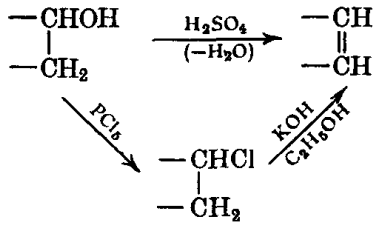
the structure of alkaloids (*cf.* terpenes, §3. VIII). By varying the " strength " of the oxidising agent, it is possible to obtain a variety of products:

(*a*) Mild oxidation is usually effected with hydrogen peroxide, ozone, iodine in ethanolic solution, or alkaline potassium ferricyanide.

(*b*) Moderate oxidation may be carried out by means of acid or alkaline potassium permanganate, or chromium trioxide in acetic acid.

(*c*) Vigorous oxidation is usually effected by potassium dichromate–sulphuric acid, chromium trioxide–sulphuric acid, concentrated nitric acid, or manganese dioxide–sulphuric acid.

This classification is by no means rigid; the " strength " of an oxidising agent depends to some extent on the nature of the compound being oxidised. In those cases where it can be done, better results are sometimes achieved by first dehydrating the compound and then oxidising the unsaturated compound thus obtained; oxidation is readily effected at a double bond.



More recently, mercuric acetate has been used to dehydrogenate certain alkaloids, thereby introducing olefinic bonds.

(vi) Fusion of an alkaloid with solid potassium hydroxide often produces relatively simple fragments, the nature of which will give information on the type of nuclei present in the molecule (*cf.* **iii***b*).

(vii) *Zinc dust distillation.* This usually gives the same products as **(vi)**, except that when the alkaloid contains oxygen the oxygen is removed.

(viii) Physical methods are also now being used, in conjunction with chemical methods, to elucidate structure, *e.g.*, infra-red spectra studies are used to identify many functional groups; ultraviolet spectra are used to indicate the likely type of structure present; and X-ray analysis has offered a means of distinguishing between alternative structures that appear to fit equally well the alkaloid in question.

(ix) *Synthesis.* The foregoing analytical work will ultimately lead to the proposal of a tentative structure (or structures) for the alkaloid under consideration. The final proof of structure, however, depends on an unambiguous synthesis of the alkaloid.

§5. Classification of the alkaloids. Long before the constitutions of the alkaloids were known, the source of the alkaloid was considered the most important characteristic of the compound. Thus there could not be a rational classification. Even today, with the structures of so many known, the classification of the alkaloids is still somewhat arbitrary owing to the difficulty of classifying into distinct groups. Even so, it is probably most satisfactory (chemically) to classify the alkaloids according to the nature of the nucleus present in the molecule. Members of the following groups are described in this book:

(i) Phenylethylamine group.
(ii) Pyrrolidine group.
(iii) Pyridine group.
(iv) Pyrrolidine-pyridine group.
(v) Quinoline group.
(vi) *iso*Quinoline group.
(vii) Phenanthrene group.

It should be noted that in many cases different alkaloids obtained from the same plant often have similar chemical structures, and so sometimes the source of the alkaloids may indicate chemical similarity.

PHENYLETHYLAMINE GROUP

Many compounds of this group are known, some natural and others synthetic. Their outstanding physiological action is to increase the blood-pressure; hence they are often referred to as the *pressor drugs*.

§6. β-Phenylethylamine. This is the parent substance of this group of alkaloids, and occurs in putrid meat (it is formed by the decarboxylation of phenylalanine, an amino-acid). β-Phenylethylamine may be readily synthesised as follows:

$$C_6H_5{\cdot}CH_2Cl + KCN \longrightarrow C_6H_5{\cdot}CH_2{\cdot}CN \xrightarrow[C_2H_5OH]{Na} C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$$

β-Phenylethylamine is a colourless liquid, b.p. 197°.

§7. (−)-Ephedrine, m.p. 38·1°. (−)-Ephedrine occurs in the genus *Ephedra*; it is one of the most important drugs in *Ma Huang* (a Chinese drug). Physiologically, its action is similar to that of adrenaline (§12), and it can be taken orally.

The molecular formula of ephedrine is $C_{10}H_{15}ON$, and since on oxidation ephedrine forms benzoic acid, the structure therefore contains a benzene ring with only one side-chain. When treated with nitrous acid, ephedrine forms a nitroso-compound; therefore the compound is a secondary amine. Since ephedrine forms a dibenzoyl derivative, one hydroxyl group must be present (one benzoyl group is accounted for by the imino group). Finally, when heated with hydrochloric acid, ephedrine forms methylamine and propiophenone.

$$C_{10}H_{15}ON \xrightarrow{HCl} CH_3{\cdot}NH_2 + C_6H_5{\cdot}CO{\cdot}CH_2{\cdot}CH_3$$

The formation of these products can be explained if the structure of ephedrine is either I or II.

$$C_6H_5{\cdot}CHOH{\cdot}CH_2{\cdot}CH_2{\cdot}NH{\cdot}CH_3 \qquad \text{I}$$

$$C_6H_5{\cdot}CHOH{\cdot}CH(NH{\cdot}CH_3){\cdot}CH_3 \qquad \text{II}$$

It has been observed, however, that compounds of structure II undergo the *hydramine fission* to form propiophenone when heated with hydrochloric acid. Thus II is more likely than I. This is supported by the fact that when subjected to the Hofmann exhaustive methylation method, ephedrine forms *sym.*-methylphenylethylene oxide, III; this cannot be produced from I, but is to be expected from II.

$$\underset{\text{II}}{C_6H_5{\cdot}CHOH{\cdot}CH(CH_3){\cdot}NHCH_3} \xrightarrow[\text{(ii) AgOH}]{\text{(i) } CH_3I} C_6H_5{\cdot}CHOH{\cdot}CH(CH_3){\cdot}N(CH_3)_3\}^+OH^- \xrightarrow[(-H_2O)]{\text{heat}}$$

$$\underset{\text{III}}{C_6H_5{\cdot}\overset{\diagup O \diagdown}{CH{\cdot}CH}{\cdot}CH_3} + (CH_3)_3N$$

Further support for II is afforded by the following evidence. Structure I contains one asymmetric carbon atom, and so replacement of the hydroxyl

group by hydrogen will result in the formation of an optically inactive compound. Structure II, however, contains two asymmetric carbon atoms, and so the replacement of the hydroxyl group by hydrogen should still give a compound that can be optically active. Experimentally it has been found that when this replacement is effected in (—)-ephedrine, the product, deoxyephedrine, is optically active. Thus II agrees with all the known facts, and this structure has been confirmed by synthesis, *e.g.*, Späth *et al.* (1920):

$$CH_3{\cdot}CH_2{\cdot}CHO \xrightarrow{Br_2} CH_3{\cdot}CHBr{\cdot}CHO \xrightarrow[HBr]{CH_3OH}$$

$$CH_3{\cdot}CHBr{\cdot}CH(OCH_3)(Br) \xrightarrow{C_6H_5MgBr} CH_3{\cdot}CHBr{\cdot}CH(OCH_3)(C_6H_5) \xrightarrow{CH_3{\cdot}NH_2}$$

$$CH_3{\cdot}CH(NH{\cdot}CH_3){\cdot}CH(OCH_3)(C_6H_5) \xrightarrow{HI} C_6H_5{\cdot}CHOH{\cdot}CH(CH_3){\cdot}NH{\cdot}CH_3$$

(±)-ψ-ephedrine

The racemic modification of ψ-ephedrine (see below) was resolved by means of tartaric acid.

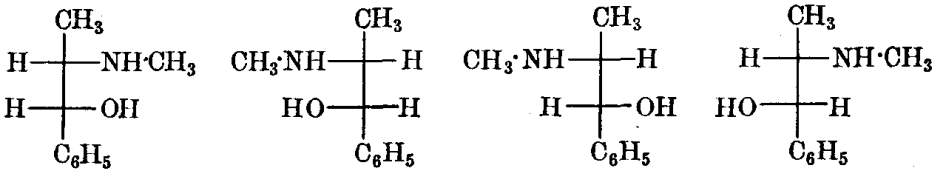
(—)-Ephedrine itself has been synthesised by Manske *et al.* (1929) by the catalytic reduction of 1-phenylpropane-1 : 2-dione (benzoylacetyl) in the presence of methylamine in methanol solution.

$$C_6H_5{\cdot}CO{\cdot}CO{\cdot}CH_3 + CH_3{\cdot}NH_2 \rightarrow C_6H_5{\cdot}CO{\cdot}C(=N{\cdot}CH_3){\cdot}CH_3 \xrightarrow{H_2—Pt} C_6H_5{\cdot}CHOH{\cdot}CH(CH_3){\cdot}NH{\cdot}CH_3$$

(±)-ephedrine

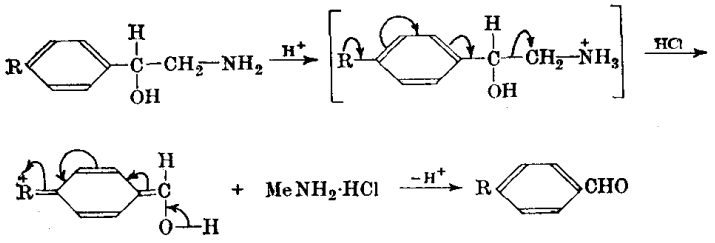
The racemic ephedrine was resolved by means of mandelic acid. Some (±)-ψ-ephedrine was also obtained in this synthesis.

Since the ephedrine molecule contains two dissimilar asymmetric carbon atoms, four optically active forms (two pairs of enantiomorphs) are theoretically possible. According to Freudenberg (1932), the configurations of ephedrine and ψ-ephedrine are:

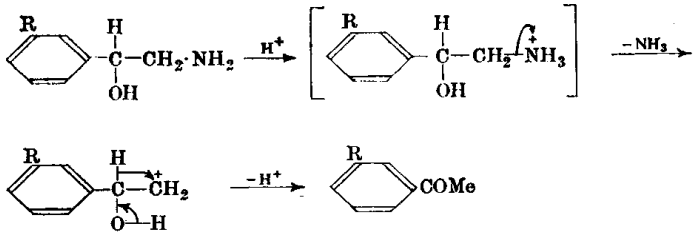


(—)-ephedrine (+)-ephedrine (—)-ψ-ephedrine (+)-ψ-ephedrine

Various mechanisms have been proposed for the hydramine fission. Chatterjee *et al.* (1961) have suggested two different mechanisms according to whether the aryl nucleus contains (i) an electron-releasing group in the *o* and/or *p*-position, *e.g.*, R = OMe, OH, Me:

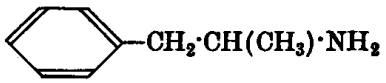


(ii) R in the *m*-position:



Thus hydramine fission gives an aldehyde or a ketone according to the nature and position of groups in the aryl nucleus. With a 4-nitro group the product is 4-nitroacetophenone (yield: very poor).

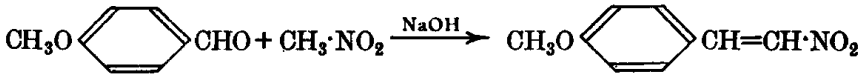
§8. **Benzedrine** (*Amphetamine*) was originally introduced as a substitute for ephedrine, but it is now used in its own right since it apparently produces a feeling of confidence.



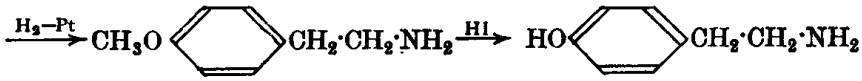
Benzedrine has been synthesised in many ways, *e.g.*, Mingoia (1940):

$$C_6H_5{\cdot}CH_2{\cdot}COCH_3 \xrightarrow[150-190^\circ]{HCONH_2} C_6H_5{\cdot}CH_2{\cdot}CH(CH_3){\cdot}NH{\cdot}CHO \xrightarrow{HCl} C_6H_5{\cdot}CH_2{\cdot}CH(CH_3){\cdot}NH$$

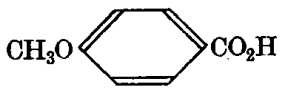
§9. **β-*p*-Hydroxyphenylethylamine** (*tyramine*), m.p. 160°, occurs in ergot, and is produced by the putrefaction of proteins (by the decarboxylation of tyrosine). Tyramine has been synthesised in various ways, *e.g.*,



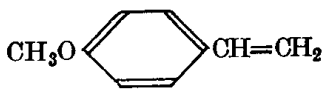
anisaldehyde



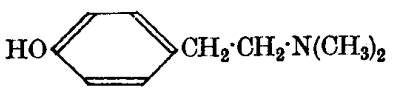
§10. **Hordenine** (*β-p*-hydroxyphenylethyldimethylamine, *Anhaline*), m.p. 117–118°, occurs naturally in germinating barley. The molecular formula of hordenine is $C_{10}H_{15}ON$; the routine tests show that hordenine is a tertiary base and that it contains a phenolic group. Since the methylation of hordenine, followed by oxidation (with alkaline permanganate), gives anisic acid, I, it therefore follows that the hydroxyl group is in the *para*-position with respect to the side-chain. Furthermore, since the methylated compound gives *p*-vinylanisole, II, after the Hofmann exhaustive methylation, the structure of hordenine is probably III.



I

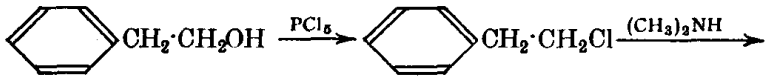


II

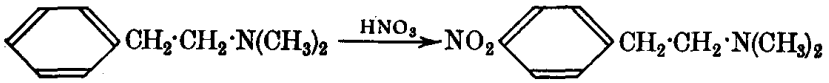


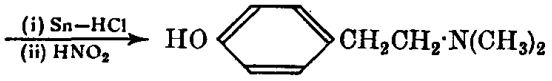
III

This has been confirmed by synthesis, *e.g.*, Barger (1909):

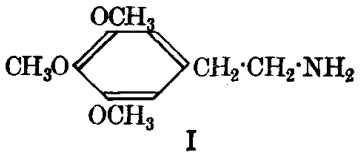


2-phenylethanol



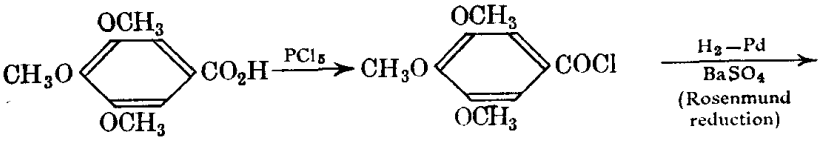


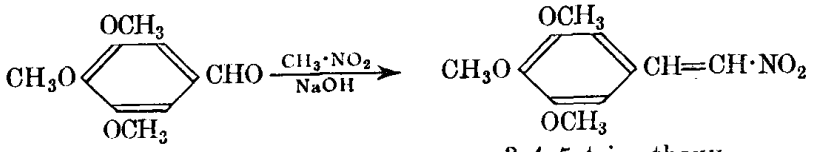
§11. **Mezcaline** (mescaline), $C_{11}H_{17}O_3N$, b.p. 180–180·5°/12 mm., occurs naturally in " mezcal buttons ". The routine tests show that mezcaline contains a primary aliphatic amino-group and three methoxyl groups. On oxidation with alkaline permanganate, mezcaline gives 3 : 4 : 5-trimethoxybenzoic acid, and thus the probable structure of mezcaline is I.



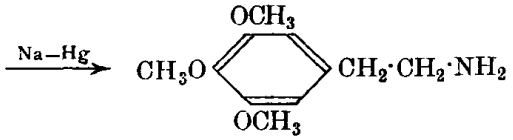
I

This has been confirmed by synthesis (Späth, 1919):



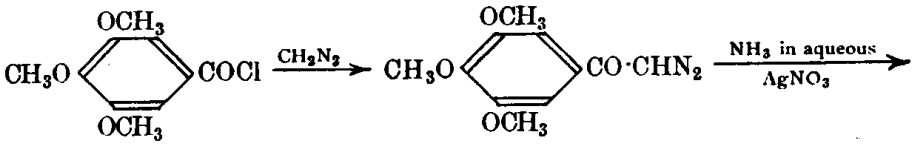


3:4:5-trimethoxy-ω-nitrostyrene

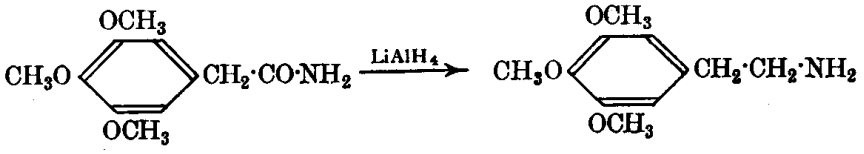


mezcaline

A more recent synthesis of mezcaline is that of Banholzer *et al.* (1952); this makes use of the Arndt–Eistert synthesis.



diazoketone

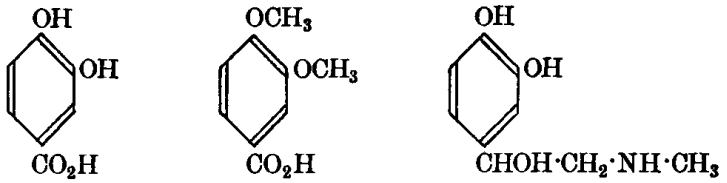


N-Methylmezcaline and *N*-acetylmezcaline also occur naturally in mezcal buttons.

