the form of esters with fatty acids (8); the unsaponifiable matter of oils contains the free alcohol.

Certain carotenoid compounds found in nature are capable of conversion in the body to vitamin A; these supply a major part of the vitamin A requirements of human diet. All-*trans* β-carotene is the most important of these compounds; it can be extracted from carrots, alfalfa and other vegetable tissues and the mixture of isomers so obtained can be separated by chromatography (9). The conversion of the readily accessible β-carotene by chemical means is a tempting possibility but so far no results capable of large-scale use have been obtained (10).

The extraction of vitamin A from fish-liver oils. The main commercial sources of vitamin A until the synthesis was made commercially possible were whale-oil and the liver oils of halibut, cod, shark and dogfish. The crude oil is saponified under nitrogen, the unsaponifiable matter is extracted with light petroleum, and after evaporation of the solvent, the residue is fractionally



I



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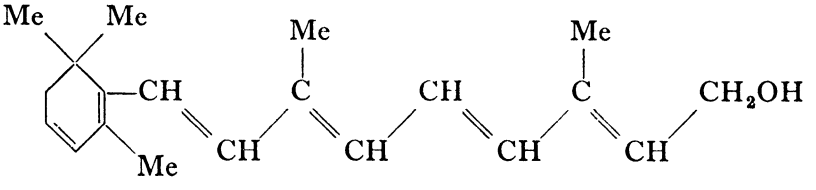


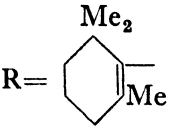
III

crystallised from methanol; the sterols crystallise first, and on cooling to −66° vitamin A is obtained. It may be purified by means of chromatography or by high-vacuum distillation (11).

Synthesis of Vitamin A. Several reviews of this subject have appeared (12, 13, 14) on which the account given below is based.

1. *From β-ionone.* This is an obvious starting-point for the synthesis of vitamin A and it was claimed in 1937 (15) that the vitamin had been successfully prepared from this source, but this was not confirmed by later workers (16, 17). More recently a new synthesis from β-ionone has been published (18).

Note. In all the following reaction schemes for the synthesis of vitamin A,



β-Ionone (IV) is combined with ethyl bromoacetate by the Reformatsky reaction to give the key intermediate β-ionylidene acetate (V). This is first reduced to the alcohol by means of lithium aluminium hydride and then oxidised to the corresponding aldehyde (VI) by manganese dioxide. The aldehyde, which is a mixture of *cis-trans* isomers, is condensed with acetone in the presence of

aluminium *tert.*-butoxide to form the C_{18} ketone (VII). A further Reformatsky reaction and dehydration of the hydroxy ester (VIIa) with iodine leads to VIII which is saponified. The acid so obtained is reduced with lithium aluminium hydride and vitamin A alcohol is produced (IX).

$$\underset{\text{IV}}{\text{R.CH=CHCOMe}} \rightarrow \underset{\text{V}}{\text{R.CH=CHC(Me)=CHCOOEt}}$$

$$\rightarrow \underset{\text{VI}}{\text{R.CH=CHC(Me)=CHCHO}}$$

$$\rightarrow \underset{\text{VII}}{\text{R.CH=CHC(Me)=CHCH=CHCOMe}}$$

$$\rightarrow \underset{\text{VIIa}}{\text{R.CH=CHC(Me)=CHCH=CHC(Me)(OH)CH}_2\text{COOEt}}$$

$$\rightarrow \underset{\text{VIII}}{\text{R.[CH=CHC(Me)=CH]}_2\text{COOEt}} \rightarrow \underset{\text{IX}}{\text{R.[CH=CHC(Me)=CH]}_2\text{CH}_2\text{OH}}$$

Similar syntheses have been published by Philips (19) and by Inhoffen (20). The ketone (VII) has been used for the preparation of vitamin A by other workers (21, 22).

β-Ionone has been used as the starting-point in another route to vitamin A (23), in which it was condensed with methyl bromocrotonate (X) to give the C_{17} acid (XI) which was converted to the C_{18} ketone (VII). Van Dorp and Arens (24) used lithium methyl for the latter stage and Heilbron (25) cadmium dimethyl. Van Dorp condensed the C_{18} ketone with ethyl bromoacetate and then dehydrated and saponified the hydroxy ester obtained forming the all-*trans* vitamin A acid (XII). The sodium salt of this acid, buffered at pH 10, has an activity comparable with that of vitamin A alcohol.

$$\text{R.CH=CHCOMe} + \underset{\text{X}}{\text{BrCH}_2\text{-CH=CHCOOMe}}$$

$$\rightarrow \underset{\text{XI}}{\text{R.CH=CHCMe=CHCH=CHCOOH}}$$

$$\rightarrow \underset{\text{VII}}{\text{R.CH=CHCMe=CHCH=CHCOMe}}$$

$$\rightarrow \text{R[CH=CHCMe=CH]}_2\text{COOEt} \rightarrow \underset{\text{XII}}{\text{R[CH=CHCMe=CH]}_2\text{COOH}}$$

In a further method in which β-ionone is used acetylenic compounds are intermediates. In 1942 Heilbron (17) described the preparation of the C_{14} aldehyde (XIII). He found that it would readily react with acetylenic compounds and in 1945 he and his co-workers (26) prepared 1-hydroxy-3-methylpent-2-ene-4-yne (XIV). Shortly afterwards Isler *et al.* (27, 28, 29) condensed these two compounds in the usual Grignard method, producing the acetylenediol (XV); this was then selectively hydrogenated at the triple bond with a palladium catalyst when partial acetylation of the compound obtained yielded the polyene glycol acetate (XVI). On treatment with iodine in light petroleum an allylic rearrangement occurred accompanied by dehydration and thus vitamin A acetate was formed (XVII). Crystalline vitamin A and a series of esters were prepared and by a similar method vitamin A methyl ether was produced. This method has been developed into a large-scale process.

$$\underset{\text{XIII}}{\text{R.CH}_2\text{CH=CMeCHO}} + \underset{\text{XIV}}{\text{HC}\equiv\text{CCMe=CHCH}_2\text{OH}}$$

$$\text{R.CH}_2\text{CH=CMeCHOHC}\equiv\text{CCMe=CHCH}_2\text{OH}$$

XV

$$\text{R.CH}_2\text{CH=CMeCHOHCH=CHCMe=CHCH}_2\text{OCOMe}$$

XVI

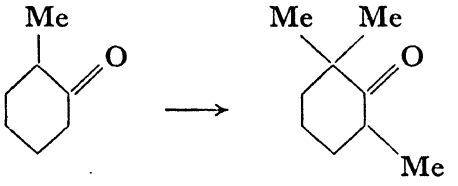
$$\text{R[CH=CHCMe=CH]}_2\text{CH}_2\text{OCOMe}$$

XVII

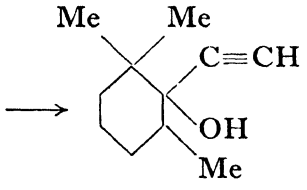
Milas (30, 31) at about the same time published a series of patents on the same type of reaction sequence. Golse and Gavarret have also worked in this field (32).

Since the C_{14} aldehyde (XIII) is ultimately derived from β-ionone all the above syntheses were therefore based on this compound as starting-material.

2. *From* cyclo*hexanone*. A synthesis of vitamin A has been described (33) in which 2-methyl*cyclo*hexanone is used as the starting-material. This compound (XVIII) is first methylated by methyl iodide in a non-polar solvent in the presence of sodamide when 2 : 2 : 6-trimethyl*cyclo*hexanone (XIX) is obtained. This trimethylketone is added to a solution of sodium acetylide in liquid ammonia, when 1-ethynyl-2 : 2 : 6-trimethyl*cyclo*hexanol (XX) is readily isolated; this is the key intermediate for this synthesis. It is condensed as the Grignard compound with 6-methylocta-3 : 5 : 7-trien-2-one (XXI) in benzene to give the ditertiary glycol (XXII) which rearranges to the C_{20} glycol (XXIII). The triple bond in this compound is then selectively hydrogenated by means of lithium aluminium hydride to the polyene glycol (XXIV) which, in the final step, is dehydrated via its acetate, yielding vitamin A acetate (XXV).

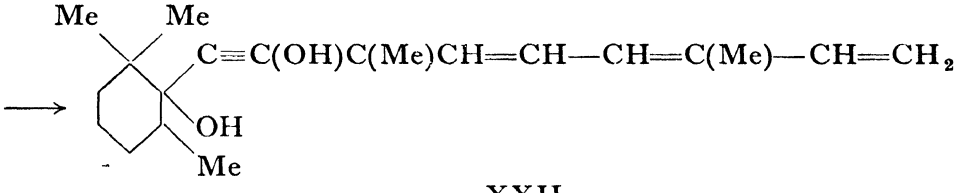


XVIII XIX

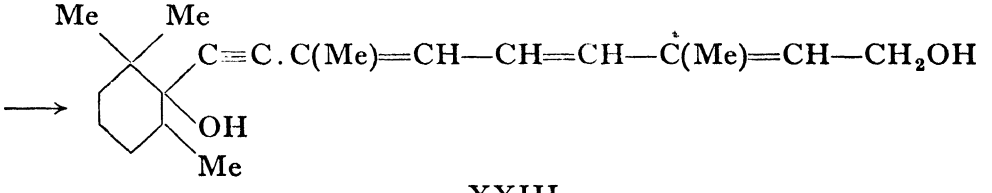


+ $MeCOCH{-}CH{=}C(Me)CH{=}CH_2$

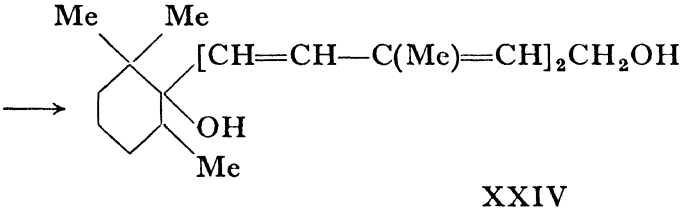
XX XXI



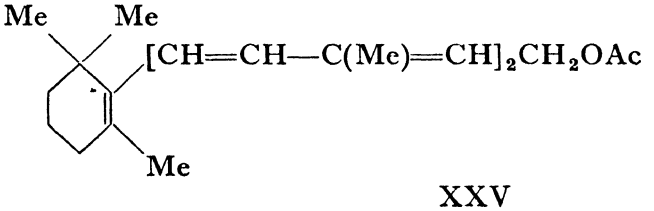
XXII



XXIII



XXIV



XXV

Properties. Vitamin A melts at 63° to 64° and has E (1 per cent, 1 cm) 1725 at 328 m. The b.p. (molecular distillation) is 120° to 125° at 5×10^{-3} mm. It is insoluble in water but soluble in methanol, acetone, chloroform, ether and light petroleum. The methyl ether melts at 33° to 34° and has an activity equivalent to that of the free alcohol. Vitamin A is available commercially as an ester with a fatty acid. The acetate melts at 57° to 58° and the palmitate at 28° to 29°. Other esters have been prepared (27, 28, 34, 35). For a comprehensive treatise see *Vitamin A* by T. Moore, published by Elsevier.

VITAMIN B GROUP

The two vitamins that were first recognised were termed 'fat-soluble vitamin A' and 'water-soluble vitamin B' which had a curative action on beri-beri and was found in rice polishings and in yeast. Later it was found that neither of these substances was a single substance. Vitamin B was recognised as a group of vitamins having different physiological functions. Some members of the group have not been recognised as having specific functions in human nutrition since no symptoms or diseases are known that can be ascribed to a deficiency of these vitamins, but the following may be regarded as essential to human health and are administered medicinally:

thiamine (vitamin B_1)	antineuritic
riboflavine (vitamin B_2)	antidermatitis
nicotinic acid and *nicotinamide*	anti-pellagra
cobalamins (vitamin B_{12})	anti-pernicious anaemia

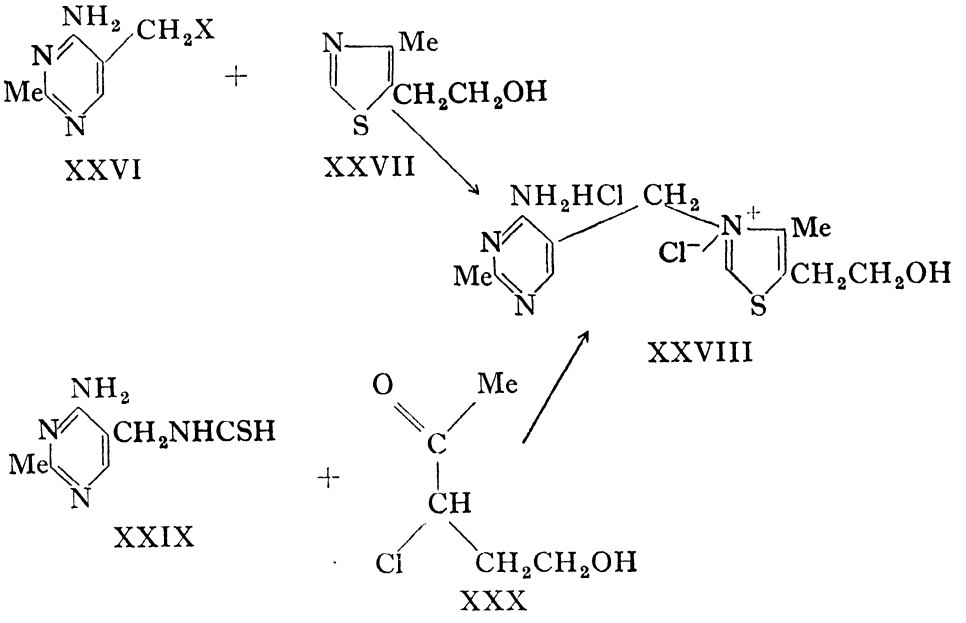
Other members of the group are the pyridoxine (vitamin B_6) derivatives (pyridoxol, pyridoxal, pyridoxamine), pantothenic acid, folic acid (pteroylglutamic acid), choline, biotin and *p*-aminobenzoic acid. These are sometimes contained in multivitamin preparations for human administration.

Thiamine hydrochloride. Aneurine hydrochloride. Vitamin B_1. 3-(4-Amino-2-methyl-5-pyrimidylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium chloride hydrochloride. $C_{12}H_{17}ON_4SCl.HCl$. (XXVIII).

Preparation. Jansen and Donath (36) were the first to obtain crystalline vitamin B_1 which they isolated from rice bran and named *aneurin*; later it was named *thiamine* by Williams in the U.S.A. and this name has now been generally adopted.

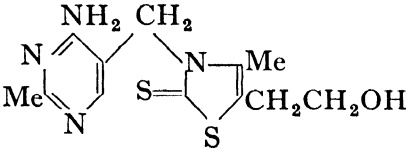
The general method of synthesis involves the reaction of a pyrimidine derivative (XXVI) with a thiazole compound (XXVII).

When X in formula XXVI is bromine, reaction with the thiazole compound yields thiamine bromide hydrobromide (37, 38); this may be converted to the required chloride either by reaction with silver chloride (39), by ion exchange (40), or the bromide may be reacted in aqueous solution with chlorine in the presence of phenol; bromine is liberated and combines with the phenol and thiamine chloride hydrochloride is obtained (41). When X is chlorine the chloride is produced directly (42).



XXVI XXVII XXVIII XXIX XXX

By the use of 4-amino-2-methyl-5-thioformamidomethylpyrimidine (XXIX) the need for a preformed thiazole nucleus can be avoided; e.g. 3-acetyl-3-chloropropanol (XXX) has been used (38, 43, 44). Other similar compounds have also been used (45). More recently certain Japanese workers have claimed that, since the formation of thiamine from its thiothiazole (XXXI) is almost quantitative, this route has advantages (46, 47, 48).



XXXI

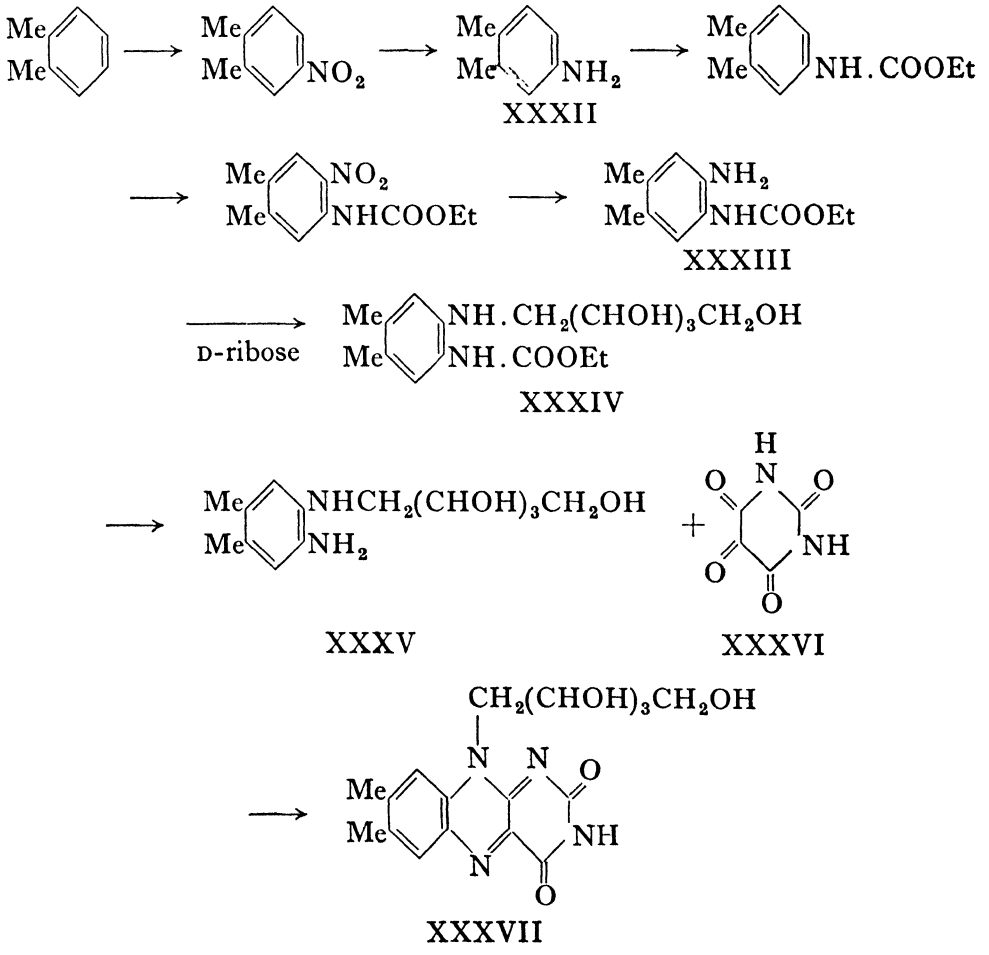
Properties. Thiamine hydrochloride forms colourless plates which melt at about 248° (dec.). It is readily soluble in water (1 g in 1 ml) and soluble in methanol, but almost insoluble in anhydrous ethanol, ether and acetone.

Riboflavine. Lactoflavin. 6 : 7 - Dimethyl - 9 - (D - 1 - ribityl)*iso*alloxazine. $C_{17}H_{20}O_6N_4$. (XXXVII). It was discovered early in the history of vitamins that milk contained a water-soluble growth factor differing from thiamine in being heat-stable (49). Many other plant and animal tissues were found to contain a substance with the same nutritional properties in that it was essential for the growth of rats. Originally it was named vitamin B_2 but this name is now given to the group of vitamins which includes riboflavine, nicotinic acid, pyridoxine and their derivatives, pantothenic acid, folic acid, 4-aminobenzoic acid, inositol, choline and biotin.

The constitution of riboflavine was elucidated by Karrer and his co-workers in 1935 (50, 51, 52).

Preparation. Riboflavine is now often produced by a microbiological process but it is also made by synthesis. The first published procedure was that of Karrer (50, 53) followed shortly afterwards by that of Kuhn (54, 55). D-Ribose is the key intermediate in both these syntheses (although methods in which its use is avoided have since been published) and its preparation by various routes has been described (56 to 59).

In the original synthesis of riboflavine *o*-xylene was nitrated to 3 : 4-dimethyl-1-nitrobenzene which, on catalytic reduction, yielded the corresponding amine (XXXII). The amino group was then protected by conversion to carbethoxy-amino and the resulting compound was first nitrated and then reduced to yield 1-carbethoxyamino-3 : 4-dimethylphenyl-6-aminobenzene (XXXIII); this substance, when condensed with D-ribose, gave 2-carbethoxy-amino-4 : 5-dimethylphenyl-D-ribamine (XXXIV) which was hydrolysed to the free amine. The resulting 2-amino-4: 5-dimethylphenyl-D-ribamine (XXXV) was then condensed with alloxan (XXXVI) to give riboflavine (XXXVII). The synthetic methods for the production of riboflavine have been reviewed by Robinson (60) and by Vogel and Knobloch (61).



The biosynthesis of riboflavine can be accomplished by a variety of micro-organisms including certain moulds, yeasts, species of *Clostridia* and *Lactobacillus*. A review of the subject has appeared (62). The mould *Eremothecium Ashbyi* is often used, in which case submerged culture with continuous agitation and aeration give the optimum conditions (63). The culture medium contains a carbohydrate together with, for example, egg albumin, 0·6 per cent, maize oil, 0·6 per cent, KH_2PO_4, 0·05 per cent, $MgSO_4.7H_2O$, 0·07 per cent, NaCl, 1 per cent, and $FeSO_4.7H_2O$, 0·001 per cent. Potassium, magnesium and sulphate ions are essential for riboflavine production and it is claimed that the use of a lipid such as maize oil increases the yield; it has also been claimed (64) that addition of barley sprouts to the culture decreases the growth of the mould, accelerates autolysis and doubles the riboflavine yield. The pH of the culture medium is 5·5 and fermentation is carried on for fifty to ninety days at 30°.

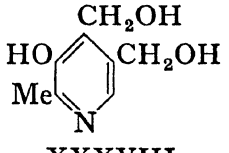
The mycelium is filtered off and to the filtrate may be added a chemical reducing agent (65) or a micro-organism such as *Streptococcus faecalis* which may be grown in the liquid (66). In either case a precipitate containing the riboflavine is obtained and is extracted with a polar solvent to yield riboflavine (67, 68).

The riboflavine may also be adsorbed from the fermentation liquor on to a fuller's earth or charcoal column and eluted therefrom.

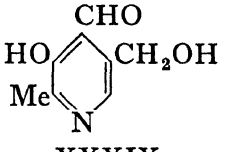
Properties. Riboflavine forms orange-yellow needles melting at 292° to 293° (dec.); it has a faint odour and a slightly bitter taste. It is sparingly soluble in water (12 mg in 100 ml at 27·5°; 260 mg in 100 ml at 100°); ethanol dissolves 4·5 mg in 100 ml at 27·5°; it is insoluble in ether, acetone, benzene and chloroform but dissolves in formaldehyde solution, formic acid and N-methylacetamide and in aqueous alkalis. The aqueous solution has a yellow-green fluorescence which is discharged by the addition of acids or alkalis. Riboflavine has no optical activity in neutral or acid solutions but is optically active in alkaline solution. It is an amphoteric substance with $K_a = 6{\cdot}3 \times 10^{-12}$ and $K_b = 0{\cdot}5 \times 10^{-5}$; the isoelectric point is at pH 6.

Crystalline riboflavine is stable in the dark but is slowly decomposed by light; it is fairly stable to heat. The tetra-acetate melts at 242° to 244° and the tetrabenzoate at 131° to 136°.

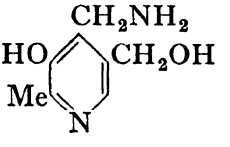
Pyridoxine group. The group of vitamins containing the compounds pyridoxol (XXXVIII), pyridoxal (XXXIX) and pyridoxamine (XL) is known as the vitamin B_6 or pyridoxine group. This vitamin occurs in nature as the last two compounds or as their phosphoric esters. All three are of equal nutritive value.



XXXVIII



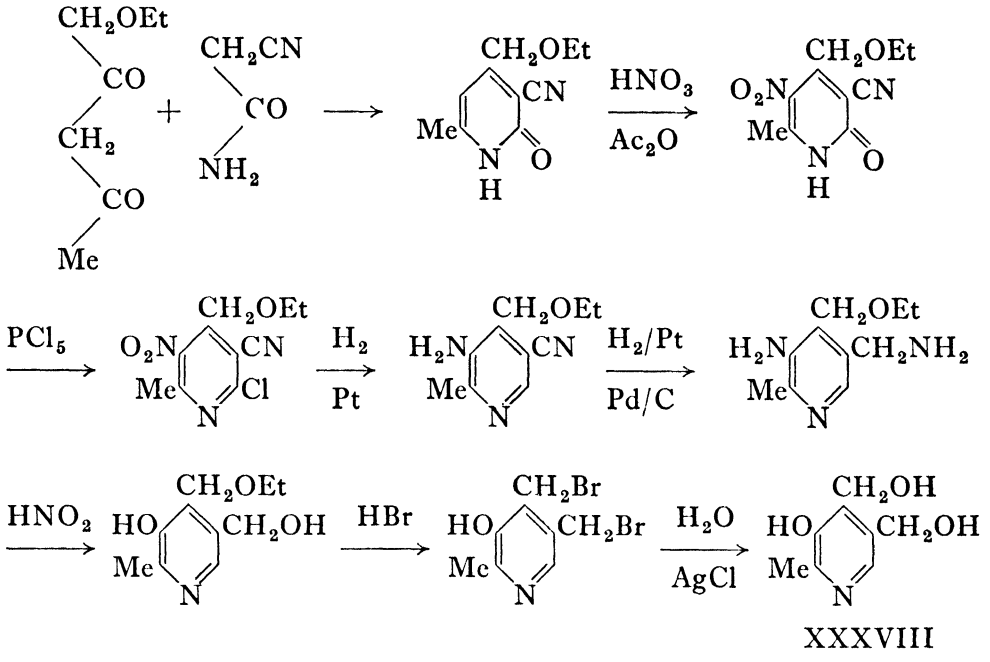
XXXIX



XL

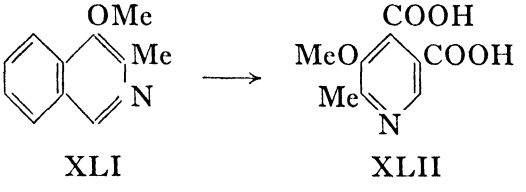
Crystalline pyridoxol (3-hydroxy-4 : 5-di(hydroxymethyl)-2-methylpyridine) was isolated in 1938 by five independent groups of workers from rice bran and yeast. The chemical structure was elucidated in 1939 (69, 70).

Preparation. Pyridoxol has been made by reactions based on a pyridone condensation; by oxidative degradation of an *iso*quinoline derivative and by synthesis from simple starting materials. The method used by Harris and Folkers in 1939 (71) was as follows.

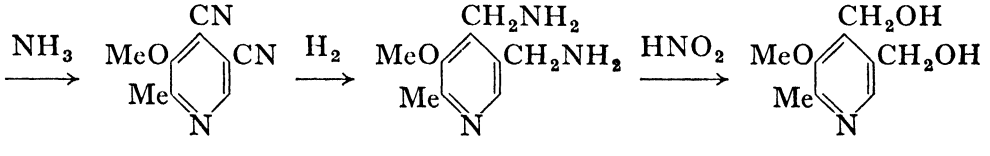


XXXVIII

Similar methods were used by other workers (72, 73). Kuhn (69) and Ichiba (74) prepared pyridoxol by partial degradation of 3-methyl-4-methoxy*iso*-quinoline (XLI) which was converted to 2-methyl-3-methoxypyridine-4 : 5-dicarboxylic acid (XLII) then via the diamide to the dicyanide which, on hydrogenation, yielded 2-methyl-3-methoxy-4 : 5-diaminomethylpyridine (XLIII). Diazotisation of this compound led to pyridoxol methyl ether (XLIV) which was converted to pyridoxol as in the Harris and Folkers synthesis.

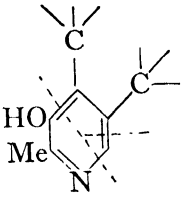


XLI XLII



XLIII XLIV

A synthesis of pyridoxol based on a hypothetical derivation from units of alanine formaldehyde and a four-carbon compound as indicated in the formula below has been published by Cohen (75, 76).



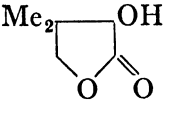
Many variations on these routes have been patented; the subject has been reviewed by Robinson (60).

Properties. Pyridoxol is used in therapy as the hydrochloride, which is a white crystalline powder melting at 205° to 212° (dec.). It dissolves in water (1 g in 5 ml at 20°), ethanol (1 g in 90 ml) and in acetone; it is slightly soluble in ether and chloroform. Pyridoxol has a characteristic absorption spectrum with a single maximum at 292 mμ at pH 3 and two maxima at 255 mμ and 325 mμ at pH 7·45.

The pyridoxine group of compounds are stable to hot acid or alkalis.

Pantothenic acid. D-1:3-Dihydroxy-2:2-dimethylbutyryl-2′-alanide. $C_9H_{17}O_5N$. (XLVII). It was shown in 1930 that a deficiency in poultry of a certain nutritional factor gave rise to a characteristic dermatitis (77) and in 1939 this factor was found to be identical with a previously described nutritional factor for micro-organisms called pantothenic acid (78). The chemical constitution of pantothenic acid was elucidated in 1940 (79, 80).

Preparation. D-Pantothenic acid has not been isolated in the free state and it is prepared commercially as its sodium or calcium salt. Until recently the usual method for the preparation of these salts has been the reaction of an alkali or alkaline earth salt of β-alanine with D-pantolactone in an anhydrous alcohol (81). Earlier workers used the reaction between pantolactone and an ester of alanine (82 to 84). In 1954 Wilson (85) described an improved method of preparation of pantothenic acid salts. Equimolecular quantities of pantolactone (XLV), β-alanine (XLVI) and a secondary amine are heated in anhydrous ethanol and to the solution is added either calcium oxide to form the calcium salt or sodium ethoxide for the sodium salt.



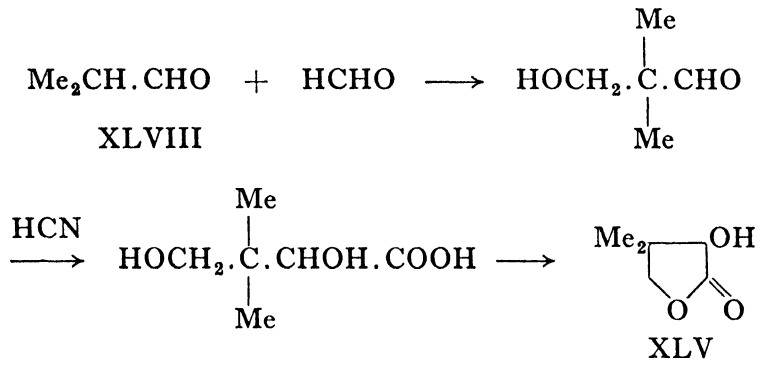
$+ \quad H_2N(CH_2)_2COOH$

XLV XLVI

$$\xrightarrow[2.\ NaOEt]{1.\ Et_2NH} HO.CH_2\overset{\overset{Me}{|}}{\underset{\underset{Me}{|}}{C}}.CHOH.CONH(CH_2)_2COONa$$

XLVII

Pantolactone has been synthesised by the following route (83, 86).



*iso*Butyraldehyde (XLVIII) is condensed with formaldehyde to yield a substituted propionaldehyde which, on reaction with hydrocyanic acid or with potassium cyanide in the presence of calcium chloride (87), yields racemic pantolactone. Variations of this method have been patented (88). The racemic compound may be resolved by conventional methods (89).

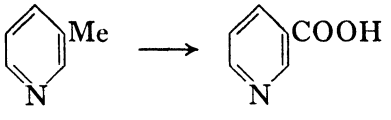
Properties. Sodium D-pantothenate is a white hygroscopic solid melting at 122° to 124° with $[\alpha]_D^{25}$ +27° in water (c=1·9). The calcium salt is less hygroscopic and melts at 170° to 172° and has a similar optical rotation. Pantothenic acid is relatively heat stable but it is readily hydrolysed and has a maximum stability in solution in the pH range 5·5 to 7·0.

The function of pantothenic acid in the body is unknown.

Nicotinic acid. Niacin. Pyridine-3-carboxylic acid. $C_6H_5O_2N$. (L). Pellagra is a nutritional deficiency disease of human beings analogous to the canine disorder known as 'black tongue'. Elvehjem (90) showed in 1937 that a liver extract possessing anti-black tongue activity contained nicotinamide and that this compound or nicotinic acid were effective in curing black tongue. Later workers proved that nicotinic acid alleviated pellagra in human beings. This compound had been isolated from rice bran and yeast twenty-five years earlier but its curative properties were then unknown.

Preparation. Nicotinic acid has been prepared commercially by the oxidation of nicotine (91) and this was the method by which it was first prepared by Huber in 1867 (92).

Quinoline or one of its derivatives such as 8-hydroxyquinoline can be oxidised to quinolic acid (pyridine-1 : 3-dicarboxylic acid) which loses CO_2 on heating forming nicotinic acid (93). All monoalkyl derivatives of pyridine on oxidation yield the corresponding acid, e.g. β-picoline (XLIX) is oxidisable to nicotinic acid (94), but the β-picoline must be free from other isomers (95).

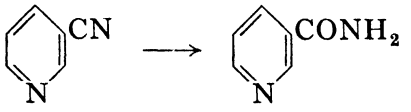


Another useful method for the preparation of nicotinic acid is that involving at the last stage the hydrolysis of 3-cyanopyridine to the acid (96, 97).

Properties. Nicotinic acid is a white crystalline solid melting at 235·5° to 236·5° and having a slightly acid taste. It is soluble in water (1 in 55 at 20°) and is readily soluble in boiling water and ethanol; it is sparingly soluble in ether. It forms salts (the hydrochloride melts at 274°) and esters (methyl ester, m.p. 38°; ethyl ester, b.p. 223° to 224°). Nicotinic acid is converted in the body to nicotinamide.

Nicotinamide. Niacinamide. Pyridine-3-carboxyamide. $C_6H_6ON_2$. (LI).

Preparation. It was first prepared by Engler in 1894 by reacting ethyl nicotinate with ammonia and this method is still used commercially (98, 99). Urea can be used instead of ammonia (100). Alternatively 3-cyanopyridine may be semi-hydrolysed to the amide (101, 102). Methods for the purification of nicotinamide have been patented (103).

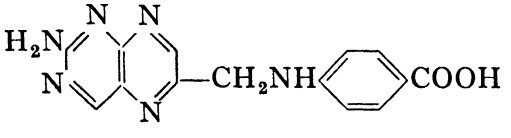


LI

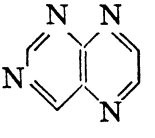
Properties. Nicotinamide is a white crystalline powder with a bitter taste. It crystallises from benzene in needles melting at 131°. It is very soluble in water (1 in 1 at 25°) and in ethanol (1 in 1·5); it is slightly soluble in ether.

Folic acid. Pteroylglutamic acid. 4-(2-Amino-4-hydroxy-6-pteridyl)-methylaminobenzoyl-L-(+)-glutamic acid. $C_{19}H_{19}O_6N_7$. (LVI). In 1940 Snell and Peterson (104) showed that certain lactic acid bacteria including *Lactobacillus casei* required a factor of unknown composition for normal growth. This *Lb. casei* factor, as it was called, was found to be essential for the production of red and white cells and platelets in the blood of various animals; it is widely distributed in foods, particularly in liver and yeast. It was isolated from spinach in 1941 and named *folic acid.* The factor was later identified and its synthesis was published in 1945 (105), the evidence from which its structure was derived being published later (106). This synthetic factor was called *pteroylglutamic acid* and had biological properties identical with those of the natural product.

Structurally pteroylglutamic acid is derived from pteroic acid (LII), a derivative of pteridine (LIII).



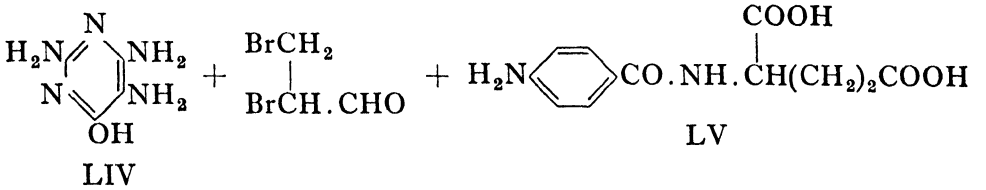
LII



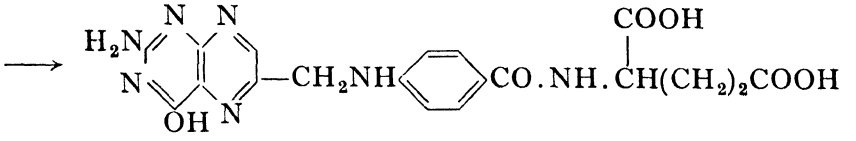
LIII

Preparation. In the first synthesis of pteroylglutamic acid (105, 107) a simultaneous condensation of the three component parts of the molecule was used.

6-Hydroxy-2 : 4 : 5-triamino-pyrimidine (LIV), a three-carbon compound, e.g. 1 : 2-dibromopropionaldehyde and N-(4-aminobenzoyl)glutamic acid (LV) were reacted together forming pteroylglutamic acid (LVI).



LIV LV



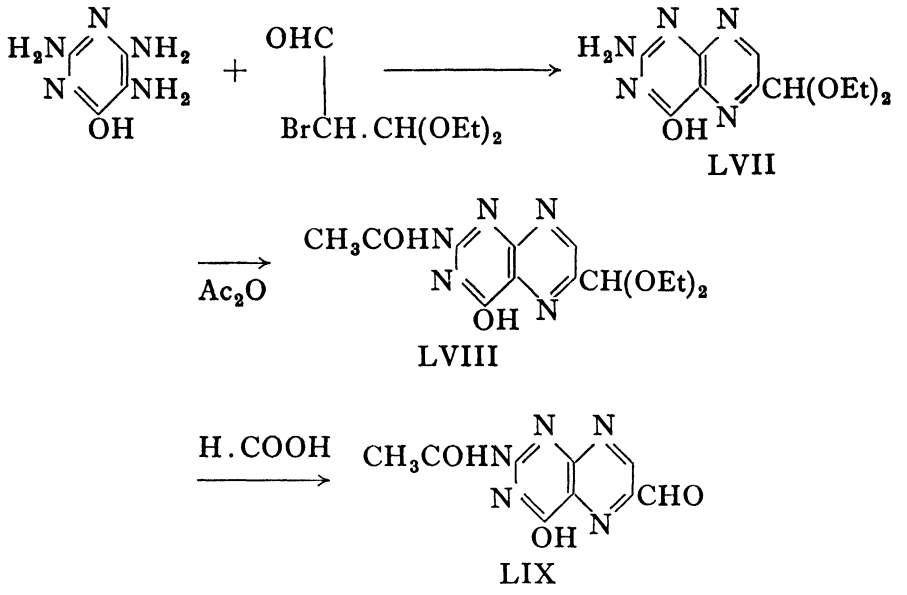
LVI

The crude product was dissolved in alkali and, after addition of barium chloride and ethanol to precipitate impurities, the solution was extracted with butanol; the aqueous phase was concentrated, acidified and cooled; the precipitate was again purified through its sodium salt.

A number of similar syntheses have been published (108 to 112).

In the second group of syntheses the pyrimidine molecule was first reacted with a three-carbon compound such as 1 : 1 : 2-tribromopropionaldehyde to give a pteridine derivative which was then further reacted with 4-aminobenzoyl-glutamic acid (109, 113 to 116). Alternatively N-(4-aminobenzoyl)glutamic acid is first reacted with the three-carbon compound and the product is condensed with a pyrimidine derivative (117 to 119). These methods (120) and many others (121) have been patented.

Pteridines of the pteroylglutamic acid group have little solubility in the usual solvents and purification of these compounds is difficult. In a recent synthesis this difficulty has been avoided by using a route whereby crystallisable intermediates are employed and thus the minimum of purification of the final product is required (122). This synthesis is of the same type as the second group described above. 6-Hydroxy-2 : 4 : 5-triaminopyrimidine hydrochloride is reacted with 1-bromo-2 : 2-diethoxypropionaldehyde in aqueous sodium bicarbonate solution, then hydrogen peroxide is added forming 2-amino-4-hydroxy-6-diethoxymethylpteridine (LVII). The latter substance is purified through the sodium derivative. Reaction with acetic anhydride yields the 2-acetamino derivative (LVIII) which, after recrystallisation, is reacted with cold concentrated formic acid when the acetal group $-CH(OEt)_2$ is converted to aldehyde -CHO. The aldehyde (LIX) is condensed with N-(4-aminobenzoyl)glutamic acid in the presence of 4-thiocresol as a reducing agent and the Schiff's base which first forms is reduced to N-acetylpteroylglutamic acid. This is first crystallised from water and then hydrolysed to pteroylglutamic acid.



Properties. Pteroylglutamic acid crystallises from water as orange-yellow needles; it has no definite melting-point but darkens and decomposes above 250°. It is slightly soluble in water (0·05 g in 100 ml at 100°), more soluble in methanol, acetic acid and phenol but insoluble in ether, acetone, benzene and chloroform. It forms salts with alkali hydroxides and carbonates and, by virtue of its amphoteric character, it dissolves in acids such as formic acid.

Pteroylglutamic acid has been used in the treatment of the macrocytic anaemia associated with sprue and in other megaloblastic anaemias.

Pteroylglutamic acid occurs in nature in combination with a chain of glutamic acid groups, e.g. the *Lb. casei* factor has a chain of three and compounds containing chains of six or seven groups have been found. 4-Aminopteroylglutamic acid is an antagonist of pteroylglutamic acid; it has been used in the treatment of leukaemia.

Vitamin B_{12} Group. Liver preparations have been used in the treatment of pernicious anaemia since 1926 (123). Many attempts were subsequently made to isolate the active factor, but no suitable assay procedure was available for the estimation of the potency of the concentrated extracts except clinical tests, the results of which were difficult to assess quantitatively; progress was therefore slow, but in 1948 a crystalline active principle, called vitamin B_{12}, was isolated independently and simultaneously, in Great Britain by E. Lester Smith (124) and in the U.S.A. by Rickes, Brink, Koniuszy, Wood and Folkers (125). The British products were tested by clinical assay while those of the American group were assayed on the micro-organism *Lactobacillus lactis* Dorner, which had been shown in 1947 to be sensitive towards clinically active fractions. When finally obtained pure and tested clinically in cases of pernicious anaemia vitamin B_{12} was found to be curative in a dosage of 0·5 to 5·0 μg daily; it is thus one of the most potent physiologically active compounds.