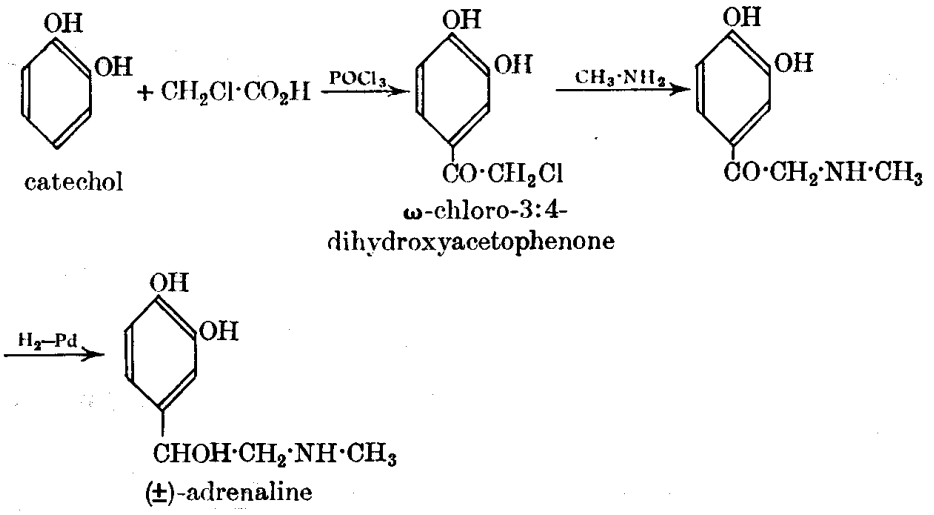
§12. Adrenaline (*Epinephrine*), $C_9H_{13}O_3N$, is a non-steroid hormone. The adrenal medulla is the source of the hormones adrenaline and noradrenaline. Adrenaline was the first hormone to be isolated in a crystalline form (Takamine, 1901; Aldrich, 1901). Adrenaline is active only when given by injection; it raises the blood-pressure, and is used locally to stop hæmorrhage.

Adrenaline is a colourless crystalline solid, m.p. 211°, and dissolves in acids and alkalis (it is insoluble in water); it is also optically active, having a lævorotation.

The phenolic character of adrenaline is indicated by its solubility in sodium hydroxide and its reprecipitation by carbon dioxide. Since it gives a green colour with ferric chloride, this led to the suggestion that adrenaline is a catechol derivative. When boiled with aqueous potassium hydroxide, adrenaline evolves methylamine; thus a methylamino group is probably present. On the other hand, when fused with potassium hydroxide, the product is protocatechuic acid, I (Takamine, 1901); methylation, followed

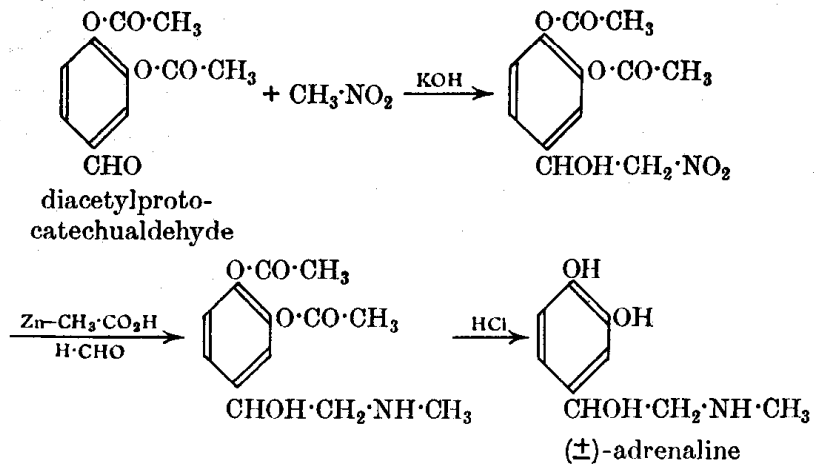


by fusion with potassium hydroxide, gives veratric acid, II, and trimethylamine (Jowett, 1904). The formation of trimethylamine indicates that the nitrogen atom must occur at the *end* of the side-chain. Since adrenaline is optically active, it must contain at least one asymmetric carbon atom. Now adrenaline contains three hydroxyl groups, two of which are phenolic (as shown by the formation of I and II). The third hydroxyl group was shown to be secondary alcoholic by the fact that when adrenaline is treated with benzenesulphonyl chloride, a tribenzenesulphonyl derivative is obtained which, on oxidation, gives a ketone (Friedmann, 1906). To account for the oxidation of adrenaline to the benzoic acid derivative, the —CHOH— group must be attached directly to the nucleus; had it been —CH_2·CHOH·, then a phenylacetic acid derivative would have been obtained. All the foregoing facts are in keeping with structure III for adrenaline, and this has been confirmed by synthesis by Stolz (1904) and Dakin (1905), with improvements by Ott (1926).

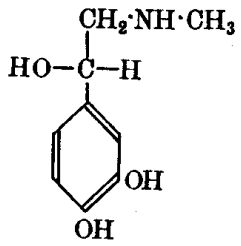


The racemic adrenaline has been resolved by means of (+)-tartaric acid.

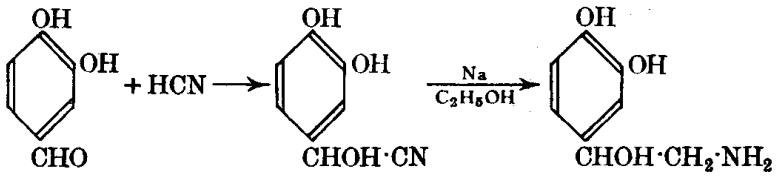
Nagai (1918) has also synthesised adrenaline as follows:



According to Dalgliesh (1953), the configuration of (−)-adrenaline is probably

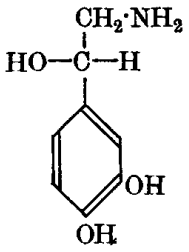


§12a. Noradrenaline (*Norepinephrine*), $C_8H_{11}O_3N$, is also present in the adrenal medulla. The natural compound is lævorotatory, and this (−)-isomer is the most powerful pressor-compound known. The structure of noradrenaline has been established by analytical work similar to that described for adrenaline, and has been confirmed by various syntheses, *e.g.*,



(±)-noradrenaline

According to Dalgliesh (1953), the configuration of (—)-noradrenaline is

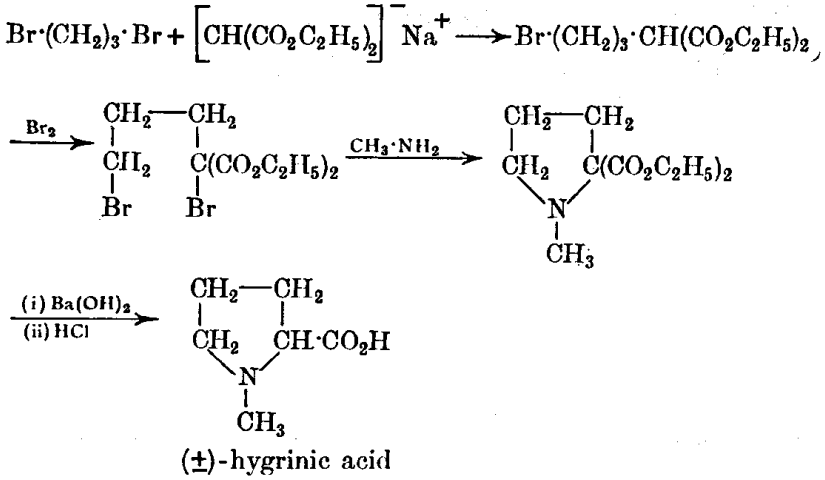


PYRROLIDINE GROUP

§13. Hygrine, $C_8H_{15}ON$, b.p. 193–195°, is one of the coca alkaloids. Its reactions show the presence of a keto group and a tertiary nitrogen atom, and when oxidised with chromic acid, hygrinic acid is formed.

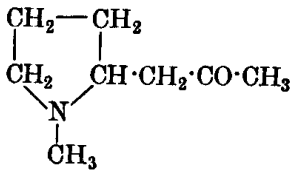
$$C_8H_{15}ON \xrightarrow{[O]} C_6H_{11}O_2N$$
hygrinic acid

Hygrinic acid was first believed to be a piperidinecarboxylic acid, but comparison with the three piperidine acids showed that this was incorrect. When subjected to dry distillation, hygrinic acid gives *N*-methylpyrrolidine; hence hygrinic acid is an *N*-methylpyrrolidinecarboxylic acid. Furthermore, since the decarboxylation occurs very readily, the carboxyl group was assumed to be in the 2-position (by analogy with the α-amino-acids). This structure, 1-methylpyrrolidine-2-carboxylic acid, for hygrinic acid was confirmed by synthesis (Willstätter, 1900).

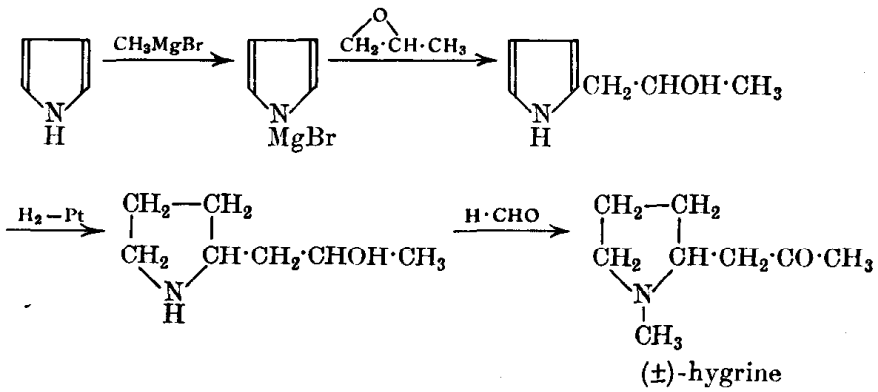


(±)-hygrinic acid

Thus a possible structure for hygrine is

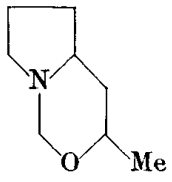


Hess (1913) claimed to have confirmed this structure by synthesis; his synthesis starts with pyrrylmagnesium bromide and propylene oxide to form pyrrylpropanol (note the rearrangement that occurs). This compound is then catalytically hydrogenated and then treated with formaldehyde; the imino nitrogen is methylated and the secondary alcoholic is oxidised to a keto group.



(±)-hygrine

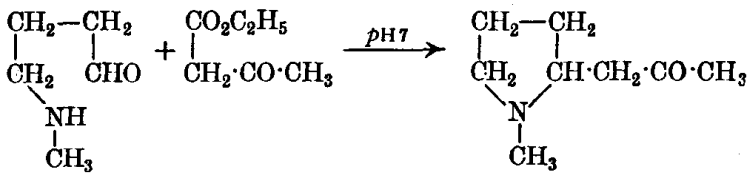
Lukeš *et al.* (1959) have repeated Hess's work and have shown that the



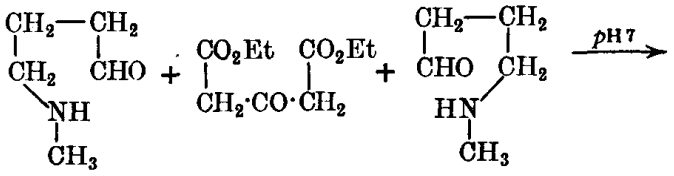
I

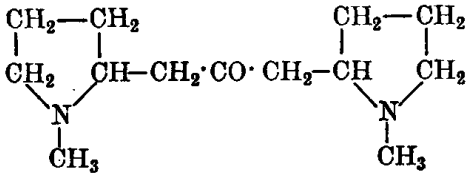
product is not hygrine but the tetrahydro-oxazine (I); it is the last stage of Hess's interpretation that has been shown to be incorrect.

Anet *et al.* (1949) have also synthesised (±)-hygrine by condensing γ-methylaminobutyraldehyde with ethyl acetoacetate in a buffered solution at a *p*H of 7 (physiological conditions).



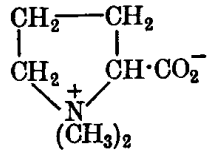
§13a. Cuscohygrine (*Cuskhygrine*), b.p. 169–170°/23 mm., occurs with hygrine. Its structure is established by the following synthesis (Anet *et al.*, 1949); γ-methylaminobutyraldehyde is condensed with acetonedicarboxylic ester:



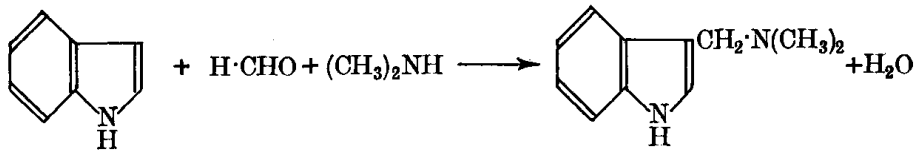


cuscohygrine

§13b. Stachydrine is obtained from the roots of *Stachys tuberifa*, from orange leaves, etc. It is the betaine (§4 C. XIII) of the quaternary ammonium compound of hygrinic acid.

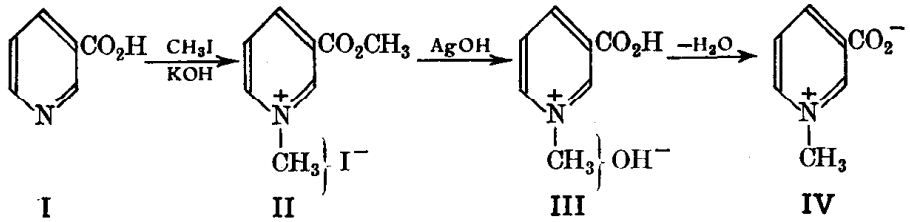


§14. Gramine has been found in barley mutants; it raises the blood-pressure in dogs when administered in small doses. Gramine has been synthesised by allowing indole to stand in an aqueous solution containing formaldehyde and dimethylamine (Snyder *et al.*, 1944).

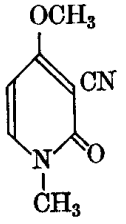


PYRIDINE GROUP

§15. Trigonelline, $C_7H_7O_2N$, m.p. 130°, is widely distributed in plants; the best source is the coffee bean. When boiled with barium hydroxide solution trigonelline produces methylamine; thus the molecule contains an *N*-methylamino group. On the other hand, when heated with hydrochloric acid at 250° under pressure, trigonelline forms methyl chloride and nicotinic acid; this suggests that the alkaloid is the methyl betaine of nicotinic acid. This structure for trigonelline has been confirmed by synthesis (Hantzsch, 1886). When heated with methyl iodide in the presence of potassium hydroxide, nicotinic acid, I, is converted into methyl nicotinate methiodide, II. II, on treatment with " silver hydroxide " solution, forms nicotinic acid methohydroxide, III, which then spontaneously loses a molecule of water to give trigonelline (a betaine), IV.

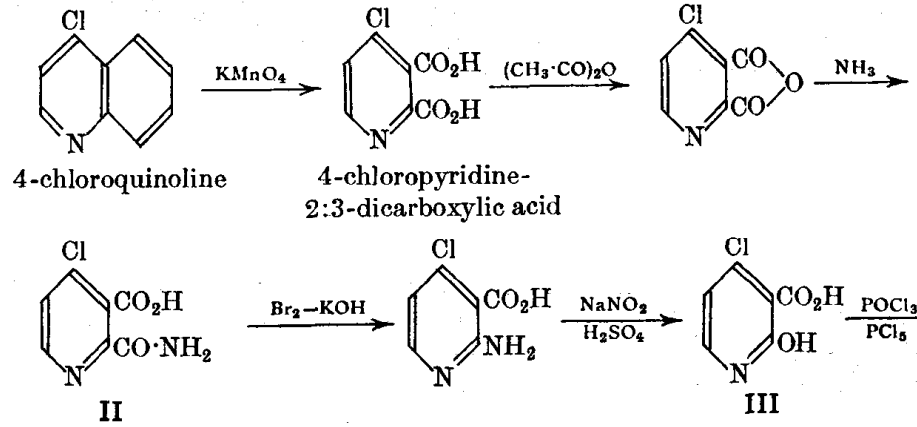


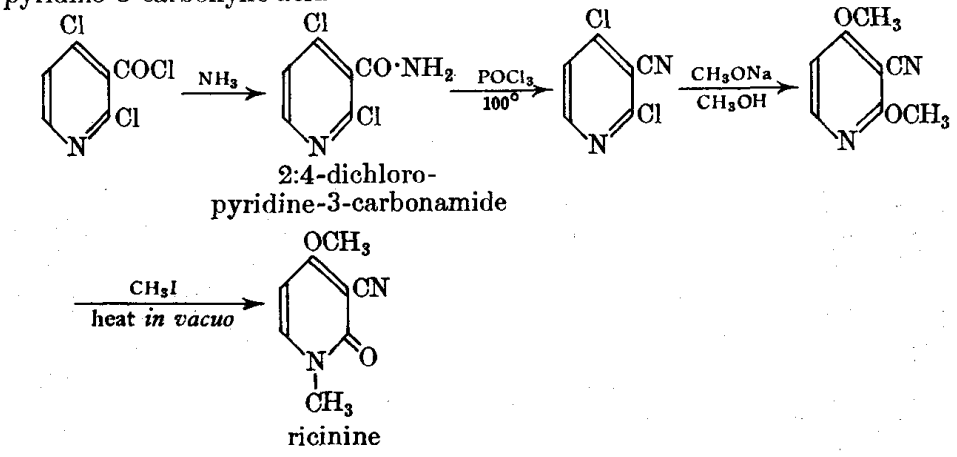
§16. Ricinine, $C_8H_8O_2N_2$, m.p. 201·5°, has been isolated from castor-oil seed; it is not a very toxic alkaloid. Degradative and synthetic work led to the suggestion that I is the structure of ricinine.



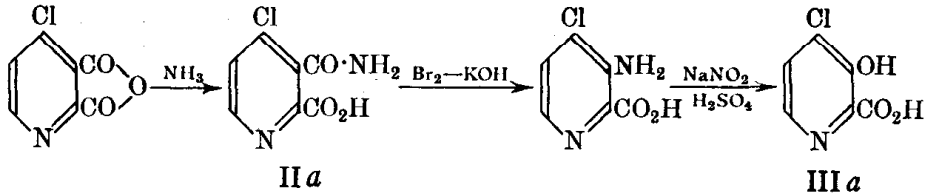
I

This has been confirmed by synthesis, *e.g.*, Späth *et al.* (1923);

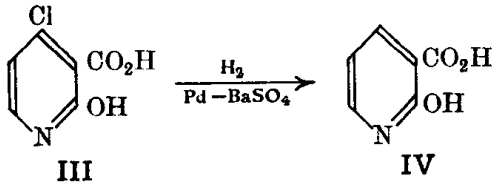




This is not an unambiguous synthesis, since II could have been 3-carbonamido-4-chloropyridine-2-carboxylic acid, II*a*, and consequently III would have been III*a*.