Soon after its isolation the molecule of vitamin B_{12} was shown to contain one atom each of cobalt and phosphorus and later it became apparent that it was one of a group of compounds with similar chemical and biological properties; these compounds are distinguished by having different groups co-ordinated with the cobalt atom; vitamin B_{12} or cyanocobalamin has a cyanide group; vitamin B_{12b} (sometimes called vitamin B_{12a}) or hydroxocobalamin has a hydroxyl group. Substitution by a nitrite group yields vitamin B_{12c} or nitritocobalamin.

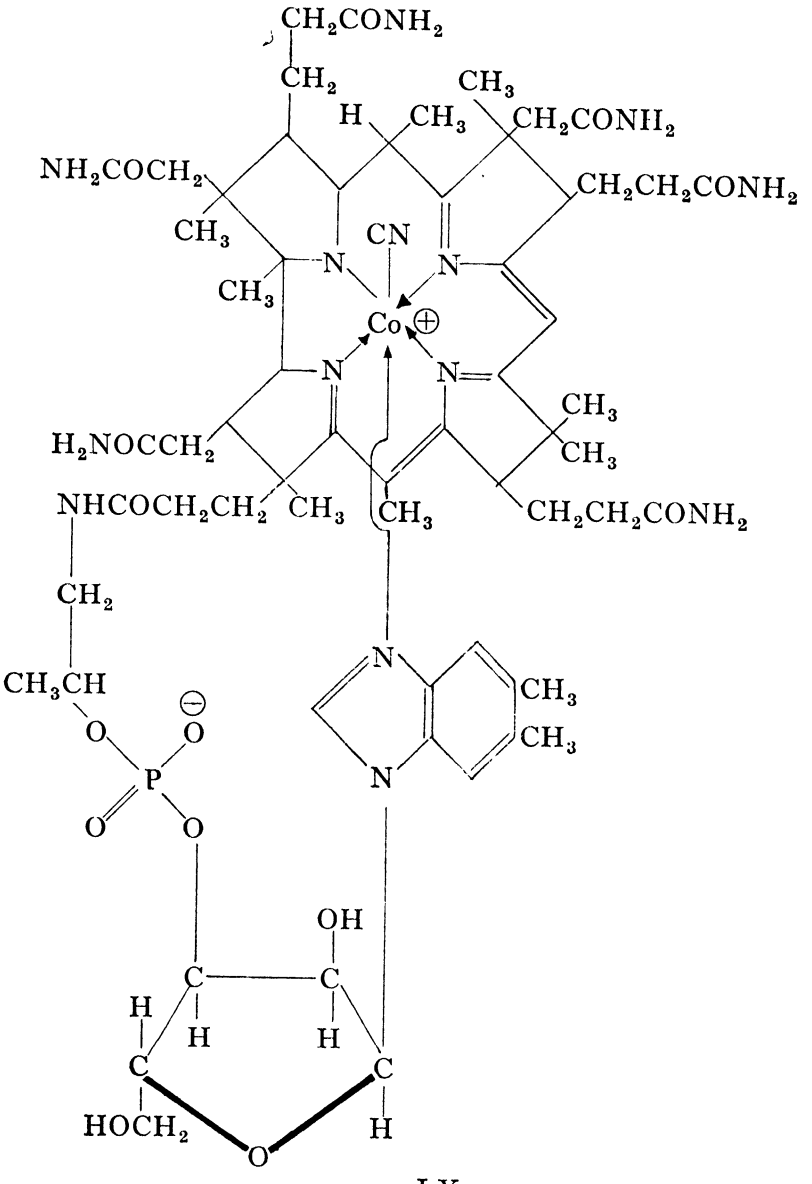
Cyanocobalamin was originally isolated from liver but it would appear that it normally has a microbiological origin. It is present in the waste liquors resulting from the production of many antibiotics including streptomycin, neomycin, chlortetracycline and chloramphenicol; it can also be isolated from sewage sludge. All commercially available cyanocobalamin is obtained by microbiological synthesis, the two organisms commonly used for this purpose being *Bacillus megatherium* and *Streptomyces* spp.

By a combination of brilliant chemical and X-ray analysis the structural formula of cyanocobalamin has been almost completely elucidated; the evidence has been summarised by Todd (126).

Cyanocobalamin. Vitamin B_{12}. $C_{63}H_{90}CoN_{14}O_{14}P$. (LX).

Preparation. When *S. olivaceus* NRRL B-1125 is used for the production of cyanocobalamin an aerobic submerged culture technique is employed (127, 128). The stock cultures are carried on agar slopes and the spores are aseptically transferred first to flasks then to a 400-gallon seed fermentor and finally to a 5,000-gallon production fermentor. The fermentors are mild-steel pressure vessels fitted with coils for steam or cooling water, agitators and air distributors. A typical culture medium has the following composition: distillers solubles, 4 per cent, soya-bean meal, 2 per cent, dextrose 1 per cent, calcium carbonate 0·5 per cent, cobaltous chloride, 2·5 parts per million. It has been claimed that the addition of cyanide to the broth leads to increased yields (129). The medium is sterilised and aerobic fermentation is carried out for four days at 28°. Foaming is inhibited by the addition of anti-foaming compounds. There are many published methods for the isolation of cyanocobalamin from the mash (130); it may be concentrated by chromatographic adsorption on charcoal (131), fuller's earth (132), alumina (133) or ion-exchange resins (134). Alternatively the broth can be filtered and extracted with phenol (135) or with a mixture of cresol and carbon tetrachloride (136). The phenol is extracted with water to give a solution from which the cyanocobalamin can be separated by chromatography and crystallised from acetone.

Properties. Cyanocobalamin crystallises from aqueous acetone or from hot water as dark red, hydrated needle-like crystals. It has no definite melting-point. It is soluble in water, methanol, ethanol and phenol and almost insoluble in acetone, ether or chloroform. Anhydrous cyanocobalamin is hygroscopic and absorbs about 12 per cent of water in moist air. It is stable in neutral aqueous solution at room temperature, but is rapidly inactivated by acids and alkalis. It is laevorotatory and exhibits a characteristic light absorption in aqueous solution having maxima at 278 mμ, 361 mμ, and 548 mμ, the values of E (1 per cent, 1 cm) being 119, 187 and 59 respectively.

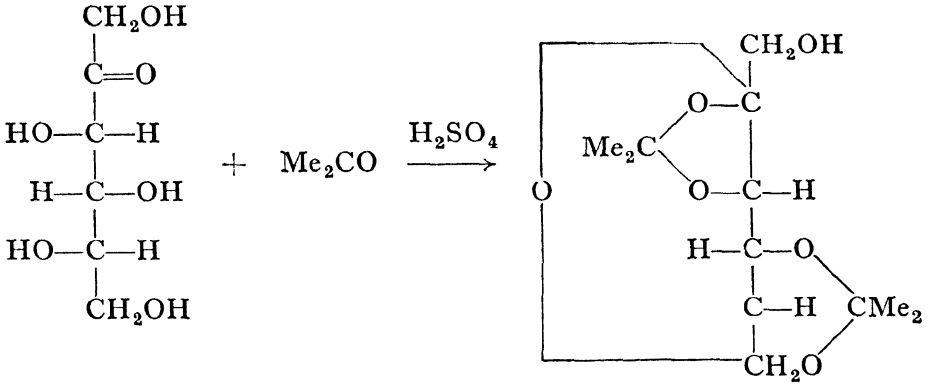


LX

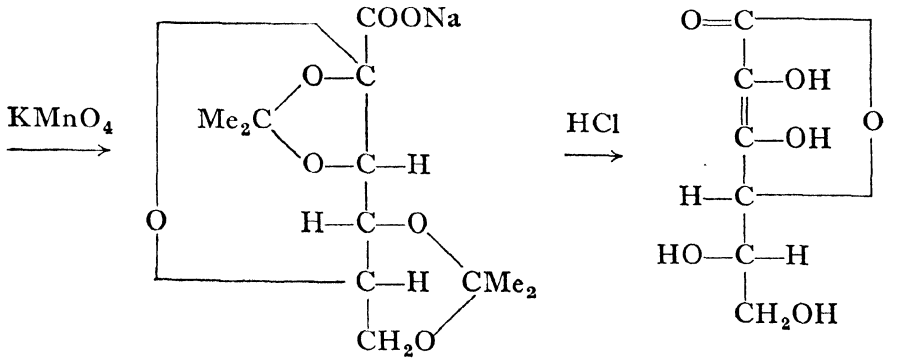
Ascorbic acid. Vitamin C. L-*threo*-2 : 3 : 4 : 5 : 6-Pentoxyhexen-2-carboxylic acid lactone. $C_6H_8O_6$ (LXIV or LXIVa). Scurvy, which is now known to be due to a deficiency of vitamin C, has been recognised as a disease for many centuries. Ascorbic acid is widely distributed in fruits and vegatables; among the richest sources are the citrus fruits and rose hips. Although the value of fresh fruit and vegetables had been recognised from time to time as prophylactic and curative agents in scurvy there appears to have been no systematic treatment of the disease with these products until comparatively recently. Early in this century experiments on animals indicated that a common active principle or vitamin was

involved and in 1924 Zilva (137) isolated ascorbic acid from lemon juice and found it to be a powerful antiscorbic. Its constitution was established in 1933 by two independent groups of workers (138, 139) and in the same year it was synthesised (140, 141). Although ascorbic may be comparatively easily isolated from natural sources such as rose hips (142) it is now prepared commercially by synthesis.

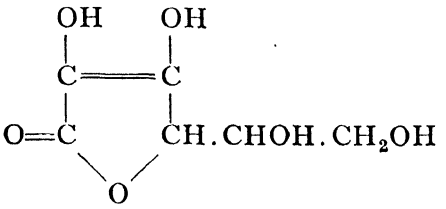
Preparation. The following process is used on a large scale.



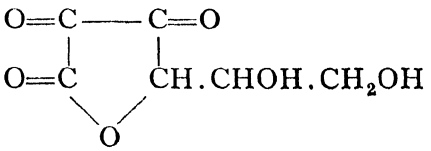
LXI LXII



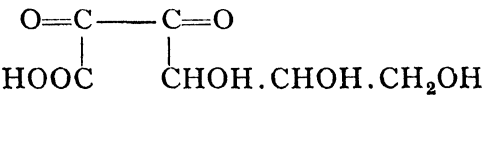
LXIII LXIV



LXIVa



LXIVb

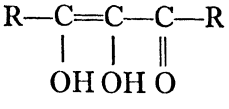


LXIVc

L-Sorbose (LXI) is the key starting material but, as it is not naturally abundant, it must first be prepared from D-glucose which is first reduced to D-sorbitol by catalytic (143) or electrolytic (144) methods. The D-sorbitol is then subjected to a ketogenic microbiological fermentation in which the >CHOH is oxidised to >C=O. For this purpose the sorbitol must be free from inhibitors such as acids and metallic ions; these may be removed by passage through an ion-exchange resin. *Acetobacter suboxidans* is the organism used in the submerged culture technique with forced aeration. The medium has the following composition per litre: sorbitol, 100 to 250 g; corn-steep liquor, containing 50 per cent solids, 5 ml; anti-foaming agent, 1 ml. The broth is sterilised by heat and, after inoculation, the fermentation is carried out at 30° to 35°. The progress of the reaction is followed by titration of the reducing sugars present. At the end of the fermentation filter-aid is added and the mass is filtered and concentrated when L-sorbose crystallises out (145). The L-sorbose is condensed with acetone in the presence of sulphuric acid in a cooled reaction vessel to yield diacetone sorbose (LXII); some monoacetone sorbose is also produced but is easily removed. The diacetone sorbose is then oxidised by potassium permanganate in sodium hydroxide solution and at the end of the reaction excess alkali is neutralised by carbon dioxide and the manganese dioxide formed during the oxidation is filtered off. The filtrate containing sodium 2 : 3 : 4 : 6-diacetone-2-oxo-L-gulonate (LXIII) and some oxalate as impurity is concentrated in a steam-heated vacuum evaporator, oxalate is precipitated as the calcium salt and the solution is acidified with sulphuric acid. The free gulonic acid obtained is dried and dissolved in chloroform; dry hydrogen chloride is passed in and ascorbic acid crystallises from the solution; it is centrifuged and dried and recrystallised from water after decolorising with activated charcoal (146).

Other methods for the preparation of ascorbic acid have been used (147 to 149).

Ascorbic acid possesses the reductone structure:



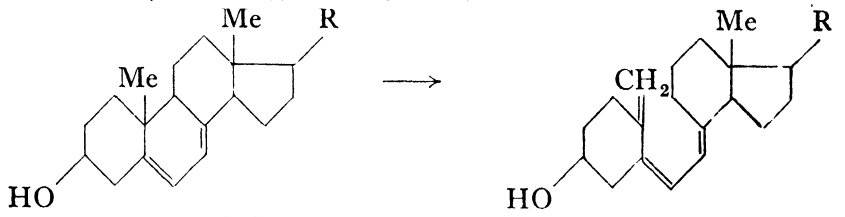
The dienol confers both reducing and acidic properties on the molecule. Because of the readiness with which ascorbic acid is oxidised isolation procedures must be carried out in the absence of oxygen, light, and metals such as copper or iron which catalyse the oxidation.

Properties. Ascorbic acid forms white crystals melting at 190° to 192°; it has a slightly acidic taste. It has a single absorption peak in the ultra-violet range at 265 m. It is a dibasic acid with $pK_1=4{\cdot}17$; $pK_2=11{\cdot}57$. Ascorbic acid dissolves in water (1 g in 3 ml), in ethanol (1 g in 50 ml) and in glycerol (1 g in 100 ml); it is insoluble in ether, benzene and chloroform.

D-Ascorbic acid has no physiological activity. Ascorbic acid (LXIVa) readily gives up two atoms of hydrogen and is converted to the diketolactone, dehydro-ascorbic acid (LXIVb) but this compound has the same biological activity as ascorbic acid. Further oxidation breaks the lactone ring with the formation of dioxogulonic acid (LXIVc) which is inactive.

Vitamin D group. This is a family of compounds differing, one from the other, in the structure of the side-chain R in formula LXVI. The most important members of the group are vitamin D_2 (*calciferol*) and vitamin D_3 (*cholecalciferol*). The name vitamin D_1 was originally applied to what was later found to be a mixture of calciferol and lumisterol.

Calciferol. Ergocalciferol. Vitamin D_2. 9 : 10-Ergostatetraene-(18 : 10, 5 : 6, 7 : 8. 22 : 23)-ol-3. $C_{28}H_{44}O$. (LXVI).



LXV LXVI

Ergosterol and calciferol, R = —CHMe.CH:CH.CHMe.$CHMe_2$
7-Dehydrocholesterol and cholecalciferol, R = CHMe.CH_2.CH_2.CH_2.$CHMe_2$

Preparation. Vitamins D_2 and D_3 are both prepared by the same general procedure; a provitamin is irradiated by ultra-violet light which forms the vitamin together with other irradiation products. In the case of calciferol the provitamin is ergosterol (LXV) which is obtained from yeast. The irradiation is carried out with light of wavelength approximately 281 mμ in a quartz container, nitrogen being bubbled through the solution in a solvent, usually ether or benzene. A mercury vapour lamp is used on the large scale and no attempt is made to filter the light. The liquid is cooled during the irradiation which lasts for about 30 minutes. The process may be made continuous. After removal of the solvent unchanged ergosterol is removed with dilute ethanol. The resinous mixture of irradiation products can be reacted with 3 : 5-dinitrobenzoic anhydride in pyridine and the calciferol 3 : 5-dinitrobenzoate crystallised and hydrolysed to give calciferol (150).

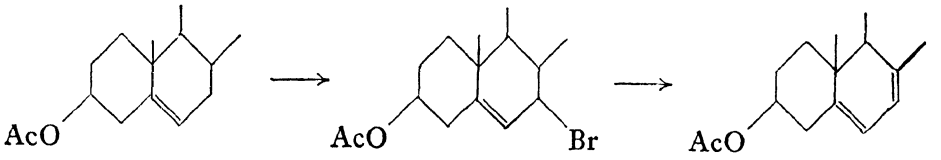
Properties. Calciferol is a white crystalline powder which is sensitive to air and light which cause the formation of a yellow colour. It melts at 115° to 117° (in an evacuated sealed tube); $[\alpha]_D^{20} = +103°$ in ethanol or +82·6° in acetone. It is insoluble in water and soluble in ethanol, ether, acetone and chloroform. The 3 : 5-dinitrobenzoate melts at 148° to 149°.

Vitamin D_3. Cholecalciferol. 9 : 10-Cholestatriene (18 : 10, 5 : 6, 7 : 8)-ol-3. $C_{27}H_{44}O$. (LXVI).

Vitamin D_3 is the member of the vitamin D group which is found in fish-liver oils, though it is usually accompanied by some calciferol. A method of preparation from fish-liver oils has been described (151). The formation of vitamin D_3 from its provitamin 7-dehydrocholesterol is analogous to the procedure described for vitamin D_2 except that the optimum wavelength for the transformation is 296·7 mμ (152).

Since 7-dehydrocholesterol is not readily obtainable it must be synthesised. In the original method (153) seven stages were necessary from cholesterol to the 7-dehydroderivative. Many workers introduced minor improvements in the

method but it was not radically changed until 1946 when the Wohl-Ziegler bromination technique (154) was applied to this synthesis (155 to 159). The brominating agent most commonly used is N-bromosuccinimide which brominates in the so-called allyl position, i.e. α to the 5 : 6 double bond in cholesteryl acetate (LXVII). In the formulae below only rings A and B of the sterol nucleus are shown.



LXVII LXVIII LXIX

Bromination of cholesteryl acetate yields 7-bromocholesteryl acetate (LXVIII) which is easily dehydrobrominated to 7-dehydrocholesteryl acetate (LXIX). This on alkaline hydrolysis is converted to 7-dehydrocholesterol.

Properties. Vitamin D_3 is a white crystalline material melting at 82° to 83°; it is insoluble in water but soluble in fat solvents. It has $[\alpha]_D^{20} = +83{\cdot}3°$ in acetone and an ultra-violet absorption spectrum with a single peak at 265 mμ. The 3 : 5-dinitrobenzoate is dimorphic and melts at 129° and at 140°; the 4-nitrobenzoate melts at 127°.

α-Tocopherol. 5 : 7 : 8-Trimethyltocol. $C_{29}H_{50}O_2$. (LXXII).

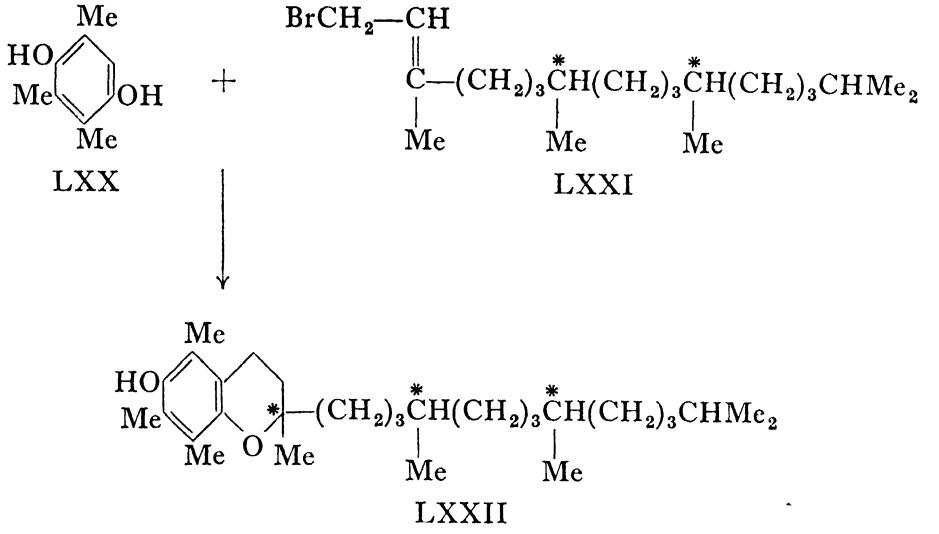
Natural vitamin E is (+)-α-tocopherol. The compounds β, γ, and δ-tocopherol are chemically closely related to α-tocopherol and have similar but less intense vitamin E activity. The effects of a diet deficient in vitamin E were first observed in 1920 (160) and α-tocopherol was isolated from a concentrate possessing vitamin E activity by Evans and his colleagues in 1936 (161); in 1938 Fernholz (162) suggested the now accepted formula for this substance.

Preparation. The tocopherols are present in vegetable oils such as soya-bean, wheat germ, cotton-seed and maize oils. The best source of natural (+)-α-tocopherol is wheat-germ oil. The wheat-germ is extracted with benzene or a similar solvent. After evaporation the residual oil is saponified by alcoholic alkali at 30° in the presence of an antioxidant. The soap solution is extracted with light petroleum. The concentrated solution is cooled and the steroids which crystallise first are filtered off; further cooling to −60° causes the vitamin E to crystallise. It may be purified by molecular distillation (163) or by chromatography (164).

(±)-α-Tocopherol (LXXII) may be prepared synthetically by condensing in a suitable solvent, trimethylquinol (LXX) and phytyl bromide (LXXI).

The atoms marked * are optically active carbon atoms, of which there are three in formula LXXII, and hence eight isomers are possible. Karrer used light petroleum as the solvent for the reaction with zinc chloride as a condensing agent (165, 166). Bergel used decalin (167) and Smith glacial acetic acid (168); formic acid has also been used (169).

Phytyl bromide is made by bromination of phytol (170) which may be extracted from plant tissues (171), although it has been synthesised (172, 173).



LXX LXXI

LXXII

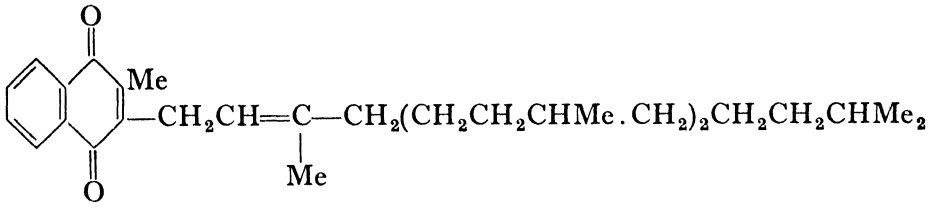
Trimethylquinol is prepared by oxidation of 1-amino-2 : 3 : 4 : 5-tetramethylbenzene (isoduridine) to trimethylquinone which is reduced with sulphurous acid to the required quinol (174 to 176). Alternatively Fremy's salt, $ON(SO_3K)_2$, can be used for the oxidation.

Properties. Natural (+)-α-tocopherol is a yellow oil boiling at 225° to 230° at 0·01 mm and melting at 2·5° to 3·5°. The refractive index is 1·5052 at 20°. It shows an absorption maximum at 292 mμ [E (1 per cent, 1 cm)=71]. The allophanate melts at 161° to 162°, the palmitate at 42° to 43° and the 2 : 4-dinitrobenzoate at 86° to 87°. Many esters have been described (177, 178). The acetate melts at 26·5° to 27·5° (179); this is the salt which is used in medicine.

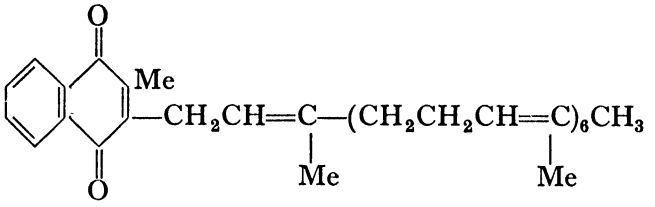
(±)-α-Tocopherol is a yellow oil melting at 0°. It has E (1 per cent, 1 cm)=70 at 292 mμ. The allophanate melts at 175° to 176°, the palmitate at 36° to 38° and the 2 : 4-dinitrobenzoate at 63°. It has been resolved into its optically active components by means of 3-bromocamphorsulphonyl chloride in pyridine (180).

In rats a deficiency of vitamin E affects the normal course of pregnancy in the female and the reproductive activity in the male. There is little evidence of its clinical value in human beings and its real function is obscure.

Vitamin K group. There are two members of this group, vitamin K_1 (phytomenadione) which is 2-methyl-3-phytyl-1 : 4-naphthoquinone, $C_{31}H_{46}O_2$ (LXXIII), and vitamin K_2 (farnoquinone) or 2-methyl-3-farnesylgeranylgeranyl-1 : 4-naphthoquinone, $C_{46}H_{64}O_2$ (LXXIV).



LXXIII

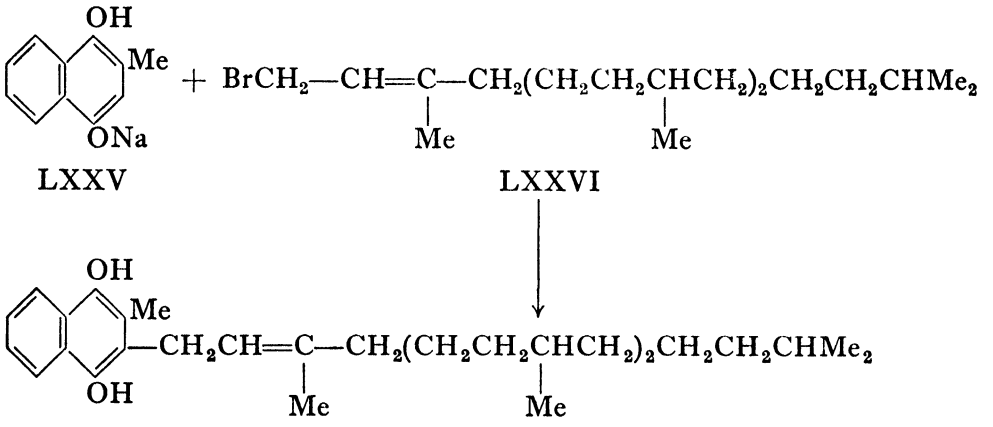


LXXIV

In addition to these two natural vitamins there are a number of synthetic compounds of related structure and having blood-coagulating properties similar to vitamin K; these are also described in this chapter.

In 1934 Dam concluded that the haemorrhagic condition of chicks raised on an artificial diet was due to avitaminosis and he called the new factor vitamin K. It was found to occur in alfalfa, spinach and other green leaves and in tomatoes and egg-yolk; vitamin K_1 was isolated from spinach in 1939 (181) and was synthesised in the same year (182, 183, 184). The structure of vitamin K_2, which is present in most bacteria, was elucidated in 1958 (185).

Preparation. Vitamin K_1 may be extracted from natural sources such as alfalfa. Chromatographic methods for the purification of the product have been patented (186). In the synthetic method of preparation (182) 2-methyl-1 : 4-naphthoquinol sodium salt (LXXV) has been reacted with phytyl bromide (LXXVI) to yield a quinol which is oxidised by air to vitamin K_1.



LXXV LXXVI

LXXIII

Other published synthetic routes are similar, although improvements have been introduced (187, 188). The 2-methyl-1 : 4-naphthoquinol used as an intermediate in the preparation of vitamin K_1 is itself an antihaemorrhagic substance called menaphthone or menadione (q.v.).

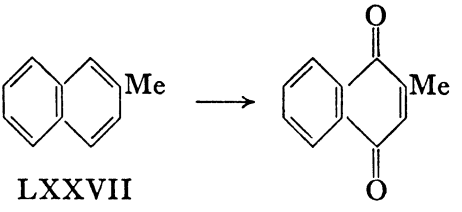
Properties. Vitamin K_1 is a yellow oil boiling at 115° to 145° at 2×10^{-4} mm pressure. It melts at −20°. It has five absorption peaks in the ultra-violet range

with E(1 per cent, 1 cm)=420 at 248 mμ. It is optically active; $[\alpha]_D^{20}=-0{\cdot}4°$ (57·5 per cent in benzene). It is soluble in ether, benzene and light petroleum, not very soluble in methanol and insoluble in water; it is sensitive to light, strong acids or alkalis.

Vitamin K_2 forms yellow crystals melting at 53·5° to 54·5°. It is sparingly soluble in benzene, light petroleum, anhydrous ethanol and acetone, but insoluble in water. The absorption spectrum is similar to that of vitamin K_1 with E(1 per cent, 1 cm)=295 at 248 mμ.

Menaphthone. Menadione. 2-Methyl-1 : 4-naphthoquinone. $C_{11}H_8O_2$. (LXXVIII). The antihaemorrhagic activity of menaphthone was discovered in 1939 (189).

Preparation. Menaphthone is most easily prepared by the oxidation of 2-methylnaphthalene (LXXVII) which is a by-product of the coal-tar industry.

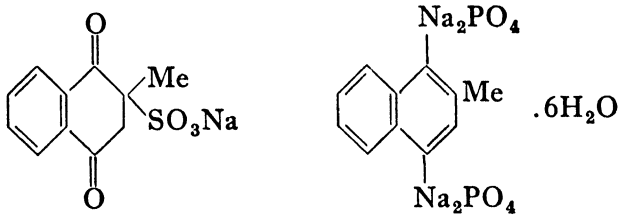


LXXVII LXXVIII

Chromic acid (190, 191, 192) or hydrogen peroxide (193) may be used as oxidising agents. Other methods of synthesis of menaphthone have been published (194, 195, 196).

Properties. Menaphthone is a bright yellow crystalline powder, which is irritating to the mucous membranes and to the skin; it has a faint characteristic odour. It melts at 105° to 107°; it is almost insoluble in water (0·013 g in 100 ml) and is slightly more soluble in ethanol.

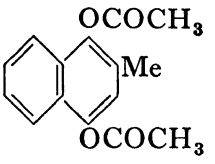
Derivatives of Menaphthone. Two water-soluble derivatives of menaphthone have been introduced into therapy. One is the sodium bisulphite compound (LXXIX), the preparation of which has been patented (197) and the other is menadiol sodium diphosphate (LXXX) which has also been patented (198).



LXXIX LXXX

Acetomenaphthone. Menadiol diacetate. 2-Methyl-1 : 4-naphthalenediol diacetate. $C_{15}H_{14}O_4$.

Preparation. 2-Methyl-1 : 4-naphthoquinone obtained by chromic acid oxidation of 2-methylnaphthalene is reduced (199) by zinc dust in a mixture of acetic acid and acetic anhydride yielding acetomenaphthone (LXXXI).



LXXXI

Properties. Acetomenaphthone is a white crystalline powder melting at 114°. It is almost insoluble in water and slightly soluble in cold ethanol but soluble in boiling ethanol (1 in 3·3); it is also soluble in acetic acid.

Acetomenaphthone is used orally for the treatment of prothrombin deficiency.

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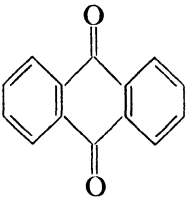
CHAPTER XIX

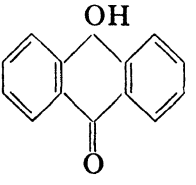
Purgatives

Introduction. Purgatives may be divided into two main groups according to their mode of action. The first group, commonly called laxatives, affects the bulk or consistency of the stools and includes salines such as magnesium and sodium sulphates, liquid paraffin, mucilaginous drugs such as agar and psyllium, and the synthetic compound dioctyl sodium sulphosuccinate (see p. 189). The second group contains purgatives whose effect is due to their irritant action on the bowel and includes the anthracene purgatives (aloes, rhubarb, senna, cascara sagrada and frangula), jalap, podophyllum, colocynth, castor oil, mercurous chloride and phenolphthalein (see p. 189). Only those purgatives, the chemical nature of whose active principles is known, will be described in this chapter.

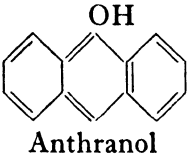
Anthracene purgatives. This group is characterised by the fact that the active principles are anthracene derivatives which are present in the drug both in the free state and in the form of glycosides. The purgative action appears to be due mainly to the latter (1). Mühlemann (2) states that the reduction products of the anthraquinone glycosides (anthranol glycosides) appear to be the active principles of these drugs, though so far these have been isolated in a pure state only from senna. Reduction of anthraquinone can form the following compounds.



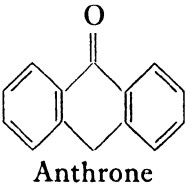
Anthraquinone



Oxanthrone



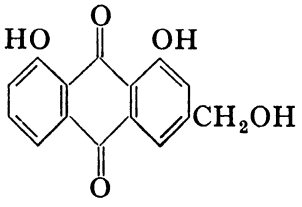
Anthranol



Anthrone

Reduction of anthraquinone glycosides with hydrogen gives products that can be isolated only with the utmost difficulty, since they were readily oxidised by the air. This may explain why, apart from the sennasides, no anthranol glycosides have been prepared in crystalline form from the drugs.

Among the aglycones that have been isolated from these drugs are *aloe-emodin* (I), *frangula-emodin* (II), *rhein* (III), and *chrysophanic acid* (IV).



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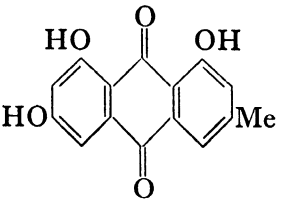

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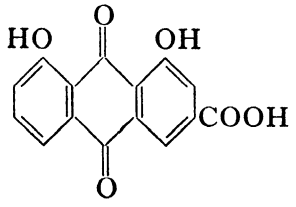

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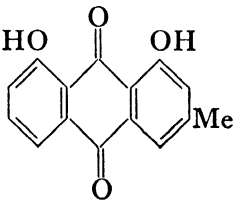

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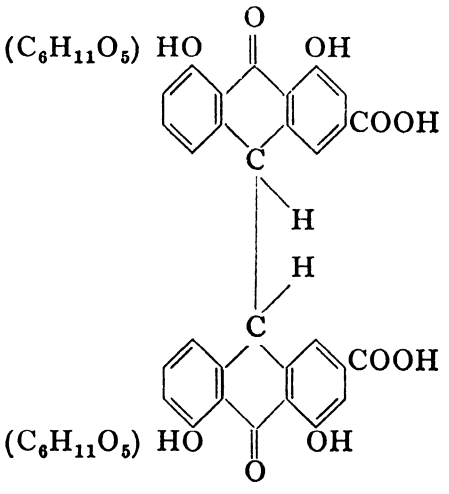
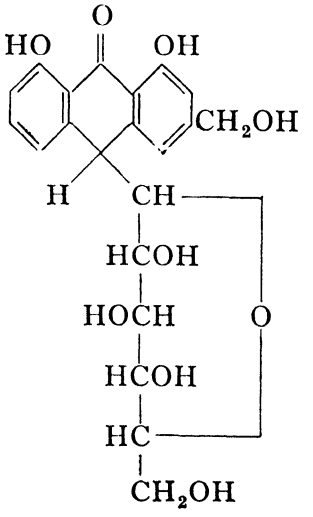


V

Senna. The drug consists of the leaves or fruits (pods) of *Cassia acutifolia* Delile or of *C. angustifolia* Vahl. It is prepared in various pharmaceutical forms for administration. It contains *rhein*, *aloe-emodin*, *kaempferol* and iso*rhamnetin* in the free state and in the form of glycosides, but the most important constituents are probably the two compounds *sennosides A and B* which have been isolated by Stoll and his colleagues (3). The drug was extracted with chloroform - ethanol to remove impurities, then with methanol containing oxalic acid; on concentrating the extract sennoside A separated out as crystals and, after

dissolving and reprecipitating, the triethylamine salt was obtained pure. The mother liquor was treated with calcium chloride and methanolic ammonia and the precipitate was suspended in methanol; addition of oxalic acid liberated sennoside B which was filtered off from the precipitated calcium oxalate and the filtrate evaporated *in vacuo*. Sennoside B crystallised after one or two days. The sennosides have the structure V (4). Sennoside A is the dextro-isomer and sennoside B is the meso compound. The aglycones are known as *sennidins A and B*.

Aloes. This drug is the solid residue obtained by evaporating the liquid which drains from the leaves cut from various species of *Aloe*. It contains the glucoside *barbaloin*, iso*barbaloin* (in Curaçao aloes), *aloe-emodin* and other anthracene derivatives. The structure of barbaloin is represented by VI (5) from which it will be seen that it is the glucoside of the anthrone corresponding to aloe-emodin (I) chemically described as 10(1 : 5-anhydroglucosyl)aloe-emodin-9-anthrone. This has been synthesised by Mühlemann (6).



VI

Rhubarb. The drug consists of the rhizome of *Rheum palmatum* Linn. and possibly other species of *Rheum* except *R. rhaponticum*. Many anthracene derivatives have been isolated from rhubarb including *rhein*, *frangula-emodin*, *aloe-emodin* and its methyl ether, and *chrysophanic acid*.

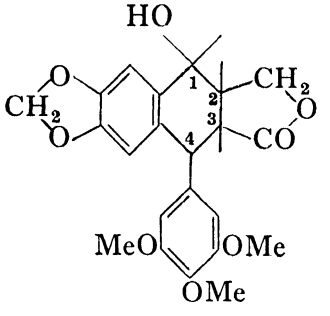
Owing to its astringent effect, due to its tannin content, rhubarb is not often used nowadays.

The rhizome of *R. rhaponticum* is excluded from the official drug. It contains no aloe-emodin, frangula-emodin or rhein but contains an anthraglucoside *rhaponticin*, which is readily separated and crystallised from ether; it also fluoresces bright blue in ultra-violet light.

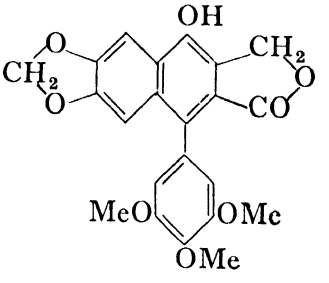
Cascara sagrada. This is the dried bark of the shrub *Rhamnus purshiana* DC. It contains *frangula-emodin*, *aloe-emodin* and iso*emodin* partly in combination as glycosides (7); it also contains a glycoside of oxanthrone (8).

Frangula. The dried bark of *Rhamnus frangula* Linn. contains, in addition to other anthracene derivatives, a crystalline glycoside *frangulin*, which, on hydrolysis, yields frangula-emodin and rhamnose.

Podophyllum. The drug consists of the dried roots and rhizome of *Podophyllum peltatum* Linn. or of *P. hexandrum* Royle (Indian podophyllum). The chief active principle is *podophyllotoxin* accompanied by its isomer *picropodophyllin* which is inert. These appear to be C_3-epimers probably having the formula VII (9). The position of the hydroxyl group has not been definitely established. Small amounts of *demethylpodophyllotoxin* and 1-O-(*β*-D-*glucopyranosyl*)-*picropodophyllin* (10) and of *dihydropodophyllotoxin* (VIII) (11) have also been found.



VII



VIII

Podophyllum is a drastic purgative which is not now much used for this purpose, but it has been found that it is effective in the removal of certain tumours such as warts and condylomata acuminata. The chemistry of the constituents of podophyllum has been reviewed by Hartwell and Schrecker (12).

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CHAPTER XX

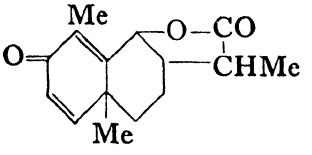
Miscellaneous Natural Drugs

Natural anthelmintics. (See p. 155 for synthetic anthelmintics).

Santonin. The drug known as *santonica* consists of the dried unexpanded flower-heads of *Artemisia cina* Berg. and of other species of *Artemisia*; the important constituent is *santonin* which is used for the expulsion of roundworms.

Santonin is prepared from santonica by treatment with milk of lime when calcium santoninate is formed and is converted into the sodium salt by treatment with sodium hydroxide and carbon dioxide. On decomposing the sodium salt with sulphuric acid, santonin is precipitated and is recrystallised from boiling water.

Structure. The structure of santonin is represented by (I) (1). Santonin shows an interesting relationship to the sesquiterpene group in that it is a derivative of 1 : 4-dimethyl-6-*iso*propylnaphthalene (II), an isomeride of cadalene from which many sesquiterpenes such as cadinene are derived. By prolonged treatment with hydrochloric acid desmotroposantonin (III) is formed, the synthesis of which has been patented (2). The total synthesis of santonin has also been published (3).



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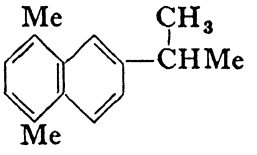

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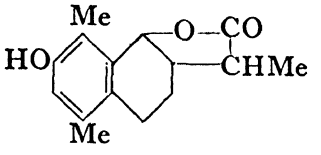


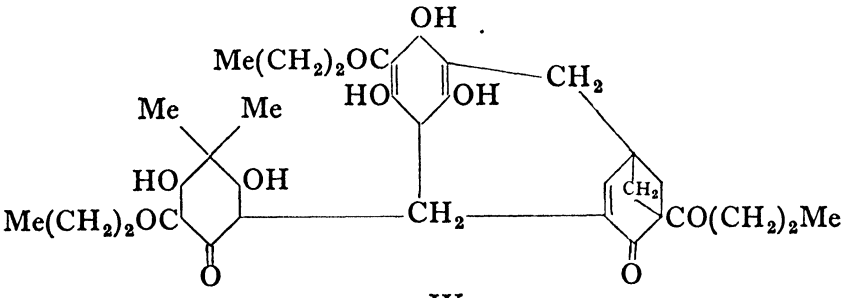
III

Properties. (—)-Santonin, $C_{15}H_{18}O_3$, crystallises in colourless shining prisms melting at 170° and having $[\alpha]_D^{20}$ —173·8° (chloroform). It may be sublimed and becomes yellow when exposed to light. Santonin is a lactone and treatment with alkalis converts it to the corresponding acid, santoninic acid.

Santonin is accompanied in santonica by β-santonin, a stereoisomeride of (—)-santonin and by ψ-santonin. The stereochemistry of santonin has been discussed by Cocker and McMurry (4).

Male Fern. Male Fern consists of the rhizome, frond-bases and apical bud of *Dryopteris filix-mas* (Linn.) Schott. It is used in the form of a soft extract for

the expulsion of tapeworms and sometimes of other intestinal parasites. The main active constituent of the drug is known as *filmarone*, but this is probably a mixture; when hydrolysed *filicic acid* and *aspidinol* are formed. *Filicin* which is extracted from the drug by ether is the lactone of filicic acid (IV). Further degradation gives filicinic acid (V) which has been synthesised (5). Another constituent is flavaspidic acid (VI) (6) which has also been synthesised (7). For a comprehensive review of the constituents of male fern see Büchi (7a).



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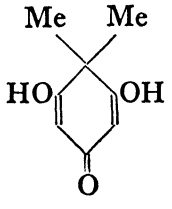

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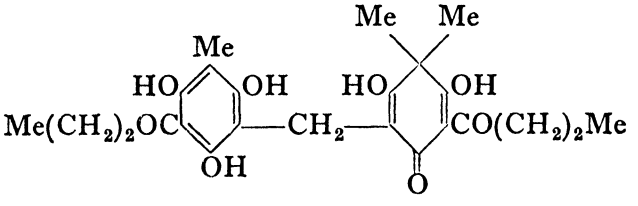
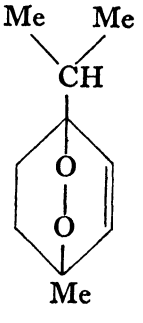


VI

Chenopodium oil. American Wormseed oil. Chenopodium oil is distilled from *Chenopodium ambrosioides* var. *anthelminticum*. The active principle is *ascaridole* of which it contains about 70 per cent. It is chiefly used for the expulsion of roundworms. The oil is a colourless or pale yellow liquid with an unpleasant odour. The weight per ml is about 0·965 g and the optical rotation −4° to −8°. Owing to the peroxide nature of ascaridole it boils vigorously when heated and may explode.