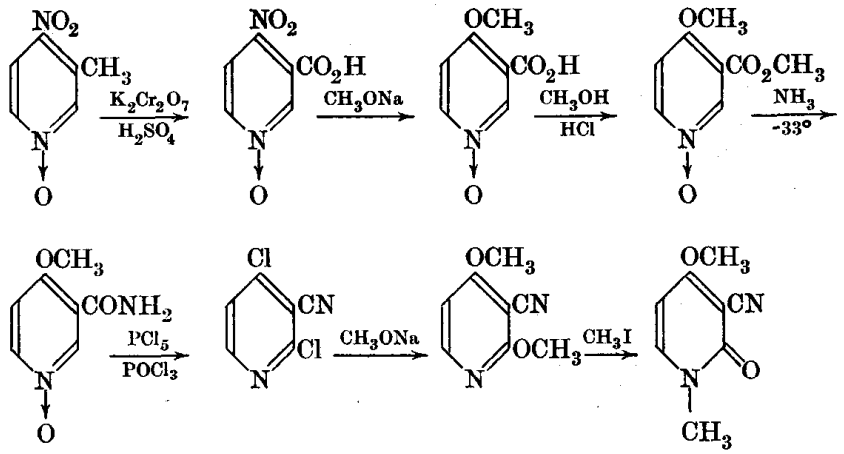


The structure of III was proved by the fact that on hydrogenation in the presence of Pd—$BaSO_4$, it gave 2-hydroxypyridine-3-carboxylic acid, IV.

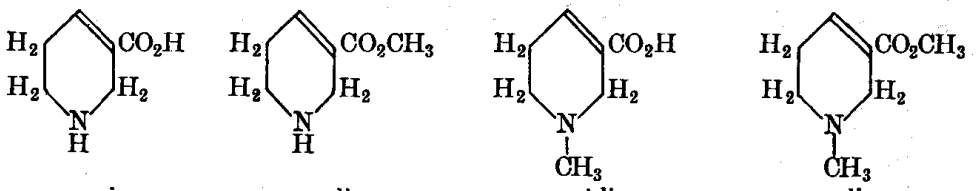


III IV

A more recent synthesis of ricinine is that of Taylor *et al.* (1956).

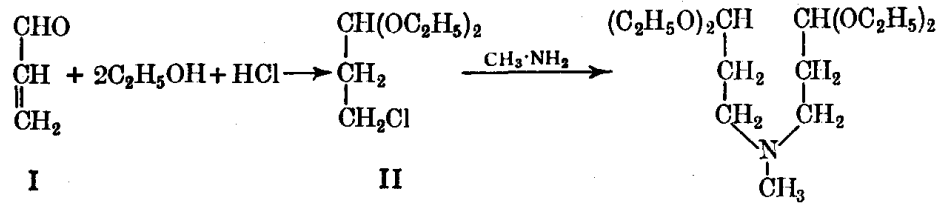


§17. Areca (or Betel) nut alkaloids. The betel nut is the source of a number of alkaloids which are all partially hydrogenated derivatives of nicotinic acid, *e.g.*,

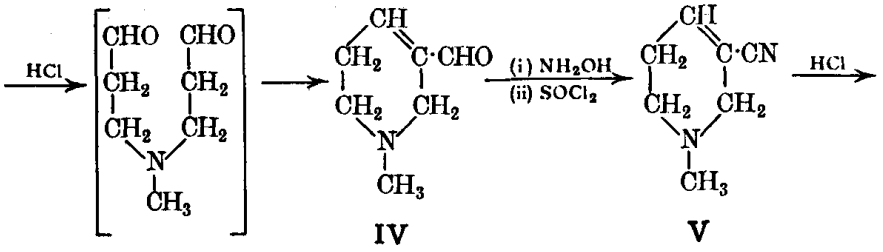


guvacine, m.p. 271-272° | guvacoline, b.p. 114°/13 mm. | arecaidine, m.p. 223° | arecoline, b.p. 209°

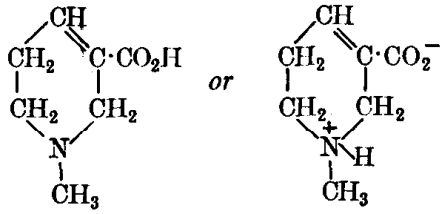
Let us consider arecaidine; its molecular formula is $C_7H_{11}O_2N$. When distilled with zinc dust, guvacine gives 3-methylpyridine; therefore this alkaloid is a pyridine derivative. Now guvacine is converted into arecaidine on heating with potassium methyl sulphate and sodium methoxide (Jahns, 1888, 1890); thus arecaidine is a methyl derivative of guvacine, and consequently is also a pyridine derivative. The usual tests show that arecaidine contains one carboxyl group, an *N*-methyl group and one double bond; hence the formula for arecaidine may be written as $C_5H_7N(CH_3)\cdot CO_2H$. Since the alkaloid is a pyridine derivative, the fragment C_5H_7N could be tetrahydropyridine. This was proved to be so by synthesis, and at the same time the positions of the double bond and carboxyl group were also established (Wohl *et al.*, 1907). Acraldehyde, I, on treatment with ethanol in the presence of hydrogen chloride, forms 3-chloropropionaldehyde acetal, II. II reacts with methylamine to form β-methyliminodipropionaldehyde tetra-acetal, III, which, on treatment with concentrated hydrochloric acid, ring closes to form 1 : 2 : 5 : 6-tetrahydro-1-methylpyridine-3-aldehyde, IV. This gives the cyano compound V on treatment with hydroxylamine, followed by dehydration of the oxime with thionyl chloride, and V is then converted into



I II III



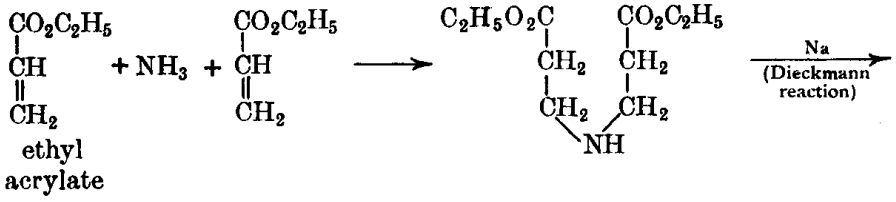
IV V



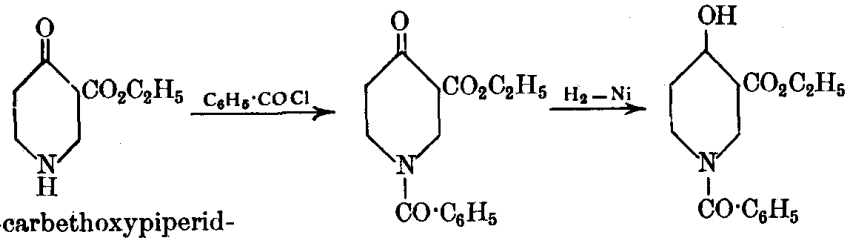
VI VI *a*

arecaidine by hydrolysis. Arecaidine is VI, or possibly VI*a*, the dipolar ion structure (*cf.* amino-acids and betaines).

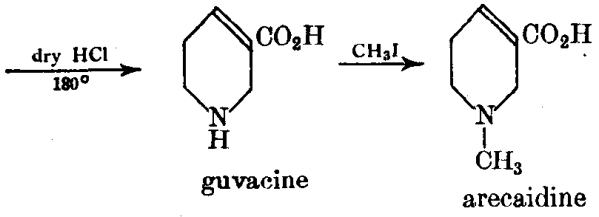
A more recent synthesis of arecaidine (and guvacine) is that of McElvain *et al.* (1946).



ethyl acrylate



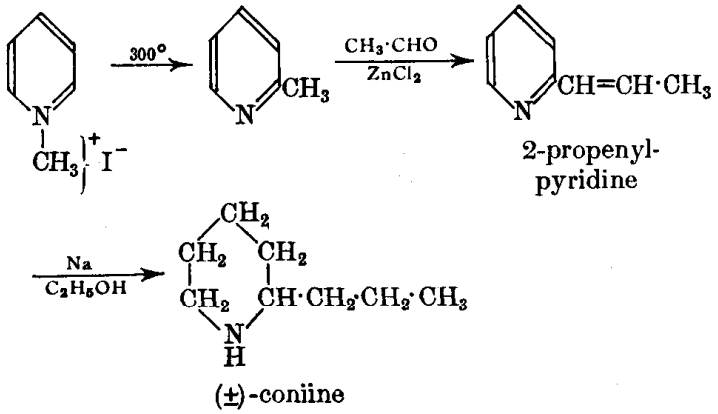
3-carbethoxypiperid-4-one



guvacine arecaidine

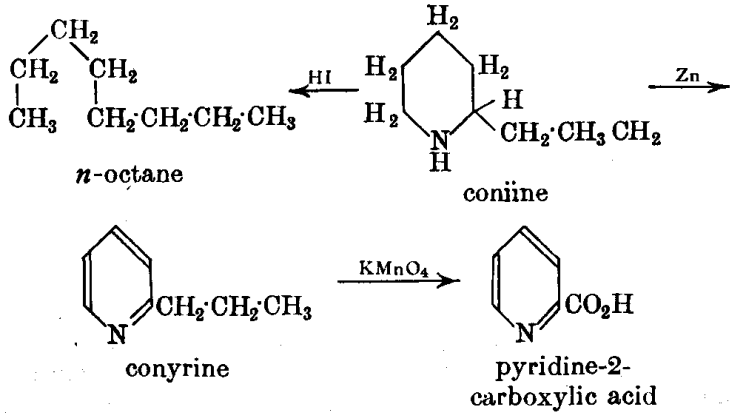
§18. Hemlock alkaloids. The most important alkaloid of this group is **coniine;** it was the first alkaloid to be synthesised. Oil of hemlock was drunk by Socrates when he was condemned to death in 399 B.C.

(+)-Coniine, $C_8H_{17}N$, b.p. 166–167°, is the form that occurs in oil of hemlock. When distilled with zinc dust, coniine is converted into conyrine, $C_8H_{11}N$ (Hofmann, 1884). Since the oxidation of conyrine with permanganate gives pyridine-2-carboxylic acid (α-picolinic acid), it follows that a pyridine nucleus is present with a side-chain in the 2-position. Thus coniine is probably a piperidine derivative with a side-chain in the 2-position. This side-chain must contain three carbon atoms, since two are lost when conyrine is oxidised. This side-chain is therefore either *n*-propyl or *iso*propyl, and it was actually shown to be *n*-propyl by the fact that when heated with

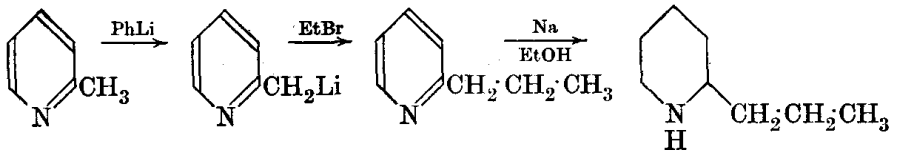


hydriodic acid at 300° under pressure, coniine forms *n*-octane. Had the side-chain been *iso*propyl, then the expected product would be *iso*-octane. From this evidence it therefore follows that coniine is 2-*n*-propylpiperidine, and this has been confirmed by synthesis (Ladenburg, 1885). The racemic coniine was resolved by means of (+)-tartaric acid, and the (+)-coniine so obtained was found to be identical with the natural compound.

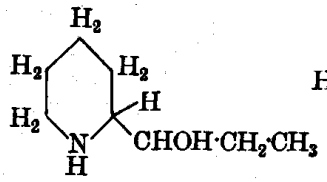
The reactions of coniine described above can therefore be formulated as follows:



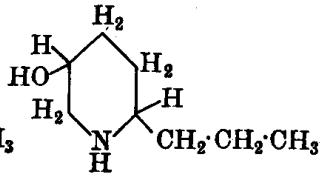
Coniine has also been synthesised from 2-methylpyridine and phenyllithium as follows (Bergmann *et al.*, 1932):



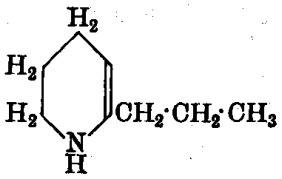
Other hemlock alkaloids are:



conhydrine

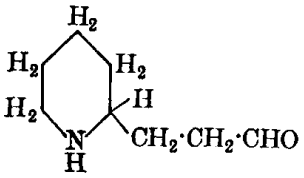


ψ-conhydrine

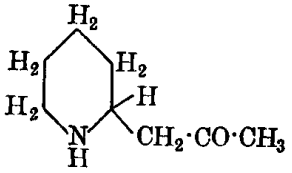


γ-coniceine

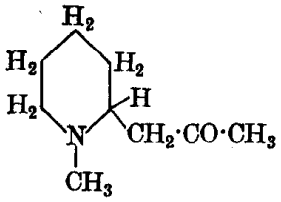
§19. Pomegranate alkaloids. The root bark of the pomegranate tree contains a number of alkaloids, the most important of which is pelletierine; three others are *iso*pelletierine, methyl*iso*pelletierine and pseudo-pelletierine. The last of these is related to atropine (§22).



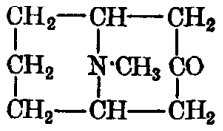
pelletierine



*iso*pelletierine

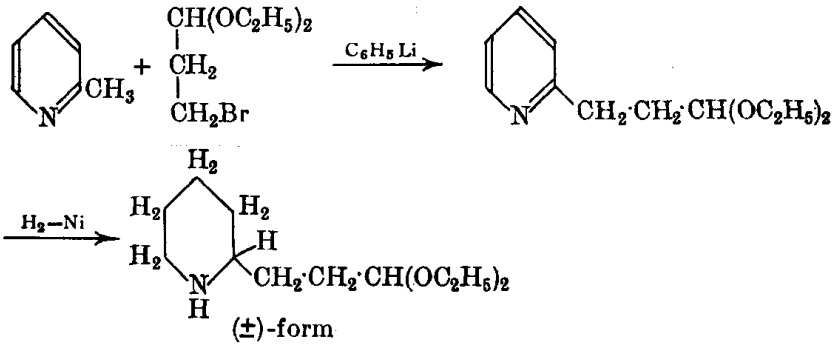


methyl*iso*pelletierine



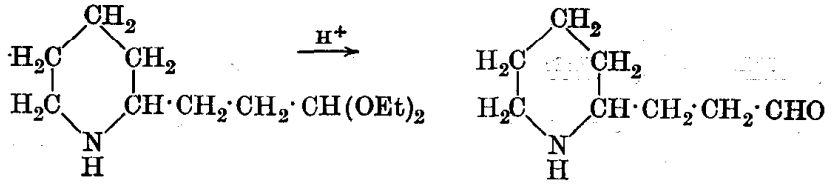
pseudo-pelletierine

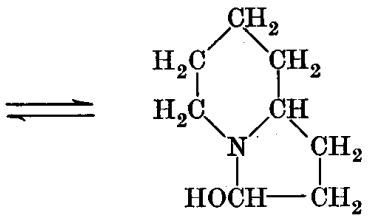
Pelletierine acetal has been synthesised by Spielman *et al.* (1941) by the action of 3-bromopropionaldehyde acetal on 2-methylpyridine (α-picoline) in the presence of phenyl-lithium, followed by catalytic reduction.



(±)-form

Pelletierine acetal was also prepared by Wibaut *et al.* (1940) who attempted to hydrolyse it to the free aldehyde; they obtained only viscous oils. Spielman *et al.* also failed to obtain the free aldehyde. Beets (1943) has therefore suggested that pelletierine can, and probably does, exist as some bicyclic structure such as I.



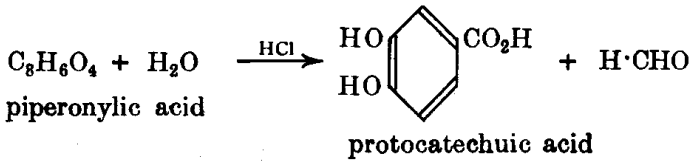


I

§20. Piperine, $C_{17}H_{19}O_3N$, m.p. 128–129·5°, occurs in pepper, especially black pepper (*Piper nigrum*). Hydrolysis of piperine with alkali gives

$$C_{17}H_{19}O_3N + N_2O \xrightarrow{KOH} \underset{\text{piperic acid}}{C_{12}H_{10}O_4} + \underset{\text{piperidine}}{C_5H_{11}N}$$

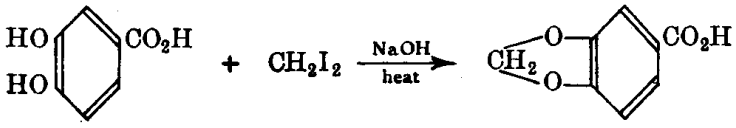
piperic acid and piperidine; thus the alkaloid is the piperidine amide of piperic acid (Babo *et al.*, 1857). Since piperidine is hexahydropyridine, the structure of piperine rests on the elucidation of that of piperic acid. The routine tests show that piperic acid contains one carboxyl group and two double bonds. When oxidised with permanganate, piperic acid gives first piperonal and then piperonylic acid. The structure of the latter is deduced from the fact that when heated with hydrochloric acid at 200° under pressure, piperonylic acid forms protocatechuic acid (3 : 4-dihydroxybenzoic acid) and formaldehyde.



piperonylic acid

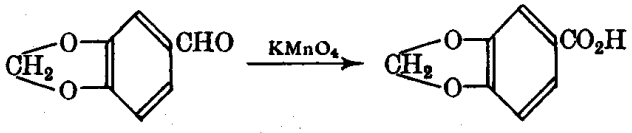
protocatechuic acid

Since one atom of carbon is eliminated, and there are no free hydroxyl groups in piperonylic acid, the structure of this acid is probably the methylene ether of protocatechuic acid, *i.e.*, piperonylic acid is 3 : 4-methylenedioxybenzoic acid; this has been confirmed by synthesis:



piperonylic acid

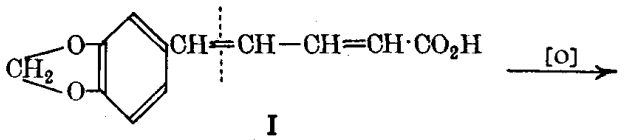
Furthermore, since piperonal (an aldehyde) gives piperonylic acid on oxidation, piperonal is therefore 3 : 4-methylenedioxybenzaldehyde.