Ascaridole has the structure VII.



VII

Picrotoxin. Picrotoxin is a glycoside obtained from the seed of *Anamirta paniculata* Colebrooke. It is used as an antidote in barbiturate poisoning. Picrotoxin is a powerful analeptic. It may be obtained from the seed by extraction with boiling ethanol; after evaporating off the ethanol the fatty residue is extracted with hot water; on cooling, the picrotoxin crystallises and may be purified by recrystallisation.

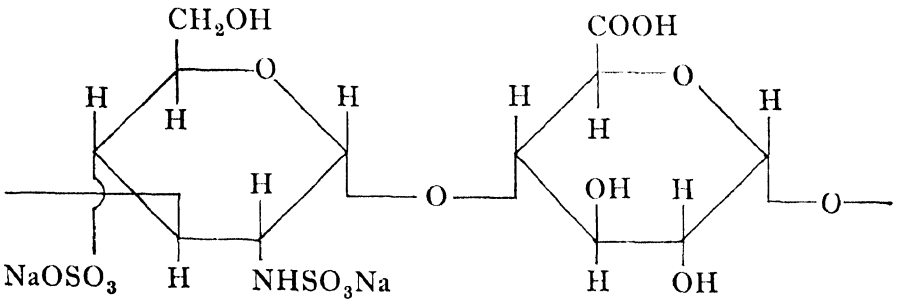
Constitution. Picrotoxin, $C_{30}H_{34}O_{13}$, is a compound of one molecule of picrotoxinin, $C_{15}H_{16}O_6$, and one molecule of picrotin, $C_{15}H_{18}O_7$ (8, 9).

Properties. Picrotoxin forms colourless shining crystals or a white crystalline powder; it is affected by light. It melts at 199° to 202° and has $[\alpha]_D^{20}$ about −30° (4 per cent in ethanol). It is slightly soluble in water, more soluble in boiling water and in ethanol (1 in 16).

Heparin. Heparin is a natural constituent of the mammalian body and has the property of delaying the clotting of the blood. It occurs mainly in the liver and lungs.

Preparation. Heparin may be prepared by the method of Charles and Scott (10). The ground fresh ox-liver or lung with weak alkali either directly or after autolysis at 37° for 24 hours. The mass is extracted for one hour with 0·5 N sodium hydroxide containing ammoniumsulphate after which it is coagulated by heating to 70°. The filtered extract is acidified to pH 2 which precipitates the heparin together with proteins. After removal of the ammonium sulphate with water the fat is removed with ethanol. The precipitate is dissolved and digested with trypsin for 36 hours. The heparin is then precipitated with ethanol from the acid solution. Further protein is removed by dissolving in dilute sodium hydroxide solution, adding acetic acid until the pH is about 5 and precipitating with cadmium chloride. The heparin may be further purified by precipitating as the brucine complex, regenerating with ammonia and precipitating as the barium salt. By treatment with sodium carbinate the barium is replaced by sodium, the sodium heparin salt being precipitated from the filtrate with ethanol.

Heparin is not a pure compound and varies from batch to batch in biological activity.



VIII

Structure. Heparin consists of a chain of alternate glucosamine and glucuronic-acid groups. It is an ethereal sulphate containing in the purest preparations of the sodium salt about 13·8 per cent of sulphur which corresponds with two sulphate groups to each glucosamine—glucuronic-acid pair. Formula VIII has been proposed for heparin (11), the chain being continued in both directions.

For a detailed discussion of the chemistry and therapeutic use of heparin see Jorpes (12).

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Appendix I

OFFICIAL OR APPROVED NAMES
with
PROPRIETARY EQUIVALENTS
and
CHEMICAL NAMES

IN this appendix are included the official names of drugs included in the British Pharmacopoeia and in the United States Pharmacopoeia together with names approved by the British Pharmacopoeia Commission and some names included in other British and United States official publications; some proprietary names of these drugs are given and also their chemical names.

Official or Approved Name	*Proprietary Names*	*Chemical Names*
Acepromazine	Notensil	2-acetyl-10-(3-dimethyl-aminopropyl)phenothiazine
Acetarsol =Acetarsone	Stovarsol, Spirocid, Orarsen, Kharophen	3-acetylamino-4-hydroxy-phenylarsonic acid
Acetazolamide	Diamox	2-acetamido-1 : 3 : 4-thiadiazole-5-sulphonamide
Acetomenaphthone	Kapilon-Oral Prokayvit-Oral Synkayvit-Oral	1 : 4-diacetoxy-2-methyl-naphthalene
Acetphenetidine, see Phenacetin (p. 40)		
Acinitrazole	Trichorad	2-acetamido-5-nitro-thiazole
Adrenaline =Epinephrine	Suprarenalin Suprarenin	
*nor*Adrenaline, see Noradrenaline		
Aldesulphone sodium		disodium salt of 4 : 4-diaminodiphenylsulphone formaldehyde sulphoxylic acid
Aldosterone	Aldocorten Electrocortin	
Allobarbitone	Dial	5 : 5-diallylbarbituric acid
Allylbarbituric acid	Sandoptal	5-allyl-5-*iso*butylbarbituric acid
Aloxidone	Malidone Malazol	3-allyl-5-methyloxazolidine-2 : 4-dione

Alphameprodine		α-3-ethyl-1-methyl-4-phenyl-4-propionoxypiperidine
Alphaprodine		α-1 : 3-dimethyl-4-phenyl-4-propionoxypiperidine
Ambazone	Iversal	1 : 4-benzoquinone amidinohydrazine thiosemicarbazone hydrate
Amethocaine hydrochloride	Anethaine Decicaine Pantocaine Pontocaine	*p*-*n*-butylaminobenzoic ester of 2-dimethylaminoethanol hydrochloride
Amidone, see Methadone		
Aminacrine	Acramine Monacrine	5-aminoacridine
4-Aminobenzoic acid	PABA	
Aminometradine	Mictine	1-allyl-6-amino-3-ethyl-1 : 2 : 3 : 4-tetrahydropyrimidine-2 : 4-dione
Amiphenazole	Daptazole	2 : 4-diamino-5-phenylthiazole
Aminophyllin	Cardophyllin Euphyllin Genophyllin	theobromine with ethylenediamine
Aminopterin		4-aminopteroylglutamic acid
Aminosalicylic acid	PAS	4-aminosalicylic acid
Amiphenazole	Paramisan	
Amobarbital, see Amylobarbitone		
Amodiaquine	Camoquin	7-chloro-4-(3-diethylaminoethyl-4-hydroxyanilino)-quinoline
Amoxecaine		*NN*-triethylethylenediamine-*N*-β-ethyl *p*-aminobenzoate
Amphetamine	Benzedrine	(±)-2-amino-1-phenylpropane
Amydricaine	Alypin	benzoyl ester of tetramethyldiaminodimethylethylcarbinol hydrochloride
Amylobarbitone	Amytal	5-ethyl-5-*iso*pentylbarbituric acid
Amylocaine	Stovaine	benzoyl ester of methylethyldimethylaminomethylcarbinol hydrochloride
Anhydrohydroxyprogesterone, see Ethisterone		
Anileridine		ethyl 1-(2-*p*-aminophenylethyl) 4-phenylpiperidine-4-carboxylate

Antazoline	Antistin Histostab	2-*N*-benzylanilinomethyl-iminazoline
Anthralin		1 : 8 : 9-anthratriol
Antipyrin, see Phenazone (p. 41)		
Aprobarbital	Alurate	5-allyl-5-*iso*propylbarbituric acid
Arterenol, see Noradrenaline		
Atropine methylbromide	Mydriasin	
Atropine methylnitrate	Eumydrin	
Aurothioglucose	Solgenal	
Azamethonium bromide	Pendiomide	3-methyl-5-azapentene-1 : 5-bis(ethyldimethyl-ammonium) dibromide
Azovan blue	Evans Blue	tetrasodium salt of 4 : 4′-bis-[7-(1-amino-8-hydroxy-2:4-disulpho)naphthylazo]-3:3′-bitolyl
BAL, see Dimercaprol		
Barbitone	Veronal	5 : 5-diethylbarbituric acid
Beclamide	Nydrane	*N*-benzyl-β-chloropropion-amide
Bemegride	Megimide	β-ethyl-β-methylglutarimide
Benactyzine	Suavitil	2-diethylaminoethyl benzilate
Benethamine penicillin	Benapen	*N*-benzyl-2-phenylethylamine salt of benzylpenicillin
Benzalkonium chloride	Roccal Zephiran	Alkyldimethylbenzyl-ammonium chloride
Benzathine penicillin	Dibencil Neolin Penidural Permapen	*NN*-dibenzylethylenediamine di(benzylpenicillin)
Benzethonium chloride	Phemeride Phemerol chloride	benzyldimethyl-*p*-(1 : 1 : 3 : 3-tetramethylbutyl)phenoxy-ethoxyethylammonium chloride
Benzhexol	Artane Pipanol	1-*cyclo*hexyl-1-phenyl-3-piperidino-1-propanol
Benzocaine	Anaesthesin	ethyl 4-aminobenzoate
Benzpyrinium bromide		1-benzyl-3-(dimethylcarb-amyloxy) pyridinium bromide
Benztropine methane-sulphonate	Cogentin	3-diphenylmethoxytropane methanesulphonate
Betameprodine		β-3-ethyl-1-methyl-4-phenyl-4-propionoxypiperidine

Betaprodine		β-1 : 3-dimethyl-4-phenyl-4-propionoxypiperidine
Bethanicol	Urecholine	β-methylcholine chloride urethane
Bialamicol	Camoform	3 : 3′-diallyl-5 : 5′-bisdiethylamino-methyl-4 : 4′-dihydroxydiphenyl
Bisacodyl	Dulcolax	di-(*p*-acetoxyphenyl)-2-pyridylmethane
Bishydroxycoumarin, see Dicoumarol		
Bismuth glycollylarsanilate	Milibis	bismuthyl-*N*-glycollylarsanilate
Bismuth sodium thioglycollate	Thiobismol	
Bismuth tribromophenate	Xeroform	
Bithionol		2 : 2′-thiobis(4 : 6-dichlorophenol)
Bromazine	Ambodryl	2-(4-bromodiphenylmethoxy)-ethyldimethylamine
Bromethol	Avertin	tribromoethanol solution
Bromisoval Bromvaletone	Bromural	2-bromo*iso*valerylurea
Buclizine	Longifene Vibazine	1-(4-*tert.*-butylbenzyl)-4-(chlorophenylbenzyl)-phenazine
Buphenine	Perdilatal	1-*p*-hydroxyphenyl-2-(1-methyl-3-phenylpropylamino)propanol
Busulphan	Myleran	1 : 4-dimethanesulphonyloxybutane
Butabarbital	Butisol	5-ethyl-5-(1-methylpropyl)-barbituric acid
Butacaine	Butyn	γ-di-*n*-butylaminopropyl-*p*-aminobenzoate
Butethamine	Monocaine	2-*iso*butylaminoethyl-*p*-aminobenzoate
Buthalitone sodium		5-allyl-5-*iso*butyl-2-thiobarbituric acid (+sodium carbonate)
Butobarbitone	Neonal Soneryl	5-*n*-butyl-5-ethylbarbituric acid
Butopyronoxyl	Indalone	butyl 4 : 5-dihydro-6 : 6-dimethyl-4-oxopyran-2-carboxylate

Butyl aminobenzoate	Butesin Planoform Scuroform	*n*-butyl 4-aminobenzoate
Camoquine		7-chloro-4-(diethylamino-methyl-4-hydroxyanilino)-quinoline
Camphotamide		camphosulphonyl-*N*-methyl-pyridine-*β*-diethylcarbon-amide
Captodiame	Covatin	*p*-butylthiodiphenylmethyl 2-dimethylaminoethyl sulphide
Caramiphen	Parpanit	2-diethylaminoethyl-1-phenyl-*cyclo*pentane-1-carboxylate
Carbachol	Moryl	carbamylcholine chloride
Carbarsone	Aminarsone Amabevan Leukarsone	*p*-carbamidophenylarsonic acid
Carbimazole	Neo-Mercazole	2-ethoxycarbonylthio-1-methylglyoxaline
Carbomycin	Magnamycin	antibiotic
Carbutamide	BZ 55 Invenol Nadisan	*N*-butyl-*N'*-sulphanilylurea
Caronamide	Staticin	4'-carboxyphenylmethane-sulphonanilide
Cetomacrogol 1000		polyethylene glycol 1000 monoacetyl ether
Cetrimide	Cetavlon	hexadecyltrimethyl-ammonium bromide
Cetrimonium chloride		hexadecyltrimethyl-ammonium chloride
Chiniofon	Avlochin Quinoxyl Yatren	7-iodo-8-hydroxyquinoline-5-sulphonic acid
Chlorambucil	Leukeran	*p*-di(2-chloroethyl)amino-phenyl-butyric acid
Chloramphenicol	Alficetyn Chloromycetin	di-(−)-*threo*-2-dichloro-acetamido-1-*p*-nitrophenyl--1 : 3-propanediol
Chlorbutol	Chloretone	trichloro-*tert.*-butanol
Chlorcyclizine	Di-paralene Histantin Perazil	(±)-1-(*p*-chlorobenzhydryl)--4-methylpiperazine

Chlorhexidine	Hibitane	bis-*p*-chlorophenyldiguanidohexane
Chlorisondamine chloride	Ecolid	4 : 5 : 6 : 7-tetrachloro-2-(2-dimethylaminoethyl)-*iso*indoline dimethochloride
Chlormerodrin	Merchloran Neohydrin	3-chloromercuri-2-methoxypropylurea
Chlormethine		di-(chloromethyl)methylamine
Chlornaphazine		2 : 2-dichlorodiethyl-β-naphthylamine
Chloroazodin	Azochloramide	*NN*-dichloroazodicarbamidine
Chloroguanide, see Proguanil		
Chloromethapyrilene, see Chloropyrilene		
Chlorophenothane, see Dicophane		
Chloropyramine, see Halopyramine		
Chloropyrilene		*N*-5-chloro-2-thienylmethyl-*N'N'*-dimethyl-*N*-2-pyridylethylenediamine
Chloroquine	Aralen Nivaquine Santoquine	7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline
Chlorothen, see Chloropyrilene		
Chlorotrianisene	TACE	tri(*p*-methoxyphenyl)chloroethylene
Chlorphenesin	Mycil	3-*p*-chlorophenoxypropane
Chlorpheniramine	Chlor-Trimeton Piriton	1-(*p*-chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane
Chlorphenoctium amsonate		2 : 4-dichlorophenoxymethyldimethyl-*n*-octylammonium amsonate
Chlorproguanil	Lapudrine	N^1-3 : 4-dichlorophenyl-N^5-*iso*propyldiguanide
Chlorpromazine	Largactil Megaphen Thorazine	3-chloro-10-(3-dimethylaminopropyl) phenothiazine
Chlorprophenpyridamine, see Chlorpheniramine		
Chlorquinaldol		5 : 7-dichloro-8-hydroxy-2-methyl-quinoline
Chlortetracycline	Aureomycin	antibiotic
Clemizole	Allercur	1-*p*-chlorobenzyl-2-pyrrolidinomethylbenziminazole
Clemizole penicillin	Megacillin Neopenyl	benzylpenicillin combined with clemizole

Cinchocaine	Nupercaine	β-diethylaminoethylamide of 2-butyloxycinchoninic acid
Cinchophen	Agotan Atophan Quinophan	2-phenylquinoline-4-carboxylic acid
Corbadrine		1-(3 : 4-dihydroxyphenyl)-2-aminopropanol
Corticotrophin	Cortrophin	
Cortisone	Cortone	
Cyanocobalamin	Anacobin Cobione Cytamin	
Cyclamate sodium	Sucaryl	sodium *cyclo*hexylsulphamate
Cyclizine	Marzine	1-methyl-4α-phenylbenzyl-piperazine
Cyclobarbitone	Phanodorm	5-ethyl-5-*cyclo*hexenyl-barbituric acid
Cyclocoumarol	Cumopyran	5′ : 6′-dihydro-6′-methyl-4′-phenylpyrano-(3′ : 2′-3 : 4-) coumarin
Cyclomethycaine	Surfacaine Surfathesin Topocaine	3-(2-methylpiperidino)-propyl *p-cyclo*hexyloxy-benzoate
Cyclopentamine	Clopane	1-*cyclo*pentyl-2-methyl-aminopropane
Cycloserine		(+)-4-amino-3-isoxazolidin-one
Dapsone	Avlosulphon	4 : 4′-diaminodiphenyl sulphone
Deanol	Atrol	2-dimethylaminoethanol
Decamethonium iodide	Eulissin Syncurine	decamethylene-1 : 10-bistri-methylammonium di-iodide
Dehydrocholic acid	Certonin Decholin Dehydrocholin	3 : 7 : 12-trioxocholanic acid
Demecolcine	Colcemid	deacetylmethylcolchicine
Deoxycortone acetate	Cortiron DOCA Percorten	deoxycorticosterone acetate
Dequalinium chloride	Dequadin	decamethylenebis-(4-amino-quinaldinium chloride)
Desoxyephedrine, see Methylamphetamine		
Dexamphetamine	Dexedrine	(+)-amphetamine

Dextromethorphan		(+)-3-methoxy-*N*-methylmorphinan
Dextromoramide	Jetrium R.875	(+)-1-(β-methyl-γ-morpholino-αα-diphenylbutyryl)-pyrrolidine
Dextrorphan		(+)-3-hydroxy-*N*-methylmorphinan
Diacetylnalorphine		diacetyl-*N*-allylnormorphine
Diamorphine	Heroin	diacetylmorphine
Dibethinium		dibenzylmethylamine
Dibucaine, see Cinchocaine		
Dichlorophenarsine hydrochloride	Chlorarsen Dichloro-Mapharsen	3-amino-4-hydroxyphenyldichloroarsine hydrochloride
Dichloroxylenol		2 : 4-dichloro-3 : 5-xylenol
Dicophane	DDT	2 : 2-di-(*p*-chlorophenyl)-1 : 1 : 1-trichloroethane
Dicoumarol	Temparin	3 : 3-methylenebis-4-hydroxycoumarin
Dicyclomine	Wyovin	2-diethylaminoethyl di*cyclo*hexyl-1-carboxylate
Diethazine	Diparcol	*N*-2-diethylaminoethylphenothiazine
Diethylcarbamazine	Banocide Ethodryl Hetrazan	1-diethylcarbamoyl-4-methylpiperazine
Diethylstilboestrol, see Stilboestrol		
Diethylthiambutene	Themalon	3-diethylamino-1 : 1-di-2′-thienylbut-1-ene
Dihydrallazine	Nepresol	1 : 4-dihydrazinophthalazine
Dihydrocodeinone	Dicodid	
Dihydromorphinone	Dilaudid	
Dihydrotachysterol	AT 10	
Di-iodohydroxyquinoline	Dioquin Embequin	8-hydroxy-5 : 7-di-iodoquinoline
Diloxanide	Entamide	*N*-dichloroacetyl-*p*-hydroxy-*N*-methylaniline
Dimenhydrinate	Dramamine	8-chlorotheophylline salt of (2-diphenylmethoxyethyl)-dimethylamine
Dimercaprol	BAL	2 : 3-dimercaptopropanol
Dimethylthiambutene		3-dimethylamino-1 : 1-di-2′-thienylbut-1-ene
Dimethyltubocurarine	Diamethine Metubine	
Dimethisterone	Secrosteron	6α : 21-dimethylethisterone

Dimoxylinium phosphate		6 : 7-dimethoxy-1-(4′-ethoxy-3′-methoxybenzyl)-3-methyl*iso*quinolinium phosphate
Diodone	Arteriodone Diodrast Perabrodil Pyelosil Pylumbrin Uriodone	diethanolamine salt of 3 : 5-di-iodo-4-pyridone-*N*-acetic acid
Dioxaphetyl butyrate		ethyl 4-morpholino-2 : 2-diphenylbutyrate
Diperodon	Diothane	3-(1-piperidyl)-1 : 2-propanediol dicarbanilate
Diphemanil methylsulphate	Diphenatil	4-diphenylmethylene-1 : 1-dimethylpiperidinium methylsulphate
Diphenan	Butolan Oxylan	*p*-benzylphenylcarbamate
Diphenhydramine	Benadryl	benzhydryl 2-dimethylaminoethyl ether
Diphenylhydantoin, see Phenytoin		
Dipipanone	Pipadone	4 : 4-diphenyl-6-piperidinoheptan-3-one
Disulfiram	Abstinyl Antabuse Cronetal	tetraethylthiuram disulphide
Dithranol	Anthralin Cignolin Dioxythranol	1 : 8-dihydroxyanthranol
Dixanthogen		diethyldixanthogen
Domiphen bromide	Bradosol	dodecyldimethyl-2-phenoxyethylammonium bromide
Doxylamine	Decapryn	2-(α-2-dimethylaminoethoxy-α-methylbenzyl)pyridine
Diflos	DFP	di-*iso*propyl fluorophosphonate
Edetic aid		ethylenediaminetetra-acetic acid
Edrophonium chloride	Tensilon	ethyl-*m*-hydroxyphenyldimethylammonium chloride
Ergometrine maleate Ergotamine tartrate	Ergotrate Femergin Gynergen	

Erythromycin	Erythrocin Ilotycin	antibiotic
Ethinamate	Valmid Valmidate	1-ethinyl*cyclo*hexyl carbamate
Ethisterone =Anhydrohydroxyprogesterone	Gestone-oral Lutocyclin Oraluton Pranone Progestoral Proluton C	17-ethinyltestosterone
Ethoheptazine	Zactane	ethyl (±)-1-methyl-4-phenyl-aza*cyclo*heptane-4-carboxylate
Ethohexadiol		2-ethylhexane-1 : 3-diol
Ethopropazine	Lysivane	*N*-(2-dimethylamino-*n*-propyl)phenothiazine
Ethotoin	Peganone	3-ethyl-5-phenylhydantoin
Ethylbiscoumacetate	Pelentan Tromexan	ethyl 4 : 4′-dihydroxycoumarin-3 : 3′-yl-acetate
Ethyl iodophenylundecylate	Ethiodan Myodil	
Ethyl methimazolate		2-carbethoxythio-1-methiminazole
Ethylmethylthiambutene		3-ethylmethylamino-1 : 1-di-2′-thienylbut-1-ene
Ethylmorphine	Dionin	
Ethyl pyrophosphate	TEPP	tetraethyl pyrophosphate
Ethylstibamine	Neostibamine Neostibosan	diethylamino-*p*-aminophenyl stibinate
Eucatropine	Euphthalmine	4-mandeloyloxy-1 : 2 : 2 : 6-tetramethylpiperidine
Florantyrone	Zanchol	γ-Fluoranthen-8-yl-γ-oxobutyric acid
Fludrocortisone		9-fluorohydrocortisone
Folic acid	Folvite	
Formamol	Helmitol	hexamine anhydromethylenecitrate
Forminitrazole		2-formamido-5-nitrothiazole
Framycetin	Soframycin	antibiotic
Furazolidone	Furoxone	3-(5-nitrofurfurylideneamino)-oxazolidin-2-one
Furostilboestrol		diethylstilboestrol furoate
Furtrethonium iodide	Furmethide	furfuryltrimethylammonium iodide

Gallamine	Flaxedil	1 : 2 : 3-tri-(2-diethylamino-ethoxy)benzene
Gamma benzene hexa-chloride	Lorexane	γ-1 : 2 : 3 : 4 : 5 : 6-hexa-chloro*cyclo*hexane
Glucosulphone	Promin	4 : 4′-diaminodiphenyl-sulphone-*NN*-di(glucose sodium sulphonate)
Glutethimide	Doriden	α-ethyl-α-phenylglutarimide
Gold sodium thiomalate	Myocrisin Crisalbine Novacrysin	
Gold sodium thiosulphate	Sanocrysin	
Halopyramine	Synopen	*N-p*-chlorobenzyl-*N′N′*-dimethyl-*N*-2-pyridyl-ethylenediamine
Halothane	Fluothane	2-bromo-2-chloro-1 : 1 : 1-trifluoroethane
Hedaquinium chloride	Teoquil	hexadecamethylenebis-(2-*iso*quinolinium) chloride
Hexachlorophane	Hexachlorophene	di-(3 : 5 : 6-trichloro-2-hydroxyphenyl)methane
Hexamethonium bromide	Vegolysen	hexamethylene-1 : 6-bistri-methylammonium di-bromide
Hexamethylene iodide	Hexathide	hexamethylene-1 : 6-bistri-methylammonium di-iodide
Hexamethonium tartrate	Vegolysen T	hexamethonium-1 : 6-bistri-methylammonium ditar-trate
Hexamine mandelate	Mandelamine	
Hexazole	Azoman Azozol	3-ethyl-4-*cyclo*hexyl-1 : 2 : 4-triazole
Hexethal	Ortal	5-ethyl-5-hexylbarbituric acid
Hexetidine	Sterisil	5-amino-1 : 3-di(2-ethyl-hexyl)hexahydro-5-methyl-pyrimidine
Hexobarbitone	Cyclonal Evipal Evipan Hexanastab	5-Δ^1-*cyclo*hexenyl-5-methyl-*N*-methylbarbituric acid
Hexoestrol	Synthovo	*meso*-$\gamma\delta$-bis(4-hydroxyphenyl) *n*-hexane
Hexylcaine	Cyclaine	1-*cyclo*hexylamino-2-propyl benzoate

Hexylresorcinol	Caprokol	*n*-hexylresorcinol
Hydrallazine	Apresoline Hydralazine	1-hydrazinophthalazine
Hydrocortisone (Cortisol)	Hydrocortone	17-hydroxycorticosterone
Hydroxamethocaine		2-dimethylaminoethyl-4-*n*-butylaminosalicylate
Hydroxyamphetamine	Paredrine	2-amino-1-*p*-hydroxyphenylpropane
Hydroxychloroquine	Plaquenil	
Hydroxydione sodium succinate	Viadril	sodium 21-hydroxypregnane-3 : 20-dione succinate
Hydroxypethidine		ethyl 4-*m*-hydroxyphenyl-1-methylpiperidine-4-carboxylate
Hydroxystilbamidine		4-4′-diamidino-2-hydroxystilbene
Hydroxytetracaine, see Hydroxamethocaine		
Hydroxyzine	Atarax	1-*p*-chlorobenzhydryl-4-[2-(2-hydroxyethoxy)-ethyl]piperazine
Hyoscine methobromide	Pamine	(—)-hyoscine methobromide
Ibrotamide		ethyl*iso*propyl-α-bromoacetamide
Inproquone		2 : 5-di(ethyleneimino)-3 : 6-dipropoxy-1 : 4-benzoquinone
Iodoalphionic acid, see Pheniodol		
Iodochlorhydroxyquin	Vioform	5-chloro-7-iodo-8-quinolinol
Iodophthalein	Opacin Opacol Stipolac	tetraiodophenolphthalein
Iodopyracet, see Diọdone		
Iodothiouracil	Itrumil	4-hydroxy-5-iodo-2-mercaptopyrimidine
Iodoxyl	Pyelectan Uropac Uroselectan B Urumbrin	disodium 3 : 5-di-iodo-*N*-methyl-4-pyridone-2 : 6-dicarboxylate
Iopanoic acid	Telepaque	α-(3-amino-2 : 4 : 6-tri-iodobenzyl)butyric acid
Iophendylate	Ethiodan Myodil Pantopaque	ethyl iodophenylundecylate
Iophenoxic acid		α-ethyl-3-hydroxy-2 : 4 : 6-tri-iodohydorcinnamic acid

Iproniazide		*N-iso*nicotinoyl-*N'-iso*propyl-hydrazine
Isoamidone Isomethadone		isomer of Amidone
Isothipendyl	Nilergex Theruhistin	10-(2-dimethylaminopropyl)-10-thia-1 : 9-diaza-anthracene
Ketobemidone	Cliradon	4-(3-hydroxymethyl)-1-methyl-4-propionylpiperidine
Laudexium methyl-sulphate	Laudolissin	Decamethylene-1 : 10-bis-1-(3 : 4-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-methyl-*iso*quinolinium methyl-sulphate
Leptazol Levallorphan	Cardiazole	1 : 5-pentamethylenetetrazole (—)-3-hydroxy-*N*-allyl-morphinan
Levarterenol, see Noradrenaline		
Levomethorphan		(—)-3-methoxy-*N*-methyl-morphinan
Levomoramide		(—)-1-(β-methyl-γ-morpholino-αα-diphenylbutyryl)-pyrrolidine
Levorphanol	Dromoran	(—)-3-hydroxy-*N*-methyl-morphinan
Lidocaine, see Lignocaine		
Lignocaine	Xylocaine	diethylaminoacet-2 : 6-xylidide
Liothyronine	Tertroxin	(—)-tri-iodothyronine
Lithium antimony thiomalate	Anthiomaline	
Lucanthone	Miracil D Nilodin	1-2'-diethylaminoethylamino-4-methylthiaxanthone
Maphenide	Marfanil Marprontil	*p*-sulphonamidobenzylamine hydrochloride
Mecamylamine	Inversine Mevasine	3-methylamino*iso*camphane
Meclozine	Ancolan	1-*p*-chlorobenzhydryl-4-*m*-methylbenzylpiperazine
Mecostrin, see Dimethyltubocurarine		

Melarsoprol		2-*p*-(4 : 6-diamino-*s*-triazin-2-ylamino)phenyl-4-hydroxymethyl-1 : 3 : 2-dithiarsoline
Melphalan		*p*-di-(2-chloroethyl)amino-L-phenylalanine
Menadiol sodium diphosphate		2-methyl-1 : 4-dihydroxynaphthalene sodium diphosphate
Menadione, see Menaphthone		
Menadoxime	Kapilon, soluble	ammonium salt of 2-methylnaphthaquinone-4-oxime *O*-carboxymethyl ether
Menaphthone	Kapilon Prokayvit	2-methyl-1 : 4-naphthaquinone
Mepacrine	Atabrine Atebrin Quinacrine	dihydrochloride of 2-chloro-5-(ω-diethylamino-α-methylbutylamino)-7-methoxyacridine
Mepazine	Pacatal	*N*-methylpiperidyl-3-methylphenothiazine
Meperidine, see Pethidine		
Mephenesin	Lissephen Myanesin Tolserol	3-(2-methylphenoxy)propane-1 : 2-diol
Mephenetoin		3-methyl-5 : 5-ethylphenylhydantoin
Mephentermine		2-methyl-1-phenyl-2-methylaminopropane
Mephobarbital, see Methylphenobarbitone		
Meprochol	Esmodil	2-methoxyprop-2-enyltrimethylammonium bromide
Mepyramine	Anthisan Neo-antergan	*N*-*p*-methoxybenzyl-*N'N'*-dimethyl-*N*-2-pyridylethylenediamine
Meralluride	Mercuhydrin	*N*-(3-hydroxymercuri-2-methoxypropylcarbamyl)-succinamic acid+theophylline
Merbromin		di-sodium 2 : 7-dibromo-4-hydroxymercurifluorescein
Mercaptamine		β-mercaptoethylamine
Mercaptomerin sodium	Thiomerin sodium	disodium salt of *N*-(3-carboxymethylthiomercuri-2-methoxypropyl)camphoramic acid

Mercuderamide		hydroxymercuripropanol-amide of *O*-carboxyphenoxy-acetic acid
Mercurobutol		4-*tert.*-butyl-2-chloromer-curiphenol
Mercurophylline sodium	Mercuzanthin	sodium salt of *N*-(3-hydroxy-mercuri-2-methoxypropyl)-camphoramic acid + theo-phylline
Mersalyl	Salyrgan	sodium salicyl-(γ-hydroxy-mercuri-β-methoxypropyl)-amide *O*-acetate
Mesulphen	Mitigal Sudermo	2 : 6-dimethylthianthrene
Metaraminol bitartrate	Aramine	(−)-1-*m*-hydroxyphenyl-2-amino-1-propanol hydrogen (+)tartrate
Methacholine chloride	Amechol Mecholyl chloride	acetyl-β-methylcholine chloride
Methadol		2-dimethylamino-4 : 4-diphenylheptan-5-ol
Methadone = Amidone	Adanon Physeptone	2-dimethylamino-4 : 4-diphenylheptan-5-one
Methadyl acetate		2-dimethylamino-4 : 4-diphenyl-5-heptyl acetate
Methallenoestril	Vallestril	3-(6-methoxy-2-naphthyl)-2 : 2-dimethylpentanoic acid
Methamphetamine, see Methylamphetamine		
Methandriol		17α-methyl-3β : 17β-dihy-droxyandrostene-5
Methanthelinium bromide	Banthine bromide	2-diethylaminoethyl xanthen-9-carboxylate methobro-mide
Methaphenilene	Diatrin	*N'N'*-dimethyl-*N*-phenyl-*N*-(2-thienylmethyl)ethyl-enediamine
Methapyrilene	Thenylene	*NN*-dimethyl-*N'*-(2-pyridyl)-*N'*-(2-thenyl)ethylenedi-amine
Metharbital	Gemonil	5 : 5-diethyl-1-methylbarbi-turic acid
Methimazole	Mercazole Tapazole	2-mercapto-1-methylimina-zole
Methiodal sodium	Abrodil Skiodan sodium	sodium iodomethanesulpho-nate

Methoestrol		$\alpha\beta$-diethyl-4 : 4′-dihydroxy-3 : 3′-dimethylstilbene
Methoin	Mesontoin	5-ethyl-3-methyl-5-phenylhydantoin
Methorphinan	Dromoran	(±)-3-hydroxy-*N*-methylmorphinan
Methotrimeprazine		10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine
Methoxamine	Vasoxine Vasylox	β-hydroxy-2 : 5-dimethoxy-α-methylphenylethylamine
Methoxyphenamine	Orthoxine	1-(2-methoxyphenyl)-2-methylaminopropane
Methyl phenidate	Ritalin	methyl 1-phenyl-2-piperidylacetate
Methylamphetamine =methamphetamine	Amphedroxin Desoxyn Methedrine	*N*-methylamphetamine
Methylbenzethonium chloride		Benzyldimethyl-{2-[2-(*p*-1 : 1 : 3 : 3-tetramethylbutylcresoxy)ethoxy]-ethyl}ammonium chloride
Methyldihydromorphinone	Metopon	
Methylergometrine	Methergin	(+)-1-hydroxy-2-butylamide of (+) lysergic acid
Methylhexaneamine	Forthane	1 : 3-dimethylpentylamine
Methylpentynol	Atempol Insomnol Oblivon Somnesin	3-methylpent-1-yn-3-ol
Methylphenobarbitone	Mebaral Prominal	5-ethyl-5-phenyl-1-methylbarbituric acid
Methyltesterone	Metandren Neo-Hombreol Perandren	17-methyl-Δ^4-androsten-17-ol-3-one
Methylthioninium chloride		tetramethylthioninium chloride
Methylthiouracil	Muracil	2-mercapto-4-hydroxy-6-methylpyrimidine
Methyprylone	Noludar	3 : 3-diethyl-5-methylpiperidine-2 : 4-dione
Morpheridine		morpholinoethylnorpethidine
Mustine		di-(2-chloroethyl)methylamine
Myleran		1 : 4-dimethylsulphonyloxybutane

Naepine	Amylsine	2-pentylaminoethyl *p*-aminobenzoate
Nalorphine	Lethidrone Nallene	*N*-allylnormorphine
Naphazoline	Privine	2-(naphthyl-1-methyl)iminazoline
Neoarsphenamine	Neosalvarsan	
Neocinchophen		ethyl 6-methyl-2-phenylquinoline-4-carboxylate
Neostigmine bromide	Prostigmine bromide	dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium bromide
Neostigmine methylsulphate	Prostigmine methylsulphate	dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulphate
Niacinamide, see Nicotinamide		
Nicopholine		morpholinonicotinic acid amide
Nicotinamide =Niacinamide	Niagrin Peloninamide	nicotinic acid amide
Nicotinyl alcohol	Ronicol	3-pyridylmethanol
Nicoumalone	Sinthrome	3-(2-acetyl-1-*p*-nitrophenylethyl)-4-hydroxycoumarin
Nikethamide	Anacardone Coramine Corvotone Cycliton Nicamide	diethylamide of pyridine-β-carboxylic acid
Nitrofurantoin	Furadantin	1-(5-nitro-2-furfurylideneamino)hydantoin
Nitrofurazone	Furacin	5-nitrofuran-2-aldehyde semicarbazone
Nitromersol	Metaphen	1-methyl-2 : 3-hydroxymercuri-4-nitrobenzene
Nitrosulphathiazole		2-(*p*-nitrophenylsulphonamido)thiazole
Noradrenaline =Norepinephrine =Levarterenol	Levophed Sympathin N	(−)-2-amino-1-(3 : 4-dihydroxyphenyl)ethanol
Norethandrolone	Nilevar	17α-ethyl-17-hydroxy-19-norandrost-4-en-3-one
Norethisterone	Norlutin Primolut N	17β-hydroxy-19-norpregn-4-en-20-yn-3-one
Normethadone		6-dimethylamino-4 : 4-diphenylhexan-3-one

Novobiocin	Albamycin Biotexin Cathomycin Streptonivicin	antibiotic
Nystatin	Mycostatin	antibiotic
Octamylamine		pentylaminomethylheptane
Oestradiol	Dimenformon Ovocyclin Progynon-DH	1 : 3 : 5(10)-oestratriene-3 : 17β-diol
Oestradiol benzoate	Dimenformon benzoate Oestroform Ovocyclin-B Progynon-B	
Oestriol	Dimenformon Ovocylin-P	3 : 16 : 17-trihydroxy-1 : 3 : 5 (10)-oestratriene
Oestrone	Ketodestrin Menformon Oestroform (oral)	3-hydroxy-1 : 3 : 5(10)-oestratriene-17-one
Oestrone benzoate	Benztrone	
Oleandomycin	Matromycin Romicil	antibiotic
Ostreogrycin	Ostreocin	antibiotic
Oxeladin		diethylaminoethoxyethyl α : α-diethylphenylacetate
Oxophenarsine hydrochloride	Mepharsen	3-amino-4-hydroxyphenyl-arsine-oxide hydrochloride
Oxophenarsine tartrate	Neohalarsine	
Oxycinchophen		3-hydroxy-2-phenylcinchoninic acid
Oxydipentonium chloride		5 : 5′-bis(trimethyl-ammonium)-dipentyl ether dichloride
Oxyphenonium bromide		2-diethylaminoethyl α-*cyclo*-hexyl-α-phenylglycollate methobromide
Oxytetracycline	Terramycin	antibiotic
Oxytocin	Pitocin Syntocinon	
Pamaquin	Plasmoquine	6-methoxy-8-(ω-diethylamino-α-methylbutyl)amino-quinoline salt of 2 : 2′-dihydroxy-1 : 1′-dinaphthylmethane-3 : 3′-dicarboxylic acid

Paracetamol	Panadol	*p*-acetamidophenol
Paramethadione	Paradione	5-ethyl-3 : 5-dimethyloxazolidine-2 : 4-dione
Parethoxycaine		diethylaminoethanol 4-ethoxybenzoate
Paroxypropione		4-hydroxypropiophenone
Pecazine	Pacatal	10-(1-methyl-3-piperidylmethyl)phenothiazine
Pempidine	Perolysen Tenormal	1 : 2 : 2 : 6 : 6-pentamethylpiperidine
Penethamate	Estopen	benzylpenicillin 2-diethylaminoethyl ester
Pentacynium		4-{2-[*N*-(5-cyano-5 : 5-diphenylpentyl)-*N*-methylaminoethyl} morpholine dimethochloride
Pentamethonium bromide	Lytensium	pentamethylene-1 : 5-bistrimethylammonium dibromide
Pentamethonium iodide	Antilusin	pentamethylene-1 : 5-bistrimethylammonium diiodide
Pentamethylenetetrazole, see Leptazol		
Pentamidine		4 : 4′-diamidino-$\alpha\omega$-diphenoxypentane
Pentaquine		6-methoxy-8-(5-*iso*propylaminopentylamino)-quinoline
Penthienate	Monodral	2-diethylaminoethyl α-hydroxy-α-*cyclo*pentyl-α-(2-thienyl) hydroxyacetate
Pentobarbitone	Nembutal	5-ethyl-5-(1-methylbutyl)-barbituric acid
Pentolinium tartrate	Ansolysen	pentamethylene-1 : 5-bis-(1-methylpyrrolidinium tartrate)
Pentylenetetrazol, see Leptazol		
Perphenazine	Fentazin Trilafon	1-[3-(2-chloro-10-phenothiazinyl)propyl]-4-(2-hydroxyethyl)piperazine
Pethidine	Demerol Dolantal Dolantin	1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester
Phenacaine	Holocaine	ethenyl-*p*-diethoxydiphenylamidine
Phenacemide	Phenurone	Phenylacetylurea

Phenactropinium chloride	Trophenium	*N*-phenacylhomatropinium chloride
Phenadoxone	Heptalgin	6-morpholino-4 : 4-diphenylheptan-3-one
Phenarsone sulphoxylate		sodium 3-amino-4-hydroxyphenylarsonate N-methanal sulphoxylate
Phenindamine	Thephorin	1 : 2 : 3 : 4-tetrahydro-2-methyl-9-phenyl-2-azafluorene
Phenindione	Dindevan P.I.D.	2-phenylindane-1 : 3-dione
Pheniodol	Biliselectan Priodax	β-(4-hydroxy-3 : 5-diiodophenyl)-α-phenylpropionic acid
Phenobarbitone	Gardenal Luminal	5-ethyl-5-phenylbarbituric acid
Phenobutiodil	Biliodil	α-(2 : 4 : 6-tri-iodophenoxy)-butyric acid
Phenomorphan		3-hydroxy-*N*-(2-phenylethyl) morphinan
Phenoxybenzamine	Dibenyline Dibenzyline	2-(*N*-benzyl-2-chloroethylamino)-1-phenoxypropane
Phenoxyethanol	Phenoxetol	2-phenoxyethanol
Phenoxymethylpenicillin Penicillin V	Distaquaine V	a biosynthetic penicillin
Phenpromethamine		*N*-β-dimethylphenylethylamine
Phensuximide	Milontin	*N*-methyl-α-phenylsuccinimide
Phentolamine	Rogitine	2-(*m*-hydroxy-*N*-*p*-totylanilinomethyl)-2-imidazoline
Phenylbutazone	Butazolidin	4-*n*-butyl-1 : 2-diphenylpyrazolidine-3 : 5-dione
Phenylephrine	Neophryn Neosynephrine	(—)-1-(*m*-hydroxyphenyl)-2-methylaminoethanol
Phenylindanedione, see Phenindione		
Phenylmercuric nitrate	Merfenil Merphenyl	phenylmercury nitrate
Phenylpropylmethylamine	Vonedrin	1-methylamino-2-phenylpropane
Phenytoin	Dilantin Epanutin Eptoin Solantin	5 : 5-diphenylhydantoin