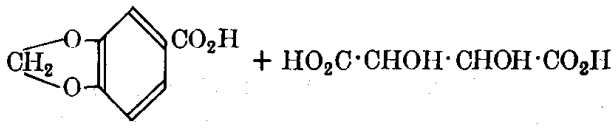
piperonal

From these results of oxidative degradation, it therefore follows that piperic acid is a benzene derivative containing only one side-chain. It is this side-chain that contains the two double bonds (the ready addition of four bromine atoms shows the presence of two *ethylenic* bonds), and since the careful oxidation of piperic acid gives tartaric acid in addition to piperonal and piperonylic acid, the side-chain is a " straight " chain. If we assume I as

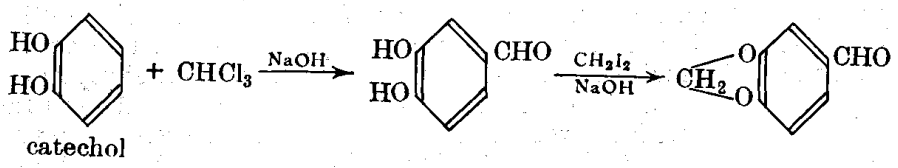
the structure of piperic acid, then all of the foregoing products of oxidation may be accounted for.



I

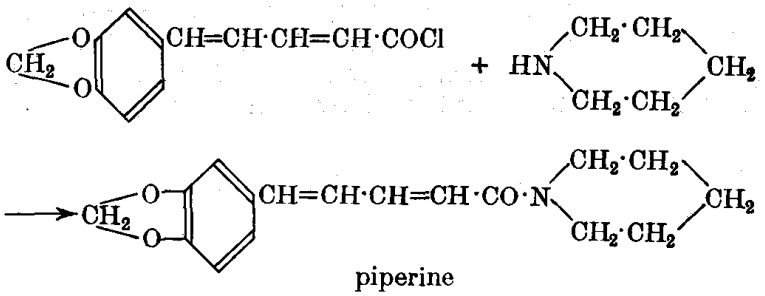


This has been confirmed by synthesis (Ladenburg *et al.*, 1894); piperonal (prepared *via* the Reimer–Tiemann reaction) is condensed with acetaldehyde in the presence of sodium hydroxide (Claisen–Schmidt reaction), and the product (a cinnamaldehyde derivative) is then heated with acetic anhydride in the presence of sodium acetate (Perkin reaction).



catechol

When the acid chloride of piperic acid (prepared by the action of phosphorus pentachloride on the acid) is heated with piperidine in benzene solution, piperine is formed; thus piperine is the piperidine amide of piperic acid.

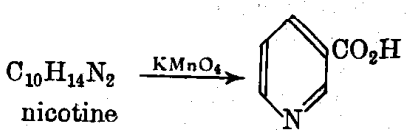


piperine

PYRROLIDINE-PYRIDINE GROUP

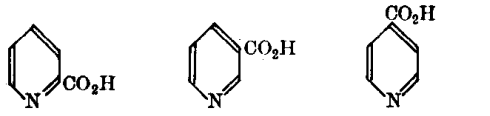
§21. Tobacco alkaloids. Many alkaloids have been isolated from the tobacco leaf, *e.g.*, nicotine, nicotimine (anabasine), nornicotine, etc.

Nicotine, $C_{10}H_{14}N_2$, b.p. 247°, is the best known and most widely distributed of the tobacco alkaloids; it occurs naturally as the (—)-form. When oxidised with dichromate–sulphuric acid (or permanganate or nitric acid), nicotine forms nicotinic acid (Huber, 1867).



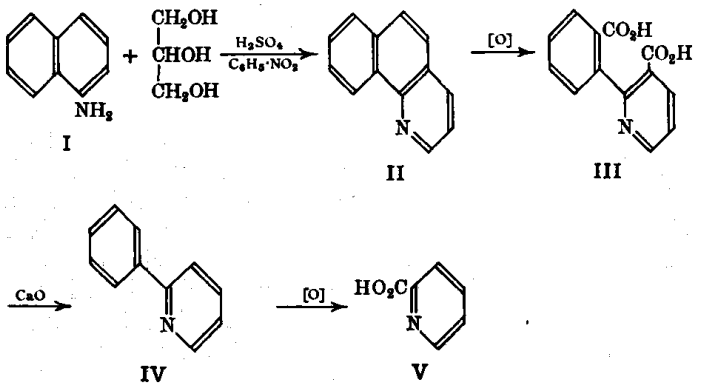
nicotine nicotinic acid

It is instructive, at this point, to see how the orientations of the three isomeric pyridinecarboxylic acids have been elucidated.

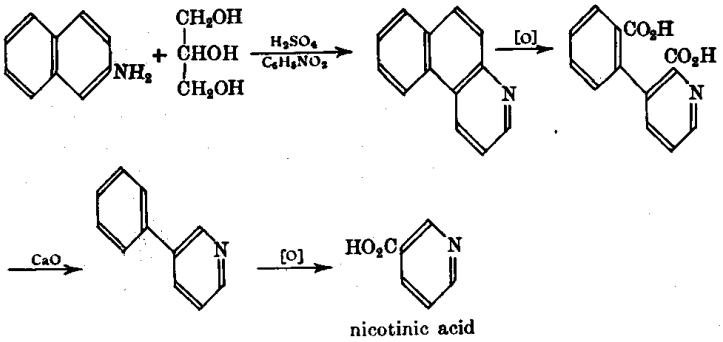


picolinic acid, m.p. 137° | nicotinic acid, m.p. 234-237° | *iso*nicotinic acid, m.p. 317°

Picolinic acid. 1-Naphthylamine, I, when subjected to the Skraup synthesis (see Vol. I), is converted into 7 : 8-benzoquinoline, II (this structure is established by its synthesis). II, on vigorous oxidation with alkaline permanganate, gives the dicarboxylic acid III which, when decarboxylated by heating with calcium oxide, is converted into 2-phenylpyridine, IV. This, on further oxidation with permanganate, gives a pyridinecarboxylic acid which must, from the structure of IV, be the 2-acid, *i.e.*, picolinic acid, V.



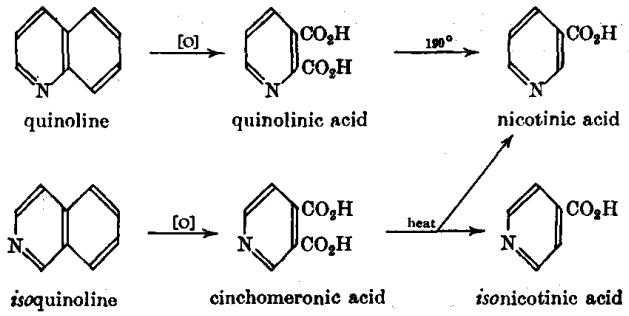
Nicotinic acid. This has been shown to be pyridine-3-carboxylic acid by a similar set of reactions, except that in this case the starting material is 2-naphthylamine.



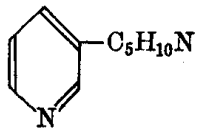
nicotinic acid

iso*Nicotinic acid.* This third isomer is therefore pyridine-4-carboxylic acid.

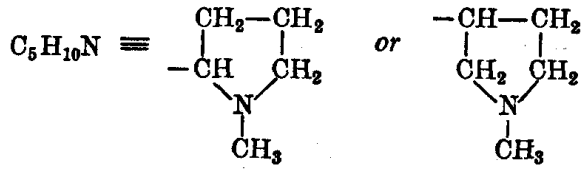
An alternative proof for the orientations of these three acids is based on the structures of quinoline and *iso*quinoline (which have been established by synthesis). Oxidation of quinoline with alkaline permanganate gives quinolinic acid which, by its method of preparation, must be pyridine-2 : 3-dicarboxylic acid. When quinolinic acid is heated to 190°, one carboxyl group is lost to produce nicotinic acid; thus nicotinic acid must be either pyridine-2- or -3-carboxylic acid. *iso*Quinoline, on oxidation with alkaline permanganate, produces cinchomeronic acid, which must therefore be pyridine-3 : 4-dicarboxylic acid. This, on gentle heating, gives a mixture of nicotinic and *iso*nicotinic acids; thus nicotinic acid must be the 3-acid, and *iso*nicotinic acid the 4-acid. Hence picolinic acid is pyridine-2-carboxylic acid.



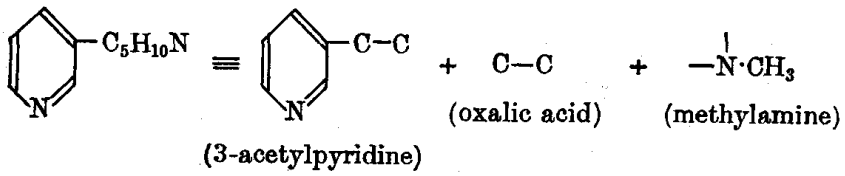
Returning to the structure of nicotine, since nicotinic acid is a product of oxidation, the alkaloid therefore contains a pyridine nucleus with a complex side-chain in the 3-position. Thus we may write the formula of nicotine as



Because of its formula, this side-chain was originally believed to be piperidine, but further work showed that this was incorrect. When nicotine zinci-chloride is distilled, the products are pyridine, pyrrole and methylamine (Laiblin, 1879). This suggests that the side-chain $C_5H_{10}N$ is a pyrrole derivative. Furthermore, when nicotine is heated with concentrated hydriodic acid at 150° (Herzig–Meyer method), methyl iodide is formed. Thus the side-chain contains an *N*-methyl group. It therefore appears that the side-chain could be *N*-methylpyrrolidine, but its point of attachment to the pyridine nucleus could be either 2 or 3 on the evidence obtained so far:

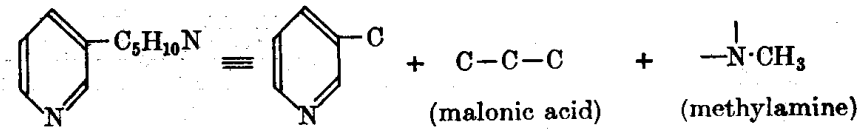


The correct structure of nicotine was obtained by Pinner (1892, 1893). Treatment of nicotine with bromine in acetic acid gives, among other products, the hydrobromide perbromide, $C_{10}H_{10}ON_2Br_2 \cdot HBr \cdot Br_2$, which, when treated with aqueous sulphurous acid, is converted into dibromocotinine, $C_{10}H_{10}ON_2Br_2$. This, on heating with a mixture of sulphurous and sulphuric acids at 130–140°, forms 3-acetylpyridine, oxalic acid and methylamine. Thus the structure of nicotine must account for the following skeleton structures:

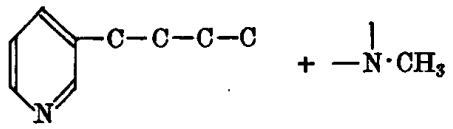


(3-acetylpyridine)

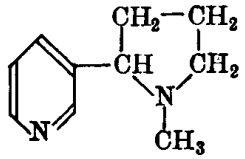
Now bromine, in the presence of hydrobromic acid, converts nicotine into dibromoticonine, $C_{10}H_8O_2N_2Br_2$, which, on heating with barium hydroxide solution at 100°, forms nicotinic acid, malonic acid and methylamine. Hence the structure of nicotine must also account for the following skeleton structures:



These two sets of reactions, taken in conjunction with one another, are satisfied by the following skeleton for nicotine:

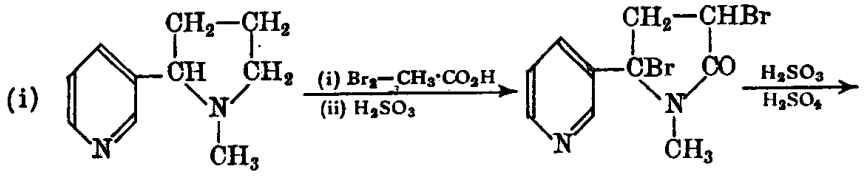


The problem now is: Where is the position of the *N*-methyl group? Nicotine behaves as a ***di-tertiary base***, and forms two isomeric " methyl iodide addition products ". Thus the nitrogen atom in the side-chain must be of the type —C—N(CH$_3$)—C—. Furthermore, it is extremely difficult to reduce nicotine beyond hexahydronicotine (the pyridine part is reduced to piperidine). Hence the side-chain must be saturated, and this can only be so if the side-chain is cyclic, *i.e.*, *N*-methylpyrrolidine ($C_5H_{11}N \equiv C_4H_8 \cdot NCH_3 \equiv C_4H_8$). The presence of this pyrrolidine nucleus also accounts for the formation of pyrrole when nicotine zincichloride is distilled (see above). All the foregoing facts are satisfied by the following structure for nicotine.

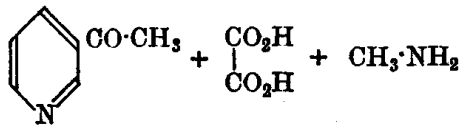


nicotine

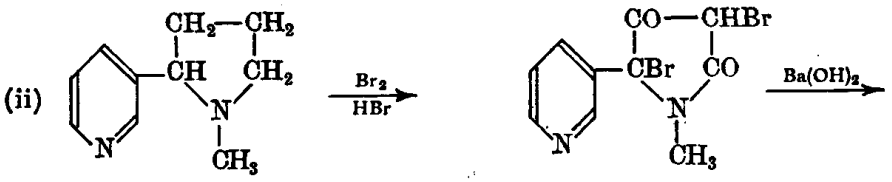
On this basis, Pinner's work may be formulated:



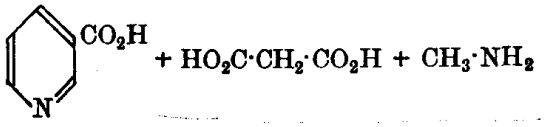
dibromocotinine



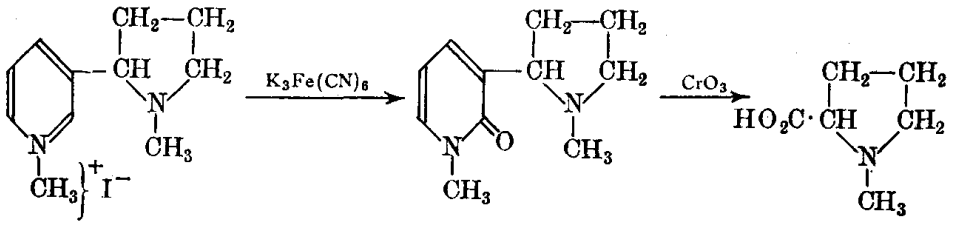
3-acetylpyridine



dibromoticonine

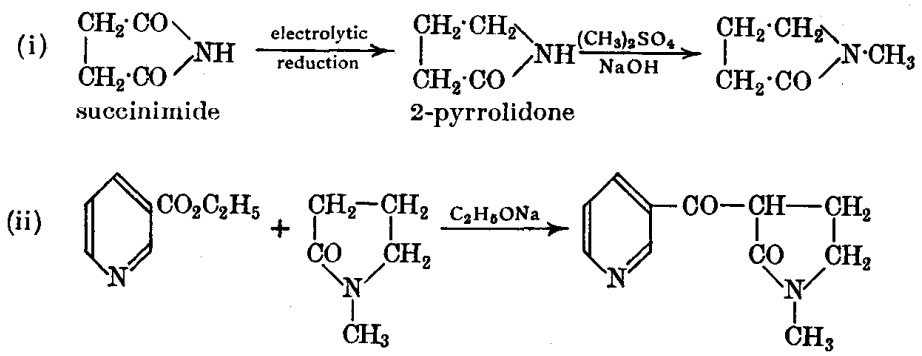


The most direct analytical evidence for the presence of the pyrrolidine nucleus has been given by Karrer (1925, 1926); nicotine hydriodide forms nicotine *iso*methiodide when warmed with methyl iodide and this, on oxidation with potassium ferricyanide, is converted into nicotone which, on oxidation with chromium trioxide, gives hygrinic acid (§13).



nicotine *iso*methiodide — nicotone — hygrinic acid

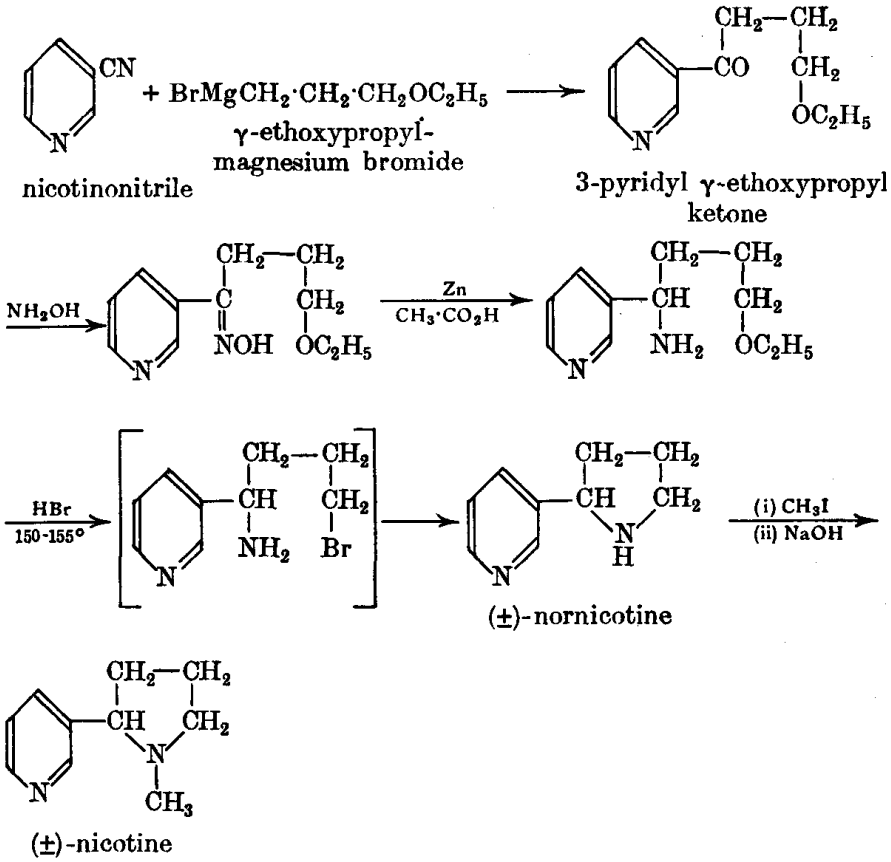
Pinner's formula for nicotine has been confirmed by synthesis, *e.g.*, *Späth and Bretschneider* (1928).



(±)-nicotine

This was resolved by means of (+)-tartaric acid; the synthetic (−)-nicotine is identical with the natural compound.

Craig (1933).



Späth *et al.* (1936) have resolved (±)-nornicotine; methylation of the (−)-form with formaldehyde and formic acid gave (−)-nicotine, identical with the natural product.

§22. Solanaceous alkaloids. This group includes atropine, hyoscyamine and scopolamine (hyoscine).

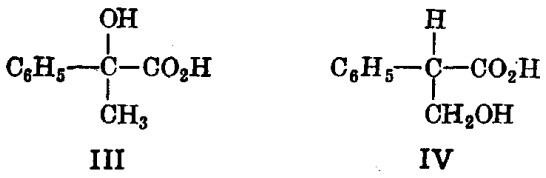
Atropine, $C_{17}H_{23}O_3N$, m.p. 118°, occurs in deadly nightshade (*Atropa belladonna*) together with hyoscyamine. Hyoscyamine is optically active (lævorotatory), but readily racemises to atropine when warmed in an ethanolic alkaline solution; thus atropine is (±)-hyoscyamine.

When warmed with barium hydroxide solution, atropine is hydrolysed to (±)-tropic acid and tropine (an alcohol); thus atropine is the tropine ester of tropic acid.

(±)-Tropic acid, $C_9H_{10}O_3$, m.p. **117°**, is a saturated compound (it does not add on bromine); the usual tests show that it contains one carboxyl group and one alcoholic group. When heated strongly, tropic acid loses a molecule of water to form atropic acid, $C_9H_8O_2$, and this, on oxidation,

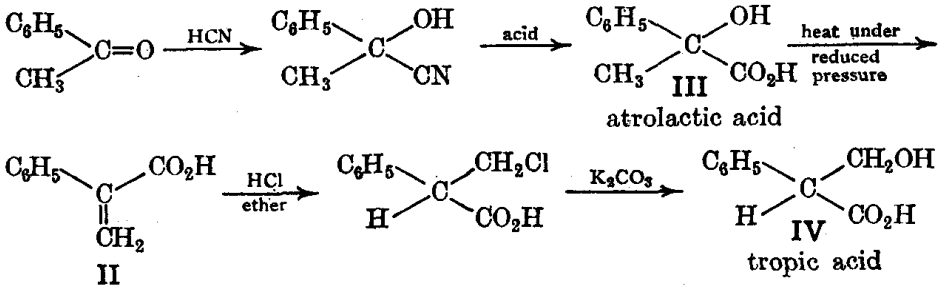
$C_6H_5\cdot CH{=}CH\cdot CO_2H$ (I) $\qquad$ $C_6H_5\cdot C(=CH_2)\cdot CO_2H$ (II)

gives benzoic acid. Thus tropic and atropic acids contain a benzene ring with one side-chain. It therefore follows that atropic acid could be either I or II. Since, however, I is known to be cinnamic acid, II must be atropic acid. Addition of a molecule of water to II would therefore give tropic



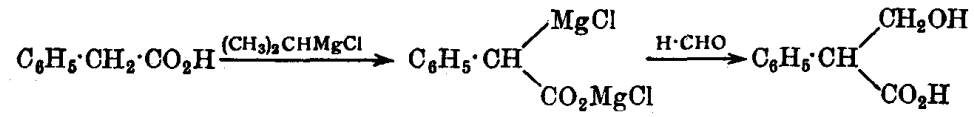
III IV

acid which, consequently, must be either III or IV. Tropic acid has been shown to be IV by synthesis, *e.g.*, Mackenzie and Wood (1919), starting from acetophenone.

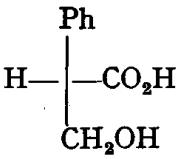


III is atrolactic acid, and its dehydration to II confirms the structure of atropic acid. It should also be noted that the addition of hydrogen chloride takes place contrary to Markownikoff's rule (see unsaturated acids, Vol. I); had the addition been in accordance with the rule, then atrolactic acid would have again been obtained. It is tropic acid that contains the asymmetric carbon atom which gives rise to the optically active hyoscyamine. The above synthesis results in (±)-tropic acid, and this has been resolved by means of quinine.

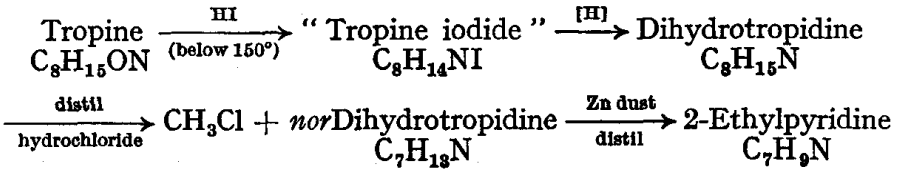
Blicke *et al.* (1952) have synthesised tropic acid by boiling phenylacetic acid with *iso*propylmagnesium chloride in ethereal solution, and then treating the product, a Grignard reagent, with formaldehyde.



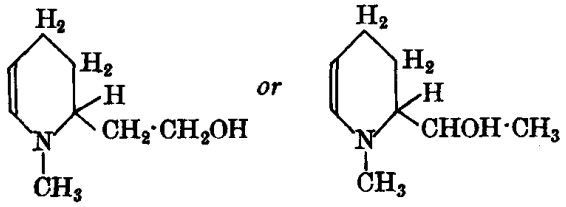
Fodor *et al.* (1961) have established the absolute configuration of (—)-tropic acid by its correlation with (—)-alanine. According to the Cahn–Ingold–Prelog convention (§5c. II), natural tropic acid is (*S*)-(—)-tropic acid.



Tropine (tropanol), $C_8H_{15}ON$, m.p. 63°, behaves as a saturated compound which contains an alcoholic group. The structure of tropine was investigated by Ladenburg (1883, 1887), who showed that the molecule contained a reduced pyridine nucleus:



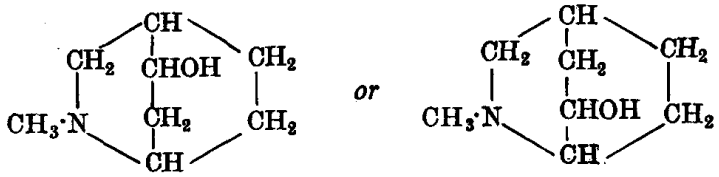
"Tropine iodide" is formed by the replacement of the alcoholic group in tropine by an iodine atom, which is then replaced by hydrogen to form dihydrotropidine (tropane). The formation of methyl chloride indicates the presence of an *N*-methyl group, and the isolation of 2-ethylpyridine shows the presence of this nucleus (in a reduced form). Largely on this evidence, Ladenburg was led to suggest the following alternative formulæ for tropine:



Merling (1891), by the oxidation of tropine with chromium trioxide, obtained (±)-tropinic acid.

$$\underset{\text{tropine}}{C_8H_{15}ON} \xrightarrow{CrO_3} \underset{(\pm)\text{-tropinic acid}}{C_8H_{13}O_4N}$$

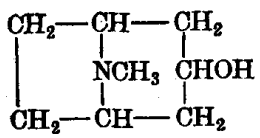
Tropinic acid is a dicarboxylic acid, and since there is no loss of carbon in its formation, the hydroxyl group in tropine must therefore be in a ring system. Thus Ladenburg's formula is untenable, and so Merling proposed the following structures for tropine:



Willstätter (1895–1901) then examined the oxidation products of tropine obtained as follows:

$$\underset{C_8H_{15}ON}{\text{Tropine}} \xrightarrow{CrO_3} \underset{C_8H_{13}ON}{\text{Tropinone}} \xrightarrow{CrO_3} \underset{C_8H_{13}O_4N}{(\pm)\text{-Tropinic acid}}$$

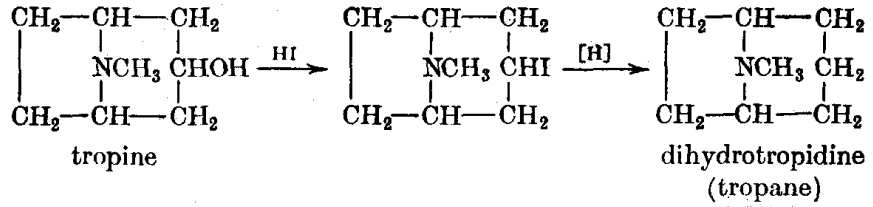
Tropinone behaved as a ketone; thus tropine is a secondary alcohol (*cf.* Merling's formula). Willstätter (1897) also showed that tropinone forms a dibenzylidene derivative with benzaldehyde, and a di-oximino derivative when treated with amyl nitrite and hydrochloric acid. Thus tropinone contains the ·CH_2·CO·CH_2· grouping, and so it follows that Merling's formula is also untenable. Willstätter therefore proposed three possible structures for tropine, but eliminated two by the consideration of various reactions of tropine, and was left with the following (which contains a pyridine and a pyrrole nucleus with the nitrogen atom common to both):

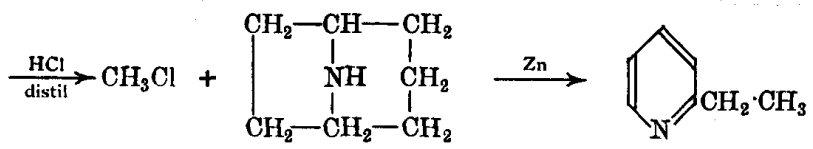


Not only did this fit the facts best, but it was also supported by the following evidence: (i) Exhaustive methylation of tropine gives tropilidene (*cyclo*-heptatriene), C_7H_8. (ii) Exhaustive methylation of tropinic acid gives an unsaturated dicarboxylic acid which, on reduction, forms pimelic acid.

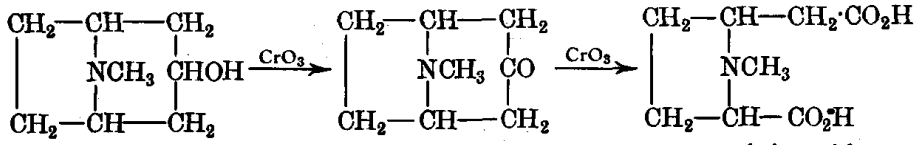
All the foregoing reactions of tropine can be readily explained on the Willstätter formula.

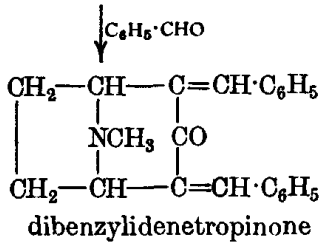
Formation of 2-ethylpyridine from tropine.



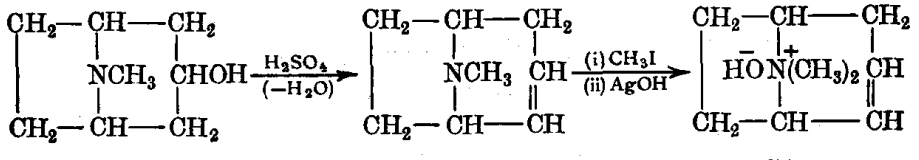


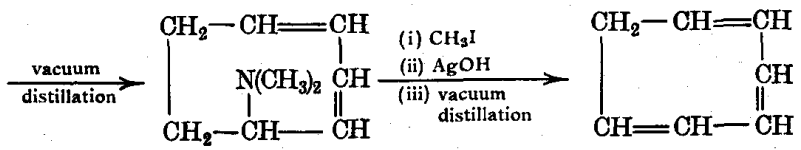
Formation of tropinone and tropinic acid from tropine.



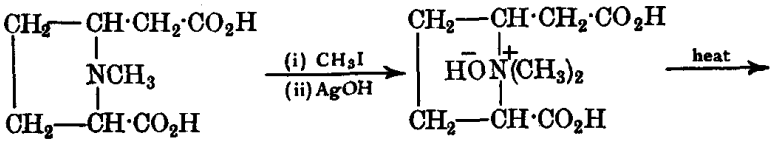


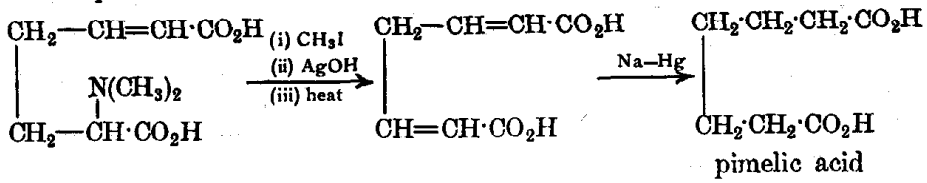
Formation of tropilidene from tropine.





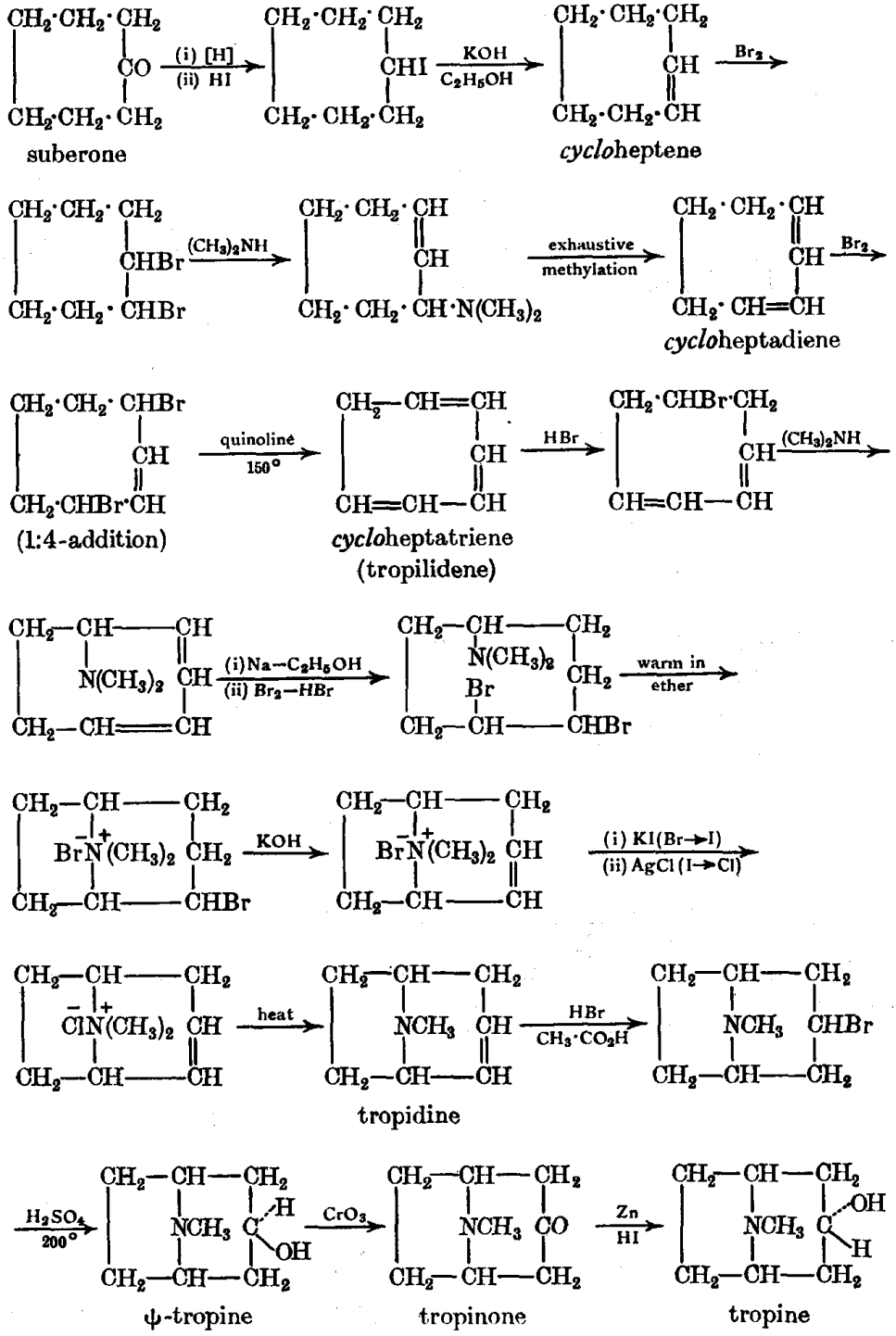
Formation of pimelic acid from tropinic acid.





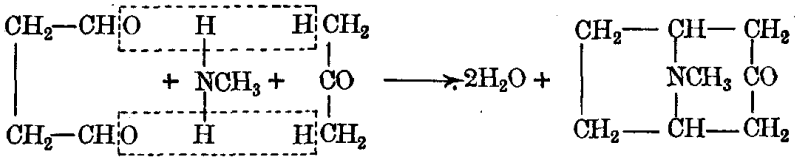
The structure of tropine has been confirmed by synthesis, one by Willstätter (1900–1903), and the other by Robinson (1917).

Willstätter's synthesis.

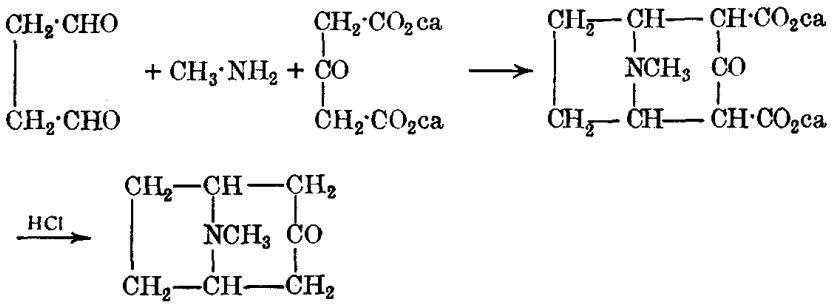


Robinson's synthesis.

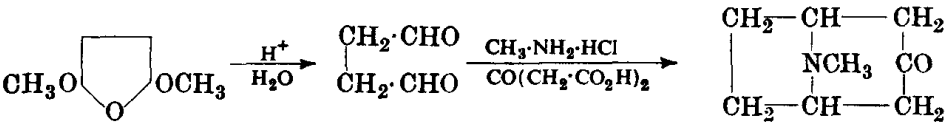
When a mixture of succinaldehyde, methylamine and acetone is allowed to stand in water for thirty minutes, tropinone is produced in very small yield.