Phethenylate	Thiantoin	5-phenyl-5-(2-thienyl)-hydantoin
Pholcodine	Ethnine Memine	morpholinylethylmorphine
Pholedrine	Pholetone Stimatone Veritain Veritol	1-(4-hydroxyphenyl)-2-methylaminopropane
Phthalylsulphacetamide	Enterocid Sterathal	*p*-(*o*-carboxybenzoyl)amino-benzenesulphonacetamide
Phthalylsulphathiazole	Sulphathalidine Thalazole Thalistatyl	2-*p*-(*o*-carboxybenzoyl)-aminobenzenesulphamido-thiazole
Phytomenadione =Phytonadione	Konakion Mephyton	2-methyl-3-phytyl-1 : 4-naphthoquinone
Pipadrol	Meratran	diphenyl(2-piperidyl)-methanol
Pipenzolate	Piptal	*N*-ethyl-3-piperidyl benzilate
Piperazine adipate	Entacyl	
Piperazine citrate	Antepar Helmezine	
Piperocaine	Metycaine	3-benzoxy-1-(2-methyl-piperidino)propane
Piperoxan	Benodaine	2-piperidinomethylbenzo-1 : 4-dioxan
Piprinhydrinate	Kolton Mepedyl	4-diphenylmethoxy-1-methyl-piperidine salt of 8-chloro-theophylline
Piridocaine		*β*-(2-piperidyl)ethyl *o*-amino-benzoate
Polymyxin B	Aerosporin	antibiotic
Polyvidone		polyvinylpyrrolidone
Poskine	Proscopine	propionylhyoscine
Potassium hydroxy-quinoline sulphate	Chinosol	
Pramoxine		4-(3-*p*-butoxyphenoxypropyl)-morpholine
Prednisolone	Codelcortone Delta-Cortef Delta-Cortril Delta-Stab Hydeltra Metacortandrolone Meticortelone	1 : 2-dehydrohydrocortisone

Prednisone	DeCortisyl Deltacortone Deltasone Deltra Metacortandracin Meticorten Ultracorten	1 : 2-dehydrocortisone
Pregnenolone		3-hydroxy-20-oxopregnene-5
Primaquine		8-(4-amino-1-methylbutyl-amino)-6-methoxyquinoline
Primidone	Mysoline	5-ethyl-5-phenylhexahydro-pyrimidine-4 : 6-dione
Probarbital		5-ethyl-5-*iso*propylbarbituric acid
Probenecid	Benemid	*p*-(di-*n*-propylsulphamyl)-benzoic acid
Procainamide	Pronestyl	4-amino-2-(dimethylamino-ethyl)benzamide
Procaine	Novocaine	diethylaminoethyl *p*-amino-benzoate
Prochlorperazine	Compazine Stemetil	1-[3-(2-chloro-10-pheno-thiazinyl)propyl]-4-methyl-piperazine
Procyclidine	Kemadrin	(±)-1-*cyclo*hexyl-1-phenyl-3-pyrrolidinopropan-1-ol
Progesterone	Gestone Lipo-Lutin Luteostab Lutocyclin Lutren Proluton	3-pregnene-3 : 20-dione
Proguanil	Guanatol Paludrin	N^1-*p*-chlorophenyl-N^5-*iso*-propyldiguanide
Promamide =Promin		Sodium 4 : 4′-diaminodi-phenylsulphone-*N* : *N*′-didextrose sulphonate
Promethazine	Phenergan	*N*-2-dimethylaminopropyl-phenothiazine
Promethoestrol	Methoestrol	3 : 4-di(4-hydroxy-3-methyl-phenyl)hexane
Promoxolane		2 : 2-di*iso*propyl-1 : 3-dioxo-lane-4-methanol
Propantheline bromide		β-di*iso*propylaminoethyl-xanthene-9-carboxylate
Prophenpyridamine	Trimeton	1-phenyl-1-(2-pyridyl)-3-dimethylaminopropane

Propoxyphene		4-dimethylamino-1 : 2-diphenyl-3-methyl-2-propionyloxybutane
Propylhexedrine	Benzedrex	1-*cyclo*hexyl-2-methylaminopropane
Propyliodone	Dionosil	*n*-propyl ester of 3 : 5-diiodo-4-pyridone-*N*-acetic acid
Propylthiouracil		4-hydroxy-2-mercapto-6-*n*-propylpyrimidine
Pyrathiazine	Pyrrolazote	10-[2-(1-pyrrolidyl)ethyl]-phenothiazine
Pyridostigmine	Mestinon	3-dimethylcarbamoyloxy-1-methylpyridinium
Pyrilamine, see Mepyramine		
Pyromethamine	Daraprim	2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyridamine
Quinacrine, see Mepacrine		
Quinalbarbitone	Seconal	sodium 5-allyl-5-(1-methylbutyl) barbituric acid
Racemethorphan		(±)-3-methoxy-*N*-methylmorphinan
Racemoramide		(±)-1-(β-methyl-γ-morpholino-αα-diphenylbutyryl)-pyrrolidine
Racemorphan	Dromoran	(±)-3-hydroxy-*N*-methylmorphinan
Racephedrine		(±)-ephedrine
Reserpine	Serpasil	
Salinazide	Nupa-sal	*N-iso*nicotinyl-*N'*-salicylidenehydrazine
Secobarbital, see Quinalbarbitone		
Sodium acetrizoate	Diaginol	sodium 3-acetamido-2 : 4 : 6-triiodobenzoate
Sodium aurothiomalate, see Gold sodium thiomalate		
Sodium aurothiosulphate, see Gold sodium thiosulphate		
Sodium calcium edetate	Calcium disodium versenate	calcium chelate of the disodium salt of edetic acid
Sodium cyclamate	Sucaryl	sodium *cyclo*hexylsulphamate
Sodium diatrizoate	Hypaque	sodium 3 : 5-diacetamido-2 : 4 : 6-triiodobenzoate

Sodium iodomethamate	Neo-Iopax	disodium 1-methyl-3 : 5-diiodo-4-pyridone-2 : 6-dicarboxylate
Sodium stibogluconate	Pentostam Solustibosan	
Sodium tetradecylsulphate		sodium 7-ethyl-2-methyl-undecyl-4-sulphate
Solapsone	Sulphetrone	tetrasodium 4 : 4′-di(3-phenyl-1 : 3-disulphopropylamino) diphenylsulphone
Spiramycin	Rovamycin	antibiotic
Stibophen	Fouadin	sodium antimony bispyrocatechol-3 : 5-sodium disulphonate
Stilboestrol	Clinestrol Pabestrol	4 : 4′-dihydroxy-$\alpha\beta$-diethylstilbene
Stilboestrol dipropionate	Pabestrol-D Syntestin	
Subathizone		4-ethylsulphonylbenzaldehyde thiosemicarbazone
Succinylsulphathiazole	Sulphasuxidine	*p*-2′-sulphonthiazolylamidosuccinanilic acid
Sulfobromophthalein	Bromsulphalein	disodium phenoltetrabromophthaleinsulphonate
Sulfoxone	Diasone	disodium 4 : 4′-di(sulphinomethylamino)diphenylsulphone
Sulphacetamide	Albucid Steramide Sulamyd	*p*-aminobenzenesulphonacetamide
Sulphadimidine	Sulphamezathine	2-(*p*-aminobenzenesulphonamido)-4 : 6-dimethylpyrimidine
Sulphaethidole	Sethadil	5-*p*-aminobenzenesulphonamido-2-ethyl-1 : 3 : 4-thiadiazole
Sulphafurazole	Gantrisin	5-(*p*-aminobenzenesulphonamido)-3 : 4-dimethyl*iso*-oxazole
Sulphaguanidine	Guamide	*p*-aminobenzenesulphonylguanidine
Sulphamethizole	Uro-lucosil	2-*p*-aminobenzenesulphonamido-5-methyl-1 : 3 : 4-thiadiazole

Sulphamethoxypyridazine	Lederkyn	6-methoxy-3-sulphanilamido-pyridazine
Sulphan blue	Blue VRS Disulphine blue VNS	sodium salt of 4 : 4′-di-(diethylamino)-4″ : 6″-di-sulphotriphenolmethanol anhydride
Sulphanilamide	Prontosil album Streptoside	*p*-aminobenzenesulphonamide
Sulphaproxyline		N^1-(4-*iso*propoxybenzoyl)-*p*-aminobenzenesulphonamide
Sulphapyridine	Dagenan M & B 693	2-(*p*-aminobenzenesulphon-amido) pyridine
Sulpharsphemamine bismuth	Bismarsen	bismuth derivative of sulph-arsphenamine
Sulphasolucin	Soluseptasine	disodium *p*-(γ-phenylpropyl-amino) benzenesulphon-amido-αγ-disulphonate
Sulphasomidine =Sulphisomide	Elkosin	6-*p*-aminobenzenesulphon-amido-2 : 4-dimethyl-pyrimidine
Sulphathiazole	Cibazol Thiazamide	2-(*p*-aminobenzenesulphon-amido)thiazole
Sulphathiourea	Badional	*p*-aminobenzenesulphonyl-thiourea
Sulphisoxazole, see Sulphafurazole		
Suramin	Antrypol Bayer 205 Germanin Naphuride	symmetrical urea of *m*-ben-zoyl-*m*-amino-*p*-methylben-zoyl-1-aminonaphthalene-4 : 6 : 8-trisulphonic acid
Suxamethonium bromide	Brevidil M	bis(2-dimethylaminoethyl) succinate bismethobromide
Suxamethonium chloride	Anectine Scoline	bis(2-dimethylaminoethyl) succinate bismethochloride
Suxethonium bromide	Brevidil E	bis(2-dimethylaminoethyl) succinate bisethobromide
Tacrine		5-amino-1 : 2 : 3 : 4-tetra-hydroacridine
Testosterone	Neo-Hombreol Perandrin	17-hydroxy-4-androsten-3-one
Tetracaine, see Amethocaine		
Tetracycline	Achromycin Tetracyn	antibiotic
Thenalidine	Sandosten	1-methyl-4-N-(2-thenyl)-anilinopiperidine
Thenyldiamine	Pyribenzamine	2-[(2-dimethylaminoethyl)-3-thenylamino]pyridine

Theophylline	Theocin	1 : 3-dimethylxanthine
Thiacetarsamide sodium		disodium salt of *p*-[di-(carboxymethylmercapto)-amino]benzamide
Thiacetazone		4-acetylaminobenzaldehyde thiosemicarbazone
Thialbarbitone	Kemithal	5-Δ^2-*cyclo*hexenyl-5-allyl-2-thiobarbituric acid
Thiamylal	Surital	5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid
Thiandizole		1-methyl-2-mercaptoimidazole
Thiazolsulfone		4 : 2′-diaminophenyl-5′-thiazolylsulphone
Thiodiglycol		2 : 2′-hydroxyethyl sulphide
Thiomersalate =thiomerosal	Merthiolate	sodium ethylmercurithiosalicylate
Thiopentone	Intraval Pentothal	5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid
Thiopropazate		1-(2-acetoxyethyl)-4-[3-(2-chloro-10-phenothiazinyl) propyl]piperazine
Thonzylamine	Neohetramine	*N*-*p*-methoxybenzyl-*N* : *N*′-dimethyl-*N*-2-pyrimidyl-ethylamine
Thyrotrophin	Thytrophin	thyrotrophic hormone
Tocamphyl		diethanolamine salt of tolylmethylcarbinol-(+)-camphoric acid ester
Tolazoline	Priscol	2-benzyliminazoline
Tolbutamide	D 860 Orinase	*N*-butyl-*N*′-toluene-*p*-sulphonylurea
Tolpromine	Proponesin	1-(1 : 2 : 3 : 6-tetrahydropyridino)-3-*o*-tolyloxypropan-2-ol
Tretamine	TEM Triethanomelamine Triethylenemelamine	2 : 4 : 6-tri(ethyleneimino)-*S*-triazine
Triamcinolone	Aristocort Ledercort	9α-fluoro-16α-hydroxyprednisolone
Trichloroethylene	Trilene	
Tricyclamol chloride	Elorine chloride Lergine	(±)-1-(3-*cyclo*hexyl-3-hydroxy-3-phenylpropyl)-1-methylpyrrolidinium chloride

Trimeprazine		10-(3-dimethylamino-2-methylpropyl)phenothiazine
Trimetaphan camphorsulphonate	Arfonad	4 : 6-dibenzyl-5-oxo-1-thia-4 : 6-diaza*tricyclo* [6 : 3 : 0 : $0^{3:7}$] undecanium
Trimethadione, see Troxidone		
Trimethidinium methosulphate	Camphidonium	(+)-3-(3-dimethylaminopropyl)-1 : 8 : 8-trimethyl-3-aza*bicyclo*[3 : 2 : 1] octane di(methylmethosulphate)
Tripelennamine		*N*-benzyl-*N*′*N*′-dimethyl-*N*-2-pyridylethylenediamine
Tropigline		tiglyltropine
Troxidone =Trimethadione	Tridione	3 : 5 : 5-trimethyloxazolidine-2 : 4-dione
Tryparsamide		sodium *N*-phenylglycineamide-*p*-arsonate
Tuaminoheptane	Tuamine	2-aminoheptane
Tyrothricin		antibiotic
Urecholine	Bethanechol	β-methylcholine chloride urethane
Vancomycin	Vancocin	antibiotic
Vinbarbitone	Delvinal	5-ethyl-5-(1-methyl-1-butenyl)barbituric acid
Vinyl ether	Vinethene	divinyl ether
Viomycin	Viocin	antibiotic
Warfarin	Coumadin	3-(2-acetyl-1-phenylethyl)-4-hydroxycoumarin
Zoxazolamine	Flexin	2-amino-5-chlorobenzoxazole

Appendix II

PROPRIETARY NAMES
with
OFFICIAL or CHEMICAL EQUIVALENTS

IN this appendix are included some of the proprietary names of drugs and the equivalent official or approved names.

ACTH	Corticotrophin
AT 10	Dihydrotachysterol
Abrodil	Methiodal sodium
Abstinyl	Disulfiram
Achromycin	Tetracycline
Acramine	Aminacrine
Adanon	Methadone
Aerosporin	Polymyxin B
Agotan	Cinchophen
Albamycin	Novobiocin
Albucid	Sulphacetamide
Aldinamide	Isoniazid
Aldocorten	Aldosterone
Aleudrin	Isoprenaline sulphate
Alficetyn	Chloramphenicol
Allercur	Clemizole
Aludrine	Isoprenaline sulphate
Alurate	Aprobarbital
Alypin	Amydricaine hydrochloride
Amabevan	Carbarsone
Ambodryl	Bromazine
Amechol	Methacholine chloride
Aminacyl	Sodium aminosalicylate
Aminarsone	Carbarsone
Amphedroxin	Methylamphetamine hydrochloride
Amylsine	Naepine
Amytal	Amylobarbitone
Anacardone	Nikethamide
Anacobin	Cyanocabalamin
Anaesthesin	Benzocaine
Ancolan	Meclozine dihydrochloride
Anectine	Suxamethonium chloride
Anethaine	Amethocaine hydrochloride
Ansolysen	Pentolinium tartrate
Antabuse	Disulfiram
Antepar	Piperazine citrate
Antergan	*N* : *N*-dimethyl-*N'*-phenyl-*N'*-benzyl-ethylenediamine
Anthiomaline	Lithium antimony thiomalate
Anthiphen	Dichlorophen
Anthisan	Mepyramine maleate
Anthralin	Dithranol
Antilusin	Pentamethonium iodide
Antistin	Antazoline
Antrenyl	Oxyphenonium bromide
Antrycide	4-amino-6-(2'-amino-6'-methylpyrimidyl-4'-amino)quinaldine-1 : 1-dimethylsulphate
Antrypol	Suramin
Apothesine	3-diethylaminopropyl cinnamate
Apresoline	Hydrallazine hydrochloride
Aralen	Chloroquine

Aramine	Metaraminol
Arfonad	Trimetaphan camphorsulphate
Aristocort	Triamcinolone
Aristol	Thymol iodide
Arrhenal	Sodium methylarsonate
Artane	Benzhexol hydrochloride
Arteriodone	Diodone
Atabrine (Atebrin)	Mepacrine hydrochloride
Atarax	Hydroxyzine hydrochloride
Atempol	Methylpentynol
Atophan	Cinchophen
Atoxyl	Sodium aminoarsonate
Atrol	Deanol
Aureomycin	Chlortetracycline
Avertin	Bromethol
Avlochin	Chiniofon
Avlosulphon	Dapsone
Avomine	Promethazine 8-chlorotheophyllinate
Azochloramide	Chloroazodin
Azoman, Azozol	Hexazole
BAL	Dimercaprol
BZ 55	Carbutamide
Badional	Sulphathiourea
Banocide	Diethylcarbamazine dihydrogen citrate
Banthine bromide	Methanthelinium bromide
Bayer 205	Suramin
Benadryl	Diphenhydramine hydrochloride
Benapen	Benethamine penicillin
Benecardin	Khellin
Benemid	Probenecid
Benodaine	Piperoxan
Ben-Ovocyclin	Oestradiol benzoate
Benylin	Diphenhydramine hydrochloride
Benzedrex	Propylhexedrine
Benzedrine	Amphetamine
Benzestrol	2 : 4-di(*p*-hydroxyphenyl)-3-ethylhexane
Benztrone	Oestradiol monobenzoate
Berculon A	Thiacetazone
Bethanechol	Urecholine
Biliodil	Phenobutiodil
Biliselectan	Pheniodol
Biotexin	Novobiocin
Bismarsen	Sulpharsphenamine bismuth
Blue VRS	Sulphan blue
Bradosol	Domiphen bromide
Brevidil E	Suxethonium bromide
Brevidil M	Suxamethonium bromide
Bromazine	2-(4-bromodiphenylmethoxy)ethyldimethylamine
Bromsulphalein	Sulphobromophthalein
Bromural	Bromvaletone
Butazolidine	Phenylbutazone
Butesin	Butyl aminobenzoate
Butisol	Butabarbital
Butolan	Diphenan
Butyn	Butacaine
CTAB	Cetrimide
Calcium sodium versenate	Sodium calcium edetate
Calsiod	Calcium *o*-iodoxybenzoate
Calsprate	Calcium acetylsalicylate
Camoform	Bialamicol hydrochloride
Camoquin	Amodiaquine
Camphidonium	Trimethidinium

Caprokol	Hexylresorcinol
Cardiazol	Leptazol
Cardophyllin	Aminophylline
Cathomycin	Novobiocin
Ceepryn chloride	Cetylpyridinium chloride
Certonin	Dehydrocholic acid
Cetavlon	Cetrimide
Chinosol	Potassium 8-hydroxyquinoline sulphate
Chlorarsen	Dichlorophenarsine hydrochloride
Chloretone	Chlorbutol
Chloromycetin	Chloramphenicol
Chlor-Trimeton	Chlorpheniramine hydrogen maleate
Choledyl	Choline theophyllinate
Cibazol	Sulphathiazole
Cignolin	Dithranol
Clinoestrol	Stilboestrol
Cliradon	Ketobemidone
Clopane	Cyclopentamine
Cobione	Cyanocobalamin
Codelcortone	Prednisolone
Cogentin	Benztropine
Colcemid	Demecolcine
Colistatin	Succinylsulphathiazole
Compazine	Prochlorperazine dimaleate
Contebin	Thiacetazone
Coramine	Nikethamide
Cortiron	Deoxycortone acetate
Cortone	Cortisone
Cortrophin	Corticotrophin
Corvotone	Nikethamide
Cotinazin	Isoniazid
Coumadin	Warfarin
Covatin	Captodiame hydrochloride
Crisalbine	gold sodium thiosulphate
Cronetal	Disulfiram
Cumopyran	Cyclocoumarol
Cyclaine	Hexylcaine
Cycliton	Nikethamide
Cyclonal	Hexobarbitone
Cyclospasmol	3 : 5 : 5-trimethyl-*cyclo*hexyl mandelate
Cytamen	Cyanocobalamin
D 860	Tolbutamide
DAPT	2 : 4-diamino-5-phenylthiazole
DFP	Diflos
DHE-45	Dihydroergotamine methanesulphonate
DOCA	Deoxycortone acetate
Dagenan	Sulphapyridine
Daptazole	Amiphenazole
Daraprim	Pyrimethamine
Darstine	5-methyl-4-phenyl-1-(1-pyridyl)-3-hexanol methobromide
Decapryn	Doxylamine
Decholin	Dehydrocholic acid
DeCortisyl	Prednisone
Dehydrocholin	Dehydrocholic acid
Decicain	Amethocaine hydrochloride
Delta-Cortef, Delta-Cortril, Delta-Stab	Prednisolone
Deltacortone, Deltasone, Deltra	Prednisone
Delvinal	Vinbarbitone
Demerol	Pethidine
Dequadin	Dequalinium chloride
Desomorphine	Dihydrodesoxymorphine
Desoxyn	Methylamphetamine
Dexedrine	Dexamphetamine sulphate
Diaginol	Sodium acetrizoate
Dial	Allobarbitone
Diamethine	Dimethyltubocurarine bromide