A much better yield (40 per cent.) is obtained by using calcium acetonedicarboxylate or ethyl acetonedicarboxylate instead of acetone; the calcium salt or ester so produced is converted into tropinone by warming with hydrochloric acid, *e.g.* (ca = Ca/2):

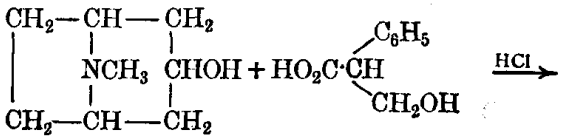


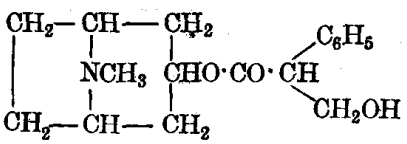
Schöpf *et al.* (1935) have obtained a yield of 70–85 per cent. by carrying out Robinson's synthesis at a *p*H of 7. Elming *et al.* (1958) have also synthesised tropinone using methylamine hydrochloride, acetonedicarboxylic acid and generating succinaldehyde *in situ* by the action of acid on 2,5-dimethoxytetrahydrofuran:



The yield was 81 per cent., but in this case "physiological conditions" were not necessary (see §28).

The final problem is to combine tropine with tropic acid; this has been done by heating the two together in the presence of hydrogen chloride (Fischer–Speier esterification; see Vol. I).





atropine

Stereochemistry of the tropines. Tropinone can be reduced to tropine, together with a small amount of *ψ*-tropine, by means of a metal and

acid, the best combination being zinc dust and hydriodic acid; or by means of electrolytic reduction. On the other hand, reduction with sodium amalgam converts tropinone into ψ-tropine. According to Mirza (1952), lithium aluminium hydride reduces tropinone quantitatively to ψ-tropine, but according to Beckett *et al.* (1957), 54 per cent. of ψ-tropine and 45 per cent. of tropine are obtained. A larger yield of the former (69 per cent.) is obtained with sodium borohydride, and reduction with sodium and *iso*butanol (in toluene) gives the maximum yield of ψ-tropine (88 per cent.).

Tropine and ψ-tropine are geometrical isomers, one isomer having the hydrogen atom on C_3 on the same side as the nitrogen bridge, and the other isomer has this hydrogen atom on the opposite side (*cf.* the borneols, §23b. VIII); Fig. 1 shows the two possible forms. Neither of these forms is optically

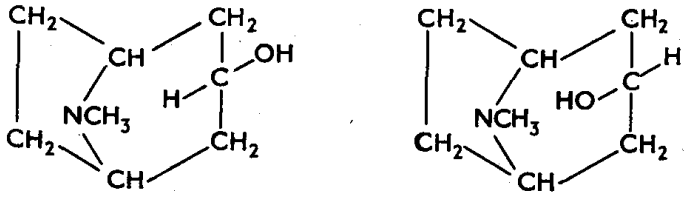


FIG. 14.1.

active, since the molecule has a plane of symmetry. C_1 and C_5 are asymmetric, but the molecule is optically inactive by internal compensation (see §7b. II), and so each isomer is a *meso*-form; C_3 is pseudo-asymmetric (see §8. IV). It should also be noted that another pair of *optically active forms* would exist if the fusion of the nitrogen bridge were *trans*; this, however, is not possible (*cf.* camphor, §23a. VIII; also cocaine, §23).

The problem now is to decide which geometrical isomer (of the two forms shown in Fig. 1) is tropine and which is ψ-tropine. Fodor (1953) has given evidence to show that ψ-tropine is the *syn*-compound (nitrogen bridge and hydroxyl group are in the *cis*-position; Fig. 1*b*), and that tropine is the *anti*-compound (nitrogen bridge and hydroxyl group are in the *trans*-position; Fig. 1*a*). The problem, however, is more involved than this, since the conformation of the piperidine ring has also to be considered. Fodor gives the configuration of the piperidine ring as the boat form in both isomers (Fig. 2).

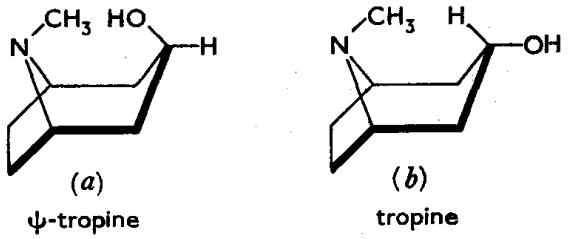


FIG. 14.2.

Zenitz *et al.* (1952) and Clemo *et al.* (1953) support these configurations from evidence obtained by measurements of the dipole moments of these two isomers; ψ-tropine has been shown to have a higher dipole moment than tropine. Zenitz *et al.* have also shown from infra-red absorption spectra measurements that ψ-tropine has intramolecular hydrogen bonding; this is only possible in the *syn*-form. Bose *et al.* (1953), however, have assumed the chair form for the piperidine ring by analogy with the chair conformation of *cyclo*hexane compounds and pyranosides (see §11. IV). Thus these authors have suggested that ψ-tropine is Fig. 3 (*a*), in which the hydroxyl

group is equatorial, and that tropine is Fig. 3 (*b*), in which the hydroxyl group is axial.

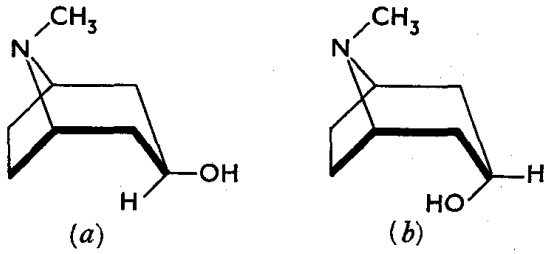
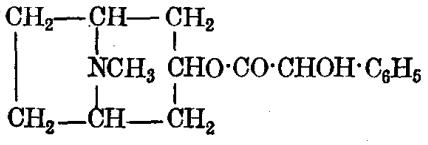


FIG. 14.3.

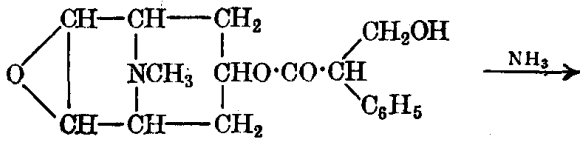
If these be the configurations, then it is difficult to explain Fodor's work (which involves rearrangements), and also the fact that there is intramolecular hydrogen bonding in *ψ*-tropine. Sparke (1953) has suggested that the chair form can readily change into the boat form; this would then explain the intramolecular hydrogen bonding. Archer and Lewis (1954) also adopt this explanation, but make the assumption that the bond energy involved in the hydrogen bond is sufficient to transform, at least partially, the more stable chair form into the less stable boat form; in *ψ*-tropine the chair and boat forms are in mobile equilibrium, the latter being the predominant form.

§22a. Tropeines and pseudotropeines. These are synthetic esters formed respectively from tropine and *ψ*-tropine with various organic acids. The tropeines (including atropine itself) are powerful mydriatics (pupil dilators) and feeble anæsthetics; the *ψ*-tropeines are the reverse. One of the most important tropeines is *homatropine* (*mandelyltropeine*), which is prepared by combining tropine with mandelic acid.

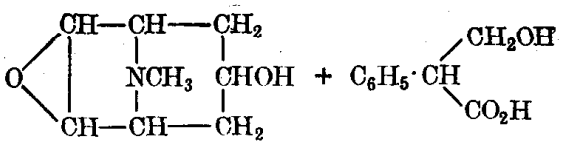


homatropine

§22b. Hyoscine (scopolamine), $C_{17}H_{21}O_4N$, is a syrup and is lævorotatory; it is obtained from various sources, *e.g.*, *Datura Metel.* Hyoscine is a constituent of travel sickness tablets, and when administered with morphine, produces " twilight sleep ". Hyoscine is the (—)-tropic ester of the aminoalcohol *scopine*; these two compounds are produced by the hydrolysis of hyoscine with ammonia.

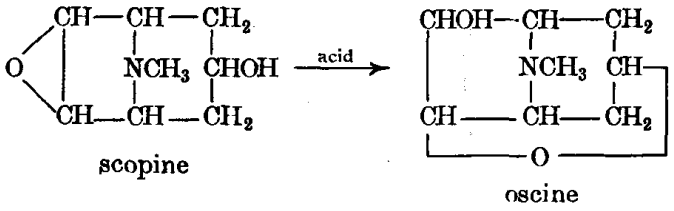


hyoscine



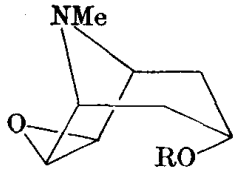
scopine tropic acid

More vigorous hydrolysis of hyoscine with acids or alkalis produces *oscine* (*scopoline*), which is formed by the isomerisation of scopine.



scopine oscine

It is interesting to note, in this connection, that the action of *ethanolic* sodium hydroxide on (—)-hyoscine at room temperature causes the latter



I

to racemise to (±)-hyoscine. Fodor *et al.* (1959) have carried out a total synthesis of (±)-hyoscine and shown its conformation to be

(I; R = CO·CHPh·CH_2OH).

§23. Coca alkaloids. In this group occur cocaine, benzoylecgonine, tropacocaine, hygrine (§13), cuscohygrine (§13a), etc.

(—)**-Cocaine,** $C_{17}H_{21}O_4N$, m.p. 98°, occurs in coca leaves; it is sparingly soluble in water, but its hydrochloride is quite soluble and is used as a local anæsthetic. When heated with water, cocaine is hydrolysed to methanol and benzoylecgonine.

$$\underset{\text{cocaine}}{C_{17}H_{21}O_4N} + H_2O \longrightarrow \underset{\text{benzoylecgonine}}{C_{16}H_{19}O_4N} + CH_3OH$$

Thus cocaine contains a carbomethoxyl group, and benzoylecgonine a carboxyl group. When benzoylecgonine is heated with barium hydroxide solution, further hydrolysis occurs, the products obtained being benzoic acid and ecgonine.

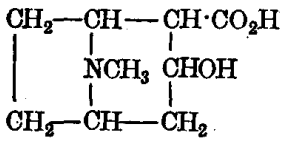
$$\underset{\text{benzoylecgonine}}{C_{16}H_{19}O_4N} + H_2O \xrightarrow{Ba(OH)_2} \underset{\text{ecgonine}}{C_9H_{15}O_3N} + C_6H_5{\cdot}CO_2H$$

Ecgonine shows the reactions of an alcohol, and so benzoylecgonine is the benzoyl derivative of a hydroxycarboxylic acid. The structure of ecgonine has been deduced from the nature of the products obtained by oxidation, *viz.*,

$$\underset{C_9H_{15}O_3N}{\text{Ecgonine}} \xrightarrow{CrO_3} \underset{C_8H_{13}ON}{\text{Tropinone}} \xrightarrow{CrO_3} \underset{C_8H_{13}O_4N}{\text{Tropinic acid}} + \underset{C_7H_{11}O_3N}{\text{Ecgoninic acid}}$$

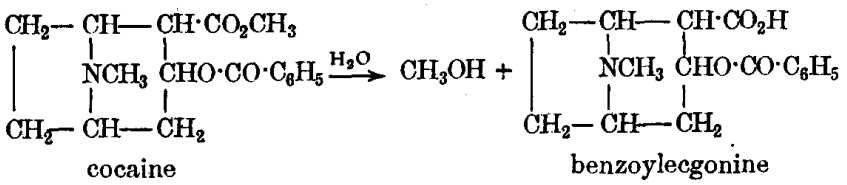
From these results, it follows that ecgonine contains the tropane structure and that the alcoholic group must be in the same position as in tropine (§22). Now in the formation of tropinone from ecgonine, a carboxyl group is lost (as we have seen, ecgonine contains a carboxyl group). Thus the carboxyl group is in a position such that the oxidation of the secondary alcoholic group in ecgonine to a keto group is accompanied by the elimination of the carboxyl group. This type of elimination is characteristic of β-ketonic acids, and this interpretation of the results is confirmed by the

fact that Willstätter *et al.* (1898) actually observed the formation of an unstable β-ketonic acid which lost carbon dioxide to give tropinone. Thus ecgonine is:

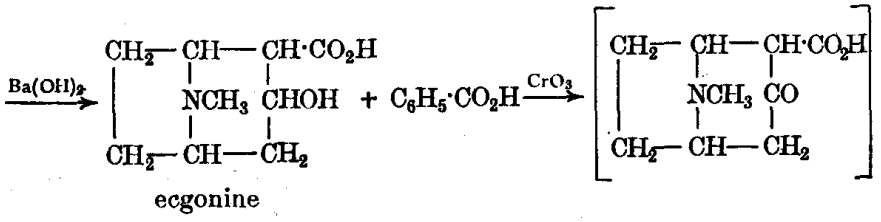


ecgonine

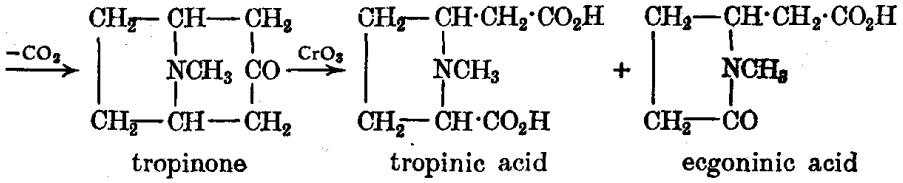
On this basis, the foregoing reactions may therefore be written:



cocaine benzoylecgonine

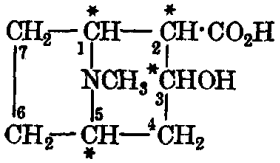


ecgonine



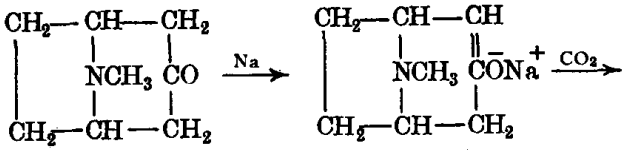
tropinone tropinic acid ecgoninic acid

The structure of ecgonine has been confirmed by synthesis (Willstätter *et al.*, 1901); the starting point is tropinone (see §22 for its synthesis). Before describing this synthesis, let us first examine the structure of ecgonine from the stereochemical point of view; it will be seen that there are four dissimilar

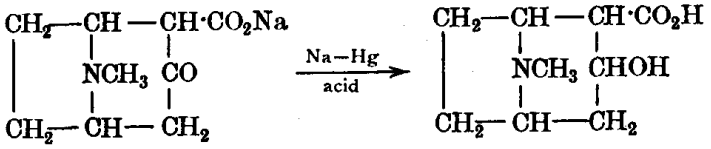


asymmetric carbon atoms present (*), and so there are $2^4 = 16$ optically active forms (eight pairs of enantiomorphs) possible (*cf.* tropine, §22). Since, however, only the *cis* fusion of the nitrogen bridge is possible in practice, C_1 and C_5 therefore have only one configuration (the *cis*-form), and so there are only eight optically active forms (four pairs of enantiomorphs) actually possible (*cf.* camphor, §23a. VIII); three pairs of enantiomorphs have been prepared synthetically.

In the original synthesis of Willstätter, the racemic ecgonine obtained was not identical with the (—)-ecgonine from (—)-cocaine, but its chemical properties were the same.

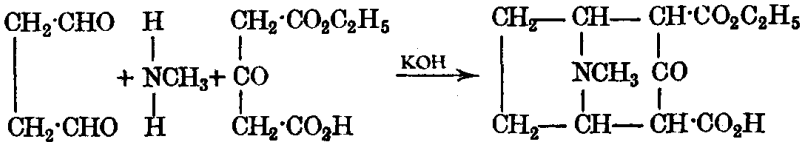


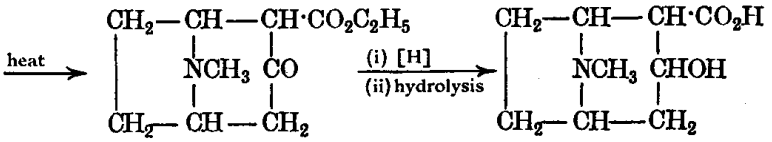
tropinone



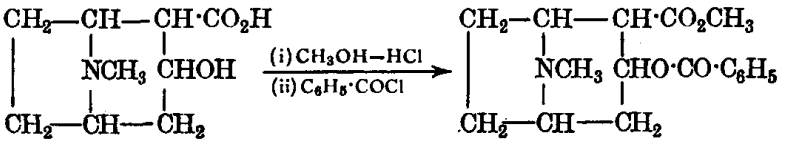
sodium tropinonecarboxylate — a (±)-ecgonine

Later, Willstätter *et al.* (1921) synthesised ecgonine by means of the Robinson method (see §22):





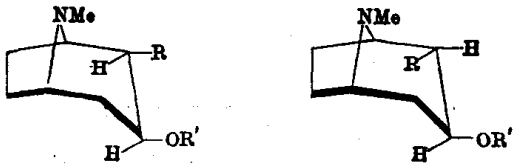
The final product was shown to be a mixture of three racemates, (±)-ecgonine, (±)-ψ-ecgonine and a third pair of enantiomorphs (Willstätter *et al.*, 1923). The racemic ecgonine was resolved, and the (—)-form esterified with methanol and then benzoylated; the product was (—)-cocaine.



(—)-ecgonine — (—)-cocaine

In a similar way, the (+)- and (—)-ψ-cocaines were obtained from the corresponding ψ-ecgonines. An interesting point in this connection is that Einhorn *et al.* (1890) showed that the prolonged action of 33 per cent. aqueous potassium hydroxide converts ecgonine into ψ-ecgonine, and Findlay (1953) has found that cocaine gives ψ-ecgonine methyl ester by the action of sodium methoxide in hot methanol.

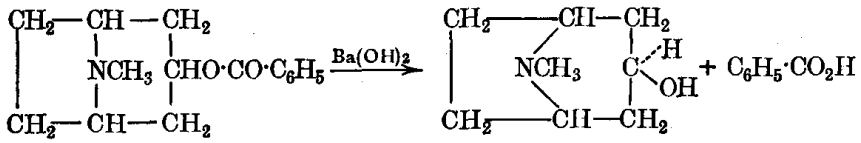
Fodor *et al.* (1953, 1954) and Findlay (1953, 1954) have established the conformations of ecgonine and ψ-ecgonine (R = CO_2H; R′ = H) and the corresponding cocaines (R = CO_2Me; R′ = COPh) (*cf.* §22):



cocaine (and ecgonine) — ψ-cocaine (and ψ-ecgonine)

Hardegger *et al.* (1955) have correlated (−)-cocaine with L-glutamic acid and have shown that the formula represents the absolute configuration of L(−)-cocaine.

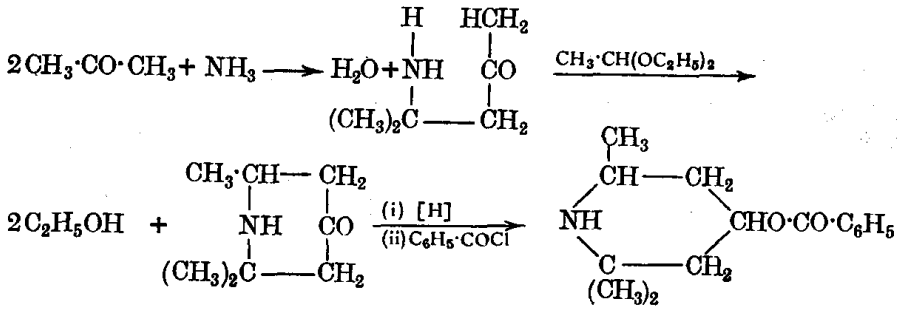
§23a. **Tropacocaine,** $C_{15}H_{19}O_2N$, m.p. 49°, occurs in Java coca leaves. When heated with barium hydroxide solution, tropacocaine is hydrolysed to *ψ*-tropine and benzoic acid; thus the alkaloid is benzoyl-*ψ*-tropine.



tropacocaine ψ-tropine

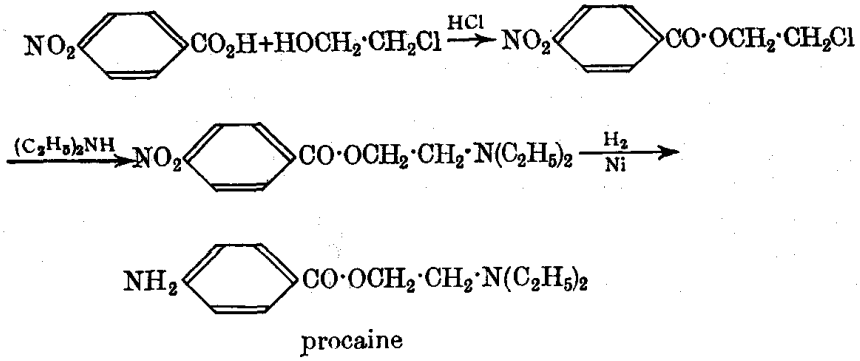
§23b. **Cocaine substitutes.** Cocaine is a very good local anæsthetic, but has certain disadvantages. The anæsthetic properties are lost if either the benzoyl group or the methyl ester group is removed; removal of the *N*-methyl group has no effect. A number of synthetic drugs have now been introduced to replace cocaine as a local anæsthetic; their anæsthetic properties are as good as those of cocaine, and they are less toxic. Two important substitutes are **β-eucaine** and **procaine (novocaine).**

β-Eucaine has been synthesised by treating acetone with ammonia and then treating the product, diacetonamine (see Vol. I), with diethyl acetal. The piperidone thereby produced is then reduced and finally benzoylated to give *β*-eucaine.



β-eucaine

Procaine has been synthesised from *p*-nitrobenzoic acid.

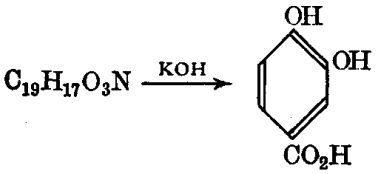


procaine

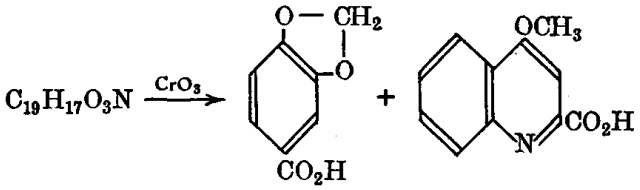
QUINOLINE GROUP

§24. **Angostura alkaloids.** A number of alkaloids have been isolated from angostura bark, *e.g.*, cusparine, galipine, galipoline, etc.

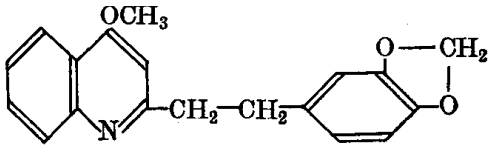
Cusparine, $C_{19}H_{17}O_3N$, m.p. 90–91°, has been shown to contain one methoxyl group (Zeisel method), and when fused with potassium hydroxide, protocatechuic acid is obtained.



On the other hand, controlled oxidation of cusparine gives piperonylic acid and 4-methoxyquinoline-2-carboxylic acid.

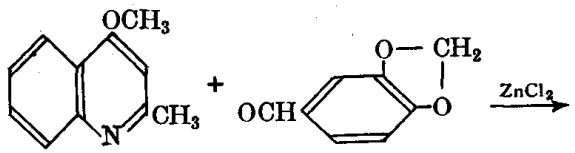


Consideration of this information led to the suggestion of the following structure for cusparine.



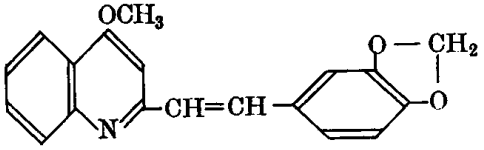
cusparine

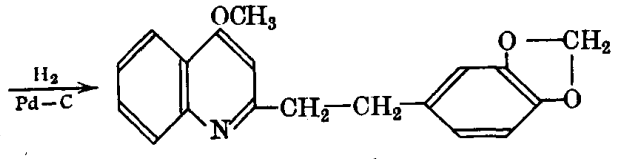
This has been confirmed by synthesis (Späth *et al.*, 1924).



4-methoxy-2-methylquinoline

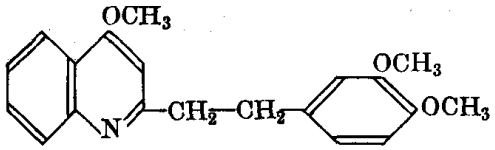
piperonal





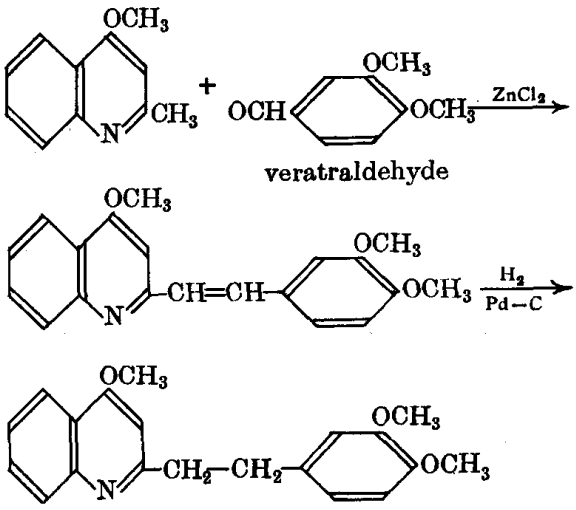
cusparine

Galipine, $C_{20}H_{21}O_3N$, m.p. 113°, contains three methoxyl groups (Zeisel method). When oxidised with chromic acid, galipine produces 4-methoxyquinoline-2-carboxylic acid and veratric acid. Thus the formula of the alkaloid is probably:



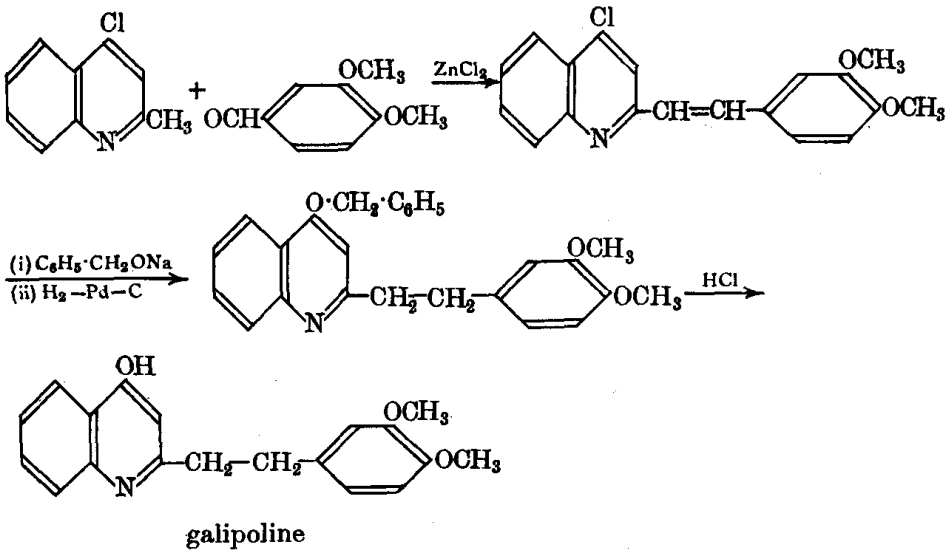
galipine

This has been confirmed by synthesis (Späth *et al.*, 1924).



galipine

Galipoline, $C_{19}H_{19}O_3N$, m.p. 193°, contains two methoxyl groups and one phenolic group. When methylated with diazomethane, galipoline is converted into galipine. Thus one of the methoxyl groups in the latter is a hydroxyl group in the former. The position of this phenolic hydroxyl was shown to be in the quinoline nucleus by synthesis (Späth *et al.*, 1924).



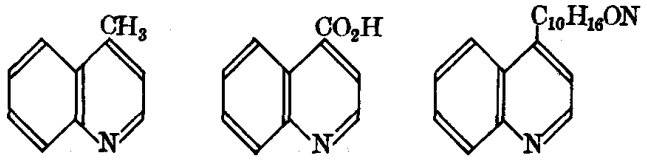
galipoline

§25. Cinchona alkaloids. Cinchonine and quinine, together with many other alkaloids, occur in the bark of various species of *Cinchona*. Cinchonine may be regarded as the parent substance of the cinchona alkaloids,

but quinine is the most important member of this group, its main use being in the treatment of malaria.

§25a. (+)-Cinchonine, $C_{19}H_{22}ON_2$, m.p. 264°, adds on two molecules of methyl iodide to form a di-quaternary compound; thus the alkaloid is a di-tertiary base. Since cinchonine forms a mono-acetate and a mono-benzoate, the molecule contains one hydroxyl group. Furthermore, this hydroxyl group is secondary alcoholic, since on oxidation, cinchonine forms the ketone *cinchoninone*. Cinchonine has been shown to contain one ethylenic double bond by the fact that it adds on one molecule of bromine or halogen acid, and that it is readily catalytically reduced, one molecule of hydrogen being added on.

Fusion of cinchonine with potassium hydroxide gives lepidine (4-methyl-quinoline), I, and on vigorous oxidation with chromic acid in sulphuric acid solution, cinchoninic acid, II, is obtained (Königs, 1894). Thus cinchonine



I II III

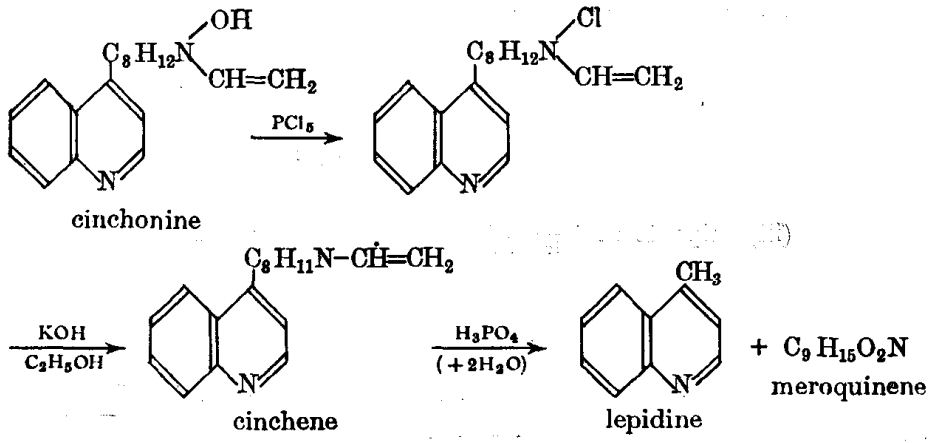
contains a quinoline nucleus with a side-chain in position 4 (III); this side-chain was referred to by Skraup as the " second-half " of the molecule. The hydroxyl group in cinchonine must be in this " second-half ", since if it were not, then a hydroxy derivative or a carboxy derivative (since the hydroxyl is alcoholic) of cinchoninic acid would have been obtained.

Oxidation of cinchonine with permanganate gives cinchotenine and formic acid (Königs, 1879).

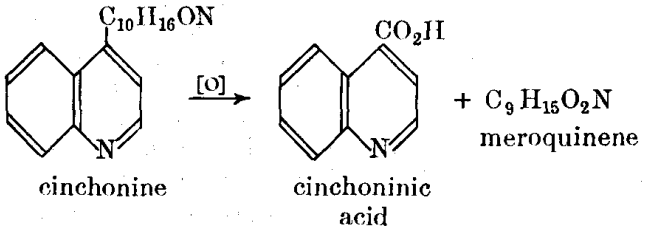
$$C_{19}H_{22}ON_2 + 4[O] \xrightarrow{KMnO_4} \underset{\text{cinchotenine}}{C_{18}H_{20}O_3N_2} + H{\cdot}CO_2H$$

This suggests that there is a $-CH{=}CH_2$ group in the side-chain in the " second-half ".

When treated with phosphorus pentachloride, followed by ethanolic potassium hydroxide, cinchonine is converted into cinchene which, when heated with 25 per cent. phosphoric acid, forms lepidine and a compound Königs named meroquinene (Königs *et al.*, 1884). With the information obtained so far, we may formulate the work of Königs as follows:



Meroquinene (meroquinenine) is also obtained, together with cinchoninic acid, when cinchonine is oxidised with chromic acid (Königs, 1894).

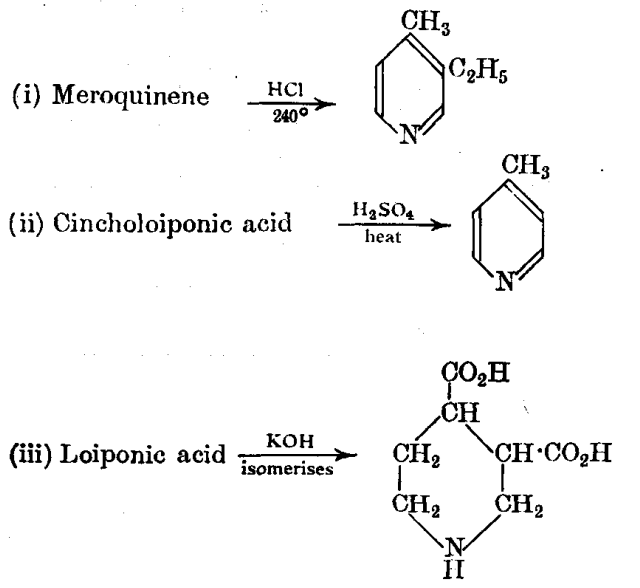


Thus the key to the structure of the " second-half " is the structure of meroquinene. The routine tests showed that meroquinene contains one carboxyl group and one double bond; the presence of the latter indicates that the $-CH=CH_2$ side-chain is still present in meroquinene. Oxidation of meroquinene with cold acid permanganate produces formic acid and cincholoiponic acid, the latter being a dicarboxylic acid (Königs, 1879). The formation of formic acid confirms the presence of the $-CH=CH_2$ side-

$$\underset{\text{meroquinene}}{C_9H_{15}O_2N} \xrightarrow[H_2SO_4]{KMnO_4} \underset{\text{cincholoiponic acid}}{C_8H_{13}O_4N} + H{\cdot}CO_2H$$

chain in meroquinene. The presence of this group has also been demonstrated by the ozonolysis of meroquinene; formaldehyde is produced (Seekles, 1923). Oxidation of cincholoiponic acid with acid permanganate produces loiponic acid, $C_7H_{11}O_4N$ (Königs, 1890). This is also a dicarboxylic acid, and since it contains one methylene group less than its precursor cincholoiponic acid, this suggests that the latter contains at least a side-chain $-CH_2{\cdot}CO_2H$.

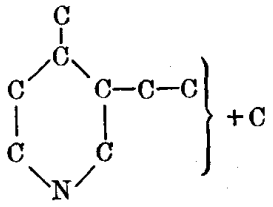
The reactions of the above three acids indicated that they were all secondary bases; that they all contained a piperidine ring is shown by the following reactions.



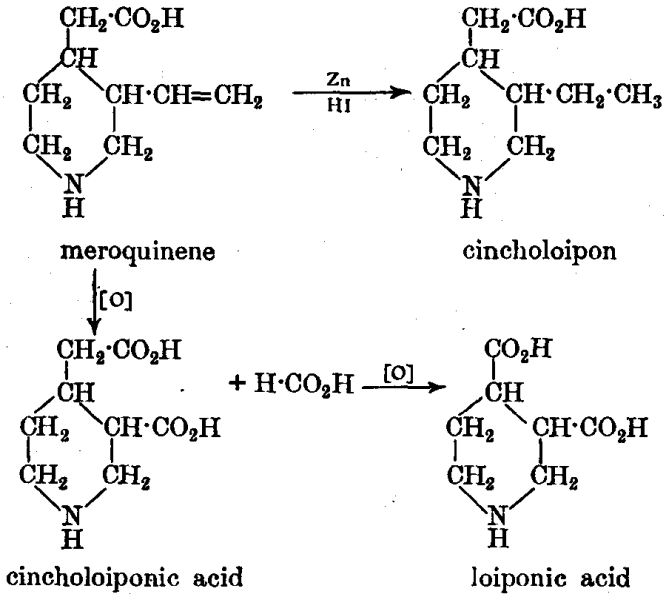
hexahydrocinchomeronic acid

The structure of hexahydrocinchomeronic acid is known from its synthesis (*cf.* §21).