Diamox	Acetazolamide
Diasone	Sulphoxone
Diatrin	Methapheniline hydrochloride
Dibenamine	*NN*-Dibenzyl-β-chloroethylamine
Dibencil	Benzathine penicillin
Dibenyline, Dibenzyline	Phenoxybenzamine hydrochloride
Dibucaine	Cinchocaine
Dichloro-Mapharsen	Dichlorophenarsine hydrochloride
Dicodid	Dihydrocodeinone bitartrate
Dilantin	Phenytoin sodium
Dilaudid	Dihydromorphinone hydrochloride
Dilurgen	Mersalyl
Dimenformon	Oestradiol
Dindevan	Phenindione, Phenylindanedione
Diodoquin	Diiodohydroxy-quinoline
Diodrast	Diodone
Dionin	Ethylmorphine
Dionosil	Propyliodone
Dioquin	Diiodohydroxy-quinoline
Diothane	Diperodon
Dioxythranol	Dithranol
Diparalene	Chlorcyclizine hydrochloride
Diparcol	Diethazine hydrochloride
Diphenatil	Diphemanil methylsulphate
Distaquaine V	Phenoxymethylpenicillin
Disulphine Blue VNS	Sulphan Blue
Dolantal, Dolantin	Pethidine hydrochloride
Dolophine	Troxidone
Doriden	Glutethimide
Doryl, see Moryl	
Dramamine	Dimenhydrinate
Dromoran	Levorphanol tartrate, Methorphinan
Dulcolax	Bisacodyl
Ecolid	Chlorisondamine chloride
Electrocortin	Aldosterone
Elkosin	Sulphasomidine
Elorine chloride	Tricyclamol chloride
Embequin	Diiodohydroxy-quinoline
Entacil	Piperazine adipate
Entamide	Diloxanide
Epanutin	Phenytoin sodium
Ephynal	Tocopheryl acetate
Epinine	1-(3 : 4-dihydroxyphenyl)-2-methylaminoethane
Eptoin	Phenytoin sodium
Equanil	Meprobamate
Ergotrate	Ergometrine maleate
Erythrocin	Erythromycin
Esidrone	Mersalyl
Esmodil	Meprochol
Estopen	Penethamate hydriodide
Ethiodan	Iophendylate
Ethnine	Pholcodine
Ethodryl	Diethylcarbamazine
Eulissin	Decamethonium iodide
Eumydrin	Atropine methylnitrate
Euphthalmine	Eucatropine hydrochloride
Euphyllin	Aminophylline
Eurax	*N*-ethyl-*o*-crotonotoluide
Evans Blue	Azovan Blue
Evipal, Evipan	Hexobarbitone
Femergin	Ergotamine tartrate
Fentazin	Perphenazine
Flaxedil	Gallamine triethiodide

Flexin	Zoxazolamine
Fluothane	Halothane
Folvite	Folic acid
Formo-Cibazol	Formaldehyde-sulphathiazole
Forthane	1 : 3-dimethylpentylamine
Fouadin	Stibophen
Fourneau 309	Suramin
Fourneau 933	Piperoxan
Furacin	Nitrofurazone
Furadantin	Nitrofurantoin
Furmethide	Furtrethonium iodide
Furoxone	Furazolidone
Gantrisin	Sulphafurazole
Gardenal	Phenobarbitone
Gemonil	Metharbital
Genasprin	Acetylsalicylic acid
Genophyllin	Aminophylline
Germanin	Suramin
Gestone	Progesterone
Gestone-oral	Ethisterone
Guamide	Sulphaguanidine
Guanatol	Proguanil
Gynergen	Ergotamine tartrate
Gynoestryl	Oestradiol
Helmezine	Piperazine citrate
Heptalgin	Phenadoxone
Heroin	Diamorphine hydrochloride
Hetrazan	Diethylcarbamazine dihydrogen citrate
Hexachlorophene	Hexachlorophane
Hexathide	Hexamethonium iodide
Hibitane	Chlorhexidine
Histantin	Chlorcyclizine
Histostab	Antazoline
Holocaine	Phenocaine
Hydeltra	Prednisolone
Hydralazine	Hydrallazine
Hydrocortone	Hydrocortisone
Hypaque	Sodium diatrizoate
Ilotocin	Erythromycin
Indalone	Butopyronoxyl
Insomnol	Methylpentynol
Intraval	Thiopentone
Invenol	Carbutamide
Inversine	Mecamylamine hydrochloride
Iodohexamidine	2-iodo-4 : 4′-diamidino-$\alpha\varepsilon$-diphenoxyhexane
Ipral	Probarbital
Isupren	Isoprenaline sulphate
Itrumil	Iodothiouracil
Iversal	Ambazone
Jetrium	Dextromoramide
Kapilon	Menaphthone
Kapilon-oral	Acetomenaphthone
Kapilon-soluble	Menadoxime
Kemadrin	Procyclidine hydrochloride
Kemithal	Thialbarbitone
Ketodestrin	Oestrone
Kharophen	Acetarsol
Kolton	Piprinhydrinate
Konakion	Phytomenadione
Lanoxin	Digoxin
Lapudrine	Chlorproguanine
Largactil	Chlorpromazine hydrochloride
Larocaine	3-diethylamino-2 : 2-dimethylpropyl *p*-aminobenzoate
Laudolissin	Laudexium methylsulphate
Lederkort	Triamcinolone
Lederkyn	Sulphamethoxypyridazine
Lergine	Tricyclamol chloride
Lethidrone	Nalorphane hydrobromide
Leucarsone	Carbarsone
Leukaran	Chlorambucil

Levodromoran	Levorphanol
Levophed	(—)-Noradrenaline bitartrate; Levarterenol
Levorphan	Levorphanol
Lipolutin	Progesterone
Lissephen	Mephenesin
Longifene	Buclizine hydrochloride
Lorexane	Gamma benzene hexachloride
Luminal	Phenobarbitone
Luteostab	Progesterone
Lutocyclin	Ethisterone
Lutren	Progesterone
Lynoral	17-Ethinyloestradiol
Lysivane	Ethopropazine hydrochloride
Lytensium	Pentamethonium bromide
M & B 693	Sulphapyridine
Magnamycin	Carbomycin
Malazol, Malidone	Aloxidone
Mandelamine	Hexamine mandelate
Mapharside	Oxophenarsine hydrochloride
Marfanil, Marprontil	Maphenide
Marsilid	1-nicotinyl-2-*iso*-propylhydrazine
Marzine	Cyclizine hydrochloride
Matromycin	Oleandomycin
Mebaral	Methylphenobarbitone
Mecholyl	Methacholine chloride
Mecothane	carbaminoyl-β-methylcholine
Medrol	6-methyl-Δ^1-hydrocortisone
Megacillin	Clemizole penicillin
Megaphen	Chlorpromazine hydrochloride
Megimide	Bemegride
Memine	Pholcodine
Mepedyl	Piprinhydrinate
Mepharsen	Oxophenarsine hydrochloride
Mephine	Mephentermine
Mephyton	Phytomenadione
Meratran	Pipadrol hydrochloride
Merbentyl	Bentyl hydrochloride
Mercazole	Methimazole
Mercloran	Chlormerodrin
Mercuhydrin	Meralluride
Mercurocol	Mercurochrome
Mercuzanthin	Mercurophylline sodium
Merphenyl nitrate	Phenylmercury nitrate
Merphyllin	Mersalyl
Merthiolate	Thiomersalate
Mestinon	Pyridostigmine bromide
Metacortandracin	Prednisone
Metacortandralone, Metacortelone	Prednisolone
Metacorten	Prednisone
Metandren	Methyltestosterone
Metaphen	Nitromersol
Methedrine	Methylamphetamine
Methergin	Methylergometrine tartrate
Methoestrol	Promethoestrol
Methscopolamine hydrobromide	Hyoscine methobromide
Meticorten	Prednisone
Meticortelone	Prednisolone
Metopon hydrochloride	Methyldihydromorphinone hydrochloride
Metrazole	Leptazol; Pentylenetetrazole
Metubine	Dimethyltubocurarine

Metycaine	Piperocaine hydrochloride
Mevasine	Mecamylamine hydrochloride
Mictine	Aminometradine
Milibis	Bismuth glycollylarsanilate
Milontin	Phensuximide
Miltown	Meprobamate
Miracil D	Lucanthone hydrochloride
Mitigal	Mesulphen
Monacrin	Aminacrine hydrochloride
Monocaine	Butethamine
Monodral	Penthienate methobromide
Monomestrol	Stilboestrol monomethyl ether
Moryl	Carbachol
Muracil	Methylthiouracil
Myanesin	Mephenesin
Mybasan	Isoniazid
Mycostatin	Nystatin
Mydriasin	Atropine methylbromide
Myleran	Busulphan
Myocrisin	Gold sodium thiomalate
Myodil	Iophendylate
Mysoline	Primidone
Myvizone	Thiacetazone
Nadisan	Carbutamide
Nallene	Nalorphine
Naphuride	Suramin
Nembutal	Pentobarbitone
Neo-Antergan	Mepyramine hydrogen maleate
Neodrenal	Isoprenaline sulphate
Neo-Epinine	Isoprenaline sulphate
Neo-Halarsine	Oxophenarsine tartrate
Neo-Hetramine	Thonzylamine
Neo-Hombreol	Testosterone propionate
Neo-Hombreol M	Methyltestosterone
Neohydrin	Chlormerodrin
Neo-Iopax	Sodium iodomethamate
Neolin	Benzathine penicillin
Neomercazole	Carbimazole
Neonal	Butobarbitone
Neopenyl	Clemizole penicillin
Neophrin	Phenylephrine hydrochloride
Neostam	Stibamine glucoside
Neostibamine	Ethylstibamine
Neostibosan	Diethylammonium *p*-stibanilate
Neosynephrine	Phenylephrine hydrochloride
Neotropin	Butyloxydiaminoazopyridine
Nepresol	Dihydrallazine
Neptal	Mercuric salicylaminoacetate
Neumandrin	Isoniazid
Neustab	Thiacetazone
Niacinamide	Nicotinamide
Niagrin	Nicotinamide
Nicamide	Nikethamide
Nicetal	Isoniazid
Nilergex	Isothipendyl
Nilevar	Norethandrolone
Nilodin	Lucanthone hydrochloride
Nirvanol	5-Ethyl-5-phenylhydantoin
Nisentil	Alphaprodine hydrochloride
Nivaquine	Chloroquine sulphate
Noludar	Methyprylone
Norlutin	Norethisterone
Nostal	5-*iso*propyl-5-bromoallylbarbituric acid
Notensil	Acepromazine maleate
Novacrysin	Gold sodium thiosulphate

Novalgin	Sodium phenyldimethylpyrazole methylaminomethanesulphonate
Novatophan	Methyl phenylcinchoninate
Novatropine	Homatropine methylbromide
Novocaine	Procaine hydrochloride
Nupa-sal	Salinazid
Nupercaine	Cinchocaine
Nydrane	Beclamide
Nydrazid	Isoniazid
Oblivon	Methylpentynol
Oenethyl	2-methylaminoheptane
Opacin, Opacol	Iodophthalein
Oraluton	Ethisterone
Orarsan	Acetarsol
Oreton	Testosterone propionate
Oreton M	Methyltestosterone
Orinase	Tolbutamide
Ortal	Hexethal
Orthoform	Orthocaine
Orthoxine	Methoxyphenamine
Ostreocin	Ostreogrycin
Ovocyclin	Oestradiol
Ovostab	Oestradiol monobenzoate
Oxylan	Diphenan
PABA	*p*-Aminobenzoic acid
PAS	*p*-Aminosalicylic acid
P.I.D.	Phenylindione
Pabestrol	Stilboestrol dipropionate
Pacatal	Mepazine
Paludrine	Proguanil
Pamine	Hyoscine methobromide
Panadol	Paracetamol
Pantocaine	Amethocaine
Pantopaque	Iodophendylate
Paradione	Paramethadione
Paramisan	4-aminosalicylic acid
Paredrine	Hydroxyamphetamine
Parpanit	Caramiphen hydrochloride
Peganone	Ethotoin
Pelentan	Ethyl biscoumacetate
Pellidol	Diacetylaminoazotoluene
Peloninamide	Nicotinamide
Pendiomide	Azamethonium bromide
Penidural	Benzathine penicillin
Pentostam	Sodium stibogluconate
Pentothal	Thiopentone
Perabrodil	Diodone
Perandren	Testosterone propionate
Perandren (oral)	Methyltestosterone
Perazil	Chlorcyclizine hydrochloride
Percorten	Deoxycortone acetate
Perdilatal	Buphenine hydrochloride
Peritrate	Pentaerythritol tetranitrate
Permapen	Benzathine penicillin
Perolysen	Pempidine
Persedon	3 : 3-diethyl-2 : 4-dioxo-1 : 2 : 3 : 4-tetrahydropyridine
Phanodorm	Cyclobarbitone
Phemeride, Phemerol chloride	Benzethonium chloride
Phenergan	Promethazine hydrochloride
Phenoxetol	Phenoxyethanol
Phenurone	Phenacemide
Pholetone	Pholedrine
Phreazol	Leptazol
Physeptone	Methadone
Pipadone	Dipipanone
Pipanol	Benzhexol

Piptal	Pipenzolate methobromide
Piriton	Chlorpheniramine
Planocaine	Procaine
Planoform	Butyl aminobenzoate
Plaquenil	Hydroxychloroquine
Plasmoquin	Pamaquine
Pontocaine	Amethocaine
Presidal	Pentacynium methylsulphate
Primolut N	Norethisterone
Priodax	Iodoalphionic acid / Pheniodol
Priscol	Tolazoline hydrochloride
Privine	Naphazoline nitrate
Pro-Banthine bromide	Propantheline bromide
Probarbital	5-ethyl-5-*iso*propylbarbituric acid
Probenecid	*p*-(di-*n*-propylsulphamyl)benzoic acid
Prodexin	Aluminium glycinate
Progestoral	Ethisterone
Progynon B	Oestradiol benzoate
Progynon DH	Oestradiol
Progynon DP	Oestradiol dipropionate
Prokayvit	Menaphthone
Prokayvit (oral)	Acetomenaphthone
Proluton	Progesterone
Proluton C	Ethisterone
Promin	Glucosulphone
Prominal	Methylphenobarbitone
Promizole	4-aminophenyl-2′-amino-5′-thiazolylsulphone
Pronestyl	Procaine amide
Prontosil album	Sulphanilamide
Prontosil soluble	disodium salt of 4′-sulphonamidophenylazo-7-acetylamino-1-hydroxynaphthalene-3 : 6-disulphonic acid
Propacil	Propylthiouracil
Propadrine	Phenylpropanolamine hydrochloride
Propamidine	4 : 4-diamidino-$\alpha\omega$-diphenoxypropane di-(β-hydroxyethanesulphonate)
Propazone	3-methyl-5 : 5-dipropyloxazolidine-2 : 4-dione
Proponesin	Tolpronine hydrochloride
Proscopine	Poskine
Proseptasine	*p*-benzylaminobenzenesulphonamide
Prostigmine	Neostigmine
Puri-nethol	Mercaptopurine
Pycazide	Isoniazid
Pyelectan	Iodoxyl
Pyelosil / Pylumbrin	Diodone
Pyribenzamine hydrochloride	Thenyldiamine hydrochloride / Tripelennamine hydrochloride
Pyridium	3-phenylazo-2 : 6-diaminopyridine hydrochloride
Pyrrolazote	Pyrathiazine
Quinacrine	Mepacrine hydrochloride
Quinacrine (soluble)	Mepacrine methanosulphonate
Quinophan	Cinchophen
Quinoxyl	Chiniofon
R 875	Dextromoramide
Rastinon	*N*-(4-methylbenzenesulphonyl)-*N*′-butylurea
Rimifon	Isoniazid
Ritalin	Methyl phenidate
Rivanol	Lactoacridine
Roccal	Benzalkonium chloride

Rogitine	Phentolamine
Rolicton	Amisometradine
Romicil	Oleandromycin
Ronicol	Nicotinyl alcohol
Rovamycin	Spiromycin
Rutonal	5-methyl-5-phenyl-barbituric acid
Salvarsan	Arsphenamine
Salyrgan	Mersalyl
Sandoptal	5-*iso*butyl-5-phenyl-barbituric acid
Sandosten	Thenalidine tartrate
Sanocrisin	Gold sodium thio-sulphate
Santoflex AW	6-ethoxy-2 : 2 : 4-trimethyl-1 : 2-dihydroquinoline
Santoquine	Chloroquine
Scoline	Suxamethonium chloride
Scuroform	Butyl aminobenzoate
Seconal	Secobarbital
Secresteron	Dimethysterone
Sedormid	5-allyl-5-*iso*propyl-barbituric acid
Seroden	Thiacetazone
Serpasil	Reserpine
Sethodil	Sulphaethidole
Sinthrome	Nicoumalone
Skiodan sodium	Methiodal sodium
Soframycin	Framycetin
Solganal	Aurothioglucose
Soluseptasine	Sulphasolucin
Solustibosan	Sodium stibo-gluconate
Somnesin	Methylpentynol
Soneryl	Butobarbitone
Spirocid	Acetarsol
Spontin	Ristocetin
Staticin	Caronamide
Stemetil	Prochlorperazine dimaleate
Stenediol	Methylandrostene-diol
Steramide	Sulphacetamide
Sterisil	Hexetidine
Stimatone	Pholedrine
Stipolac	Iodophthalein
Stovaine	Amylocaine hydro-chloride
Stovarsol	Acetarsol
Streptonivicin	Novobiocin
Styrion	Polyaminostyrene
Suavitil	Benactyzine hydro-chloride
Sucaryl	Cyclamate sodium
Sudermo	Mesulphen
Sulamyd	Sulphacetamide
Sulfamilon	Maphenide
Sulpharsenol	Sulpharsphenamine
Sulpha-methazine Sulpha-mezathine	Sulphadimidine
Sulpharsan	Sulpharsphenamine
Sulphasuxidine	Succinylsulphathia-zole
Sulphathalidine	Phthalylsulphathia-zole
Sulphetrone	Solapsone
Sulphostab	Sulpharsphenamine
Suprarenalin Suprarenin	Adrenaline
Surfacaine Surfathesin	Cyclomethycaine sulphate
Surital	Thiamylal
Sympathin N	Noradrenaline
Sympatol	Phenylephrine hydro-chloride
Syncurine	Decamethonium iodide
Synopen	Halopyramine hydro-chloride
Syntestrin	Stilboestrol dipro-pionate
Synthovo	Hexoestrol
Syntocinon	Oxytocin (synthetic)
Syntropan	phosphate of 3-di-ethylamino-2 : 2-dimethylpropanol ester of tropic acid

TACE	Chlorotrianisene
TEM	Tretamine
TEPP	Tetraethyl pyrophosphate
Tapazole	Methimazole
Telepaque	Iopanoic acid
Temparin	Dicoumarin
Tenormal	Pempidine
Tensilon	Edrophonium chloride
Teoquil	Hedaquinium chloride
Terramycin	Oxytetracycline
Tertroxin	Liothyronine sodium
Testoviron	Methyltestosterone
Tetracyn	Tetracycline
Thalistatyl	Phthalylsulphathiazole
Theelin	Oestrone
Theelol	Oestriol
Themalon	Diethylthiambutene
Thenylene	Methapyrilene
Theocin	Theophylline
Thephorin	Phenindamine hydrogen tartrate
Theruhistin	Isothipendyl
Thiantoin	Phethenylate
Thiazamide	Sulphathiazole
Thio-Bismol	Bismuth sodium thioglycollate
Thiomerin sodium	Mercaptomerin sodium
Thiomersalate	Thiomersal
Thioparamizone, Tibione	Thiacetazone
Thorazine	Chlorpromazine hydrochloride
Tolserol	Mephenesin
Tolysin	Neocinchophen
Topocaine	Cyclomethycaine
Tozocide	6′-(4-quinaldylamino)hexyl-4-aminoquinaldinium iodide hydriodide
Trafuril	tetrahydrofurfuryl-nicotinic acid ester
Trasentin H	Adiphenine
Triazole	Hexazole
Trichlorad	Acinitrazole
Tridione	Troxidone
Triethanomelamine, Triethylenemelamine	Tretamine
Trilafon	Perphenazine
Trilene	Trichloroethylene
Trimeton	Prophenpyridamine
Triostam	Sodium antimonyl gluconate
Triphal	Sodium aurothiobenziminazole carboxylate
Tromexan	Ethyl biscoumacetate
Trophenium	Phenactropinium
Tuamine	Tuaminoheptane
Tubarine	(+)-Tubocurarine chloride
Tubomel	Isoniazid
Tutocaine	3-dimethylamino-1 : 2-dimethylpropyl *p*-aminobenzoate
Ultracorten	Prednisone
Urecholine chloride	Bethanicol chloride
Uriodone	Diodone
Urolucosil	Sulphamethizole
Uropac, Uroselectan B, Urumbrin	Iodoxyl
Vallestril	Methallenoestril
Valmid, Valmidate	Ethinamate
Vancosin	Vancomycin
Vasylox	Methoxamine hydrochloride
Vazadrine	Isoniazid
Vegolysen	Hexamethonium bromide

Vegolysen T	Hexamethonium tartate
Veritain, Veritol	Pholedrine
Veronal	Barbitone
Viadril	Hydroxydione sodium succinate
Vibazine	Buclizine hydrochloride
Vinesthene	Vinyl ether
Viocin	Viomycin
Vioform	Iodochlorhydroxyquin
Vonedrine	Phenylpropylmethylamine
Wyovin	Dicyclomine hydrochloride
Xeroform	Bismuth tribromophenate
Xylocaine	Lignocaine
Yatren	Chiniofon
Zactane	Ethoheptazine
Zanchol	Florantyrone
Zephiran	Benzalkonium chloride

Index

For proprietary names of drugs see Appendix II (p. 396), but a few drugs that are described in the text under proprietary names are also included in the index. Official or approved names of drugs that are not described in the text will be found in Appendix I (p. 369).

When more than one reference to a subject is given the more important is printed in **bold** type.

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