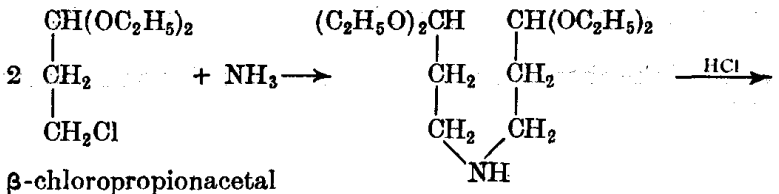
Consideration of the above results shows that a possible skeleton structure of meroquinene is:



The problem then is to find the position of the remaining carbon atom. This carbon atom cannot be an *N*-methyl group, since all three acids are secondary bases. As we have seen, meroquinene contains a $—CH{=}CH_2$ group in the side-chain. A possible position for the extra carbon atom is the side-chain containing this unsaturated group; *i.e.*, the side-chain is an allyl group, $—CH_2{\cdot}CH{=}CH_2$. All the foregoing facts can be explained on this basis, but the following fact cannot, *viz.*, that reduction of meroquinene gives cincholoipon, $C_9H_{17}O_2N$, a compound which contains one carboxyl group and *one ethyl group*. Thus the unsaturated side-chain cannot be allyl (this should have given a propyl group on reduction); the side-chain is therefore vinyl. This leaves only one possible position for the extra carbon atom, *viz.*, 4; this would give a $—CH_2{\cdot}CO_2H$ group at this position, and the presence of such a group has already been inferred (see above). All the reactions of meroquinene can therefore be explained on the following structures:

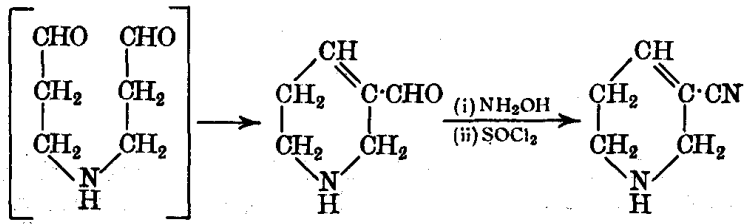


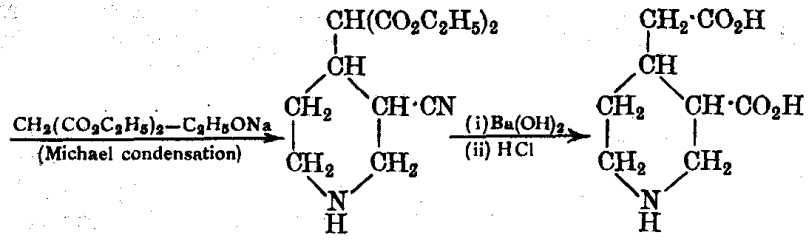
This formula for meroquinene is supported by the synthesis of cincholoiponic acid (Wohl *et al.*, **1907**; *cf.* §17) (see next page).



β-chloropropionacetal

iminodipropionacetal

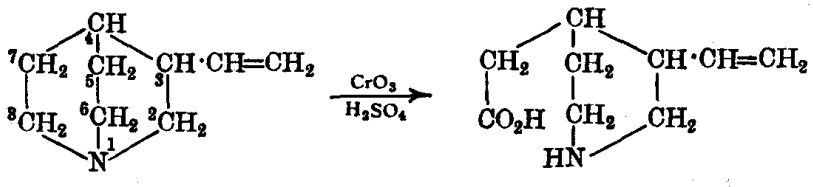




(±)-cincholoiponic acid

The racemic cincholoiponic acid was acetylated, and then this derivative was resolved by means of brucine; the (+)-form was identical with the acid obtained from meroquinene.

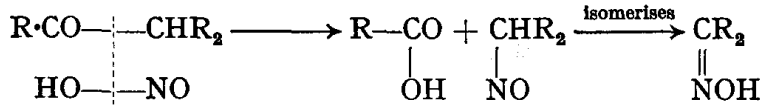
Since meroquinene is obtained from cinchonine by oxidation, the carbon atom of the carboxyl group in meroquinene will be the point of linkage to the " quinoline-half " at which scission of the " second-half " occurs. Since cinchonine is a di-tertiary base, the " second-half " therefore contains a tertiary nitrogen atom. But meroquinene is a *secondary* base, and it therefore follows that in its formation the tertiary nitrogen atom is converted into a secondary nitrogen atom, *a carboxyl group also being produced at the same time.* A possible explanation for this behaviour is that the tertiary nitrogen atom is a part of a bridged ring, one C—N bond being broken when cinchonine is oxidised:



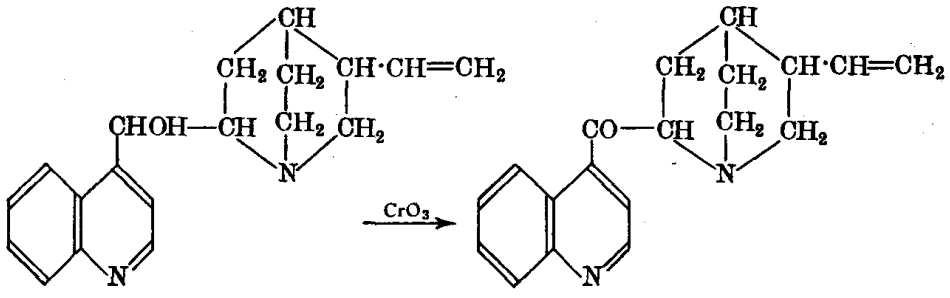
3-vinylquinuclidine meroquinene

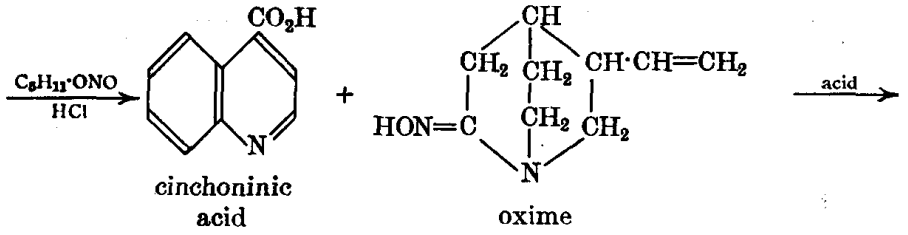
Thus, in cinchonine, the " quinoline-half " must be joined *via* its side-chain at position 4 to the " quinuclidine-half " at position 8. The remaining problem is to ascertain the position of the secondary alcoholic group in the " second-half ". Rabe *et al.* (1906, 1908) converted cinchonine into the ketone cinchoninone by gentle oxidation (chromium trioxide). This ketone, in which both nitrogen atoms are still tertiary, on treatment with amyl

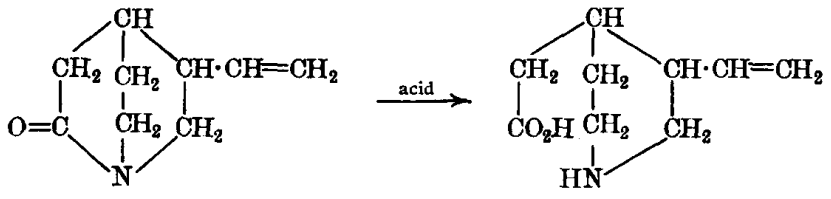
nitrite and hydrogen chloride, gives cinchoninic acid and an oxime. The formation of an acid and an oxime indicates the presence of the group —CO·CH—, *i.e.*, a methyne group adjacent to a carbonyl group:



The structure of the oxime obtained from cinchoninone was shown to be 8-oximino-3-vinylquinuclidine by its hydrolysis to hydroxylamine and meroquinene. If we assume that the secondary alcoholic group connects the " quinoline-half " to the quinuclidine nucleus, then the foregoing reactions may be written as follows, on the assumption that the structure of cinchonine is as given.

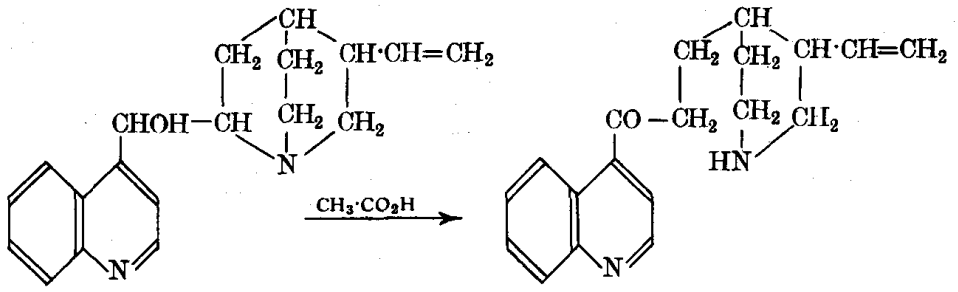






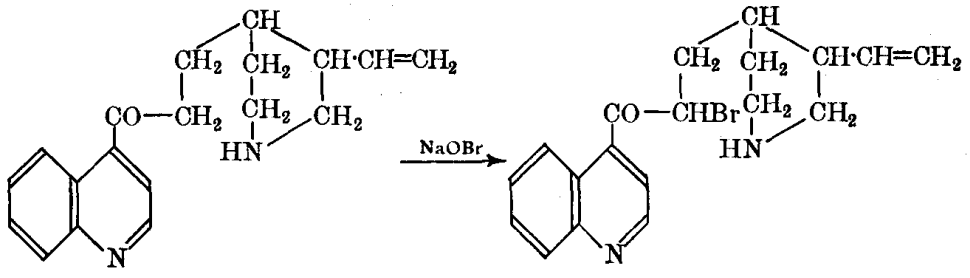
The above structure of cinchonine contains four dissimilar asymmetric carbon atoms, *viz.*, 3, 4, 8, and the carbon atom of the CHOH group (see 3-vinylquinuclidine for numbering). One pair of enantiomorphs is (±)-cinchonine, and another pair is (±)-*cinchonidine*; the configurations of C_3 and C_4 are the same in both, since both give the *same* 8-oximino-3-vinylquinuclidine (see §25b).

A partial synthesis of cinchonine has been carried out by Rabe (1911, 1913). This starts from cinchotoxine, which is prepared by the prolonged action of acetic acid on cinchonine; the latter isomerises (Rabe *et al.*, 1909).

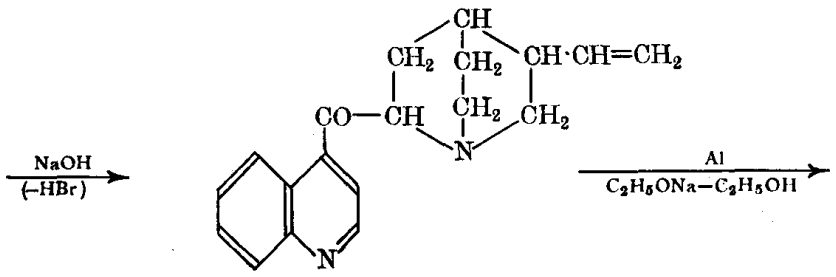


cinchonine cinchotoxine

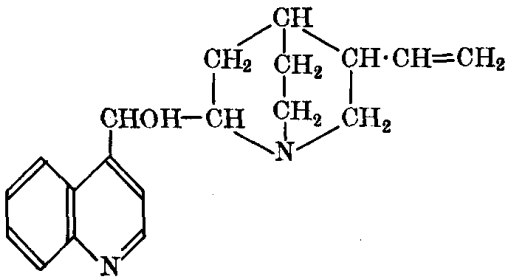
This isomerisation is an example of the *hydramine fission* (see §7). The conversion of cinchotoxine into cinchonine was carried out as follows:



cinchotoxine



cinchoninone



(±)-cinchonine

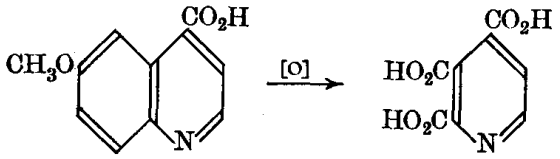
§25b. (—)-Quinine, $C_{20}H_{24}O_2N_2$, m.p. 177°, is used as a febrifuge and as an antimalarial. Since quinine adds on two molecules of methyl iodide to form a di-quaternary salt, it is therefore a di-tertiary base. When heated with hydrochloric acid, quinine eliminates one carbon atom as methyl chloride; therefore there is one methoxyl group present in the molecule. Since quinine forms a mono-acetate and a mono-benzoate, one hydroxyl group must be present, and that this is secondary alcoholic is shown by the fact that oxidation of quinine with chromium trioxide produces quininone, a ketone.

$$\underset{\text{quinine}}{C_{20}H_{24}O_2N_2} \xrightarrow{CrO_3} \underset{\text{quininone}}{C_{20}H_{22}O_2N_2}$$

Quinine also contains one ethylenic double bond, as is shown by the fact that it adds on one molecule of bromine, etc. (*cf.* cinchonine). Oxidation of quinine with chromic acid produces, among other products, quininic acid.

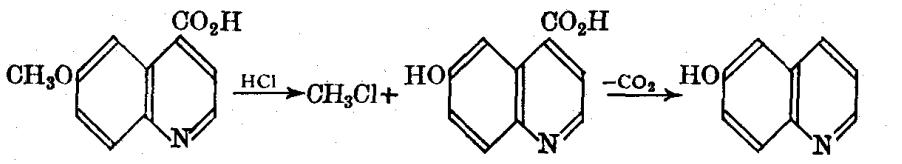
$$\underset{\text{quinine}}{C_{20}H_{24}O_2N_2} \xrightarrow[H_2SO_4]{CrO_3} \underset{\text{quininic acid}}{C_{11}H_9O_3N}$$

On the other hand, controlled oxidation of quinine with chromic acid gives quininic acid and meroquinene. Thus the " second-half " in both quinine and cinchonine is the same, and so the problem is to elucidate the structure of quininic acid. When heated with soda-lime, quininic acid is decarboxylated to a methoxyquinoline, and since, on oxidation with chromic acid, quininic acid forms pyridine-2 : 3 : 4-tricarboxylic acid, the methoxyl group must be a substituent in the benzene ring (of quinoline), and the carboxyl group at position 4 (Skraup, 1881). The position of the methoxyl group was ascertained by heating quininic acid with hydrochloric acid and then



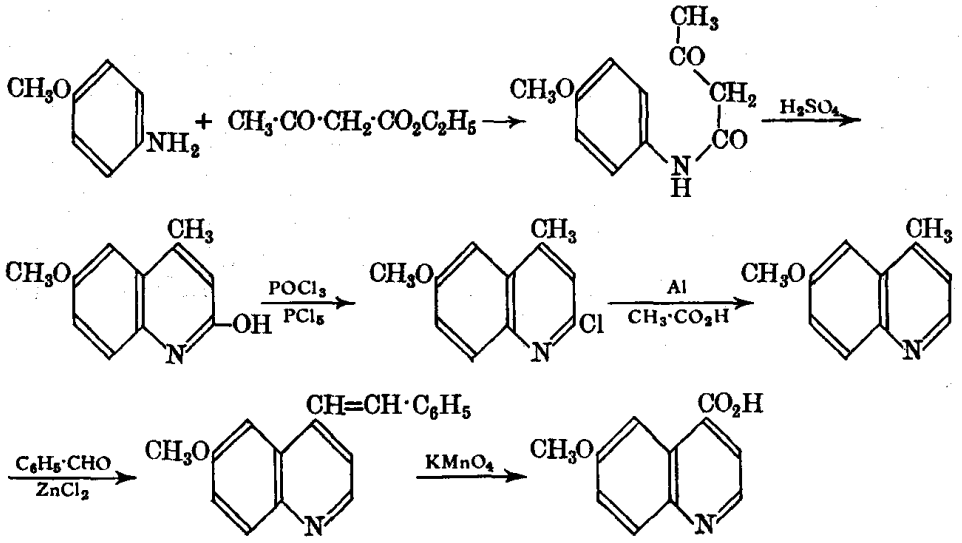
quininic acid pyridine-2:3:4-tricarboxylic acid

decarboxylating the demethylated product; 6-hydroxyquinoline (a known compound) was obtained. Thus quininic acid is 6-methoxycinchoninic acid.



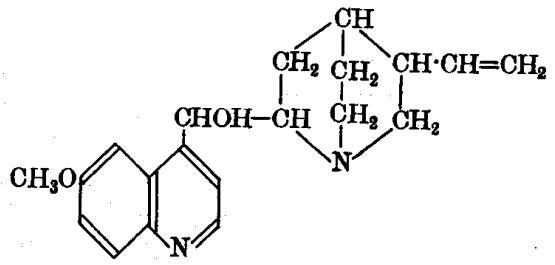
quininic acid 6-hydroxyquinoline

This structure for quininic acid has been confirmed by synthesis (Rabe *et al.*, 1931).



The direct oxidation of 6-methoxy-4-methylquinoline to quininic acid is extremely difficult; oxidation of the methyl group is accompanied by the oxidation of the benzene ring, the final product being pyridine-2 : 3 : 4-tricarboxylic acid (see §26).

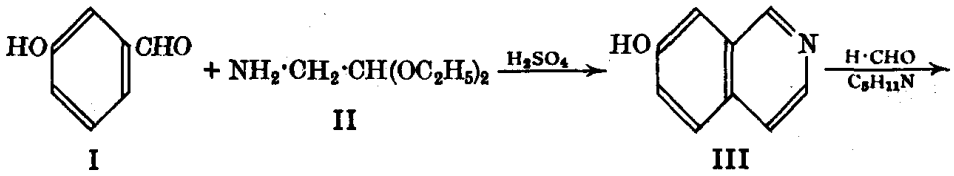
Thus, on the basis of the foregoing evidence, the structure of quinine is:



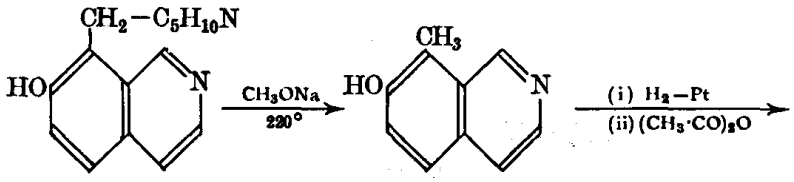
quinine

This formula contains the same four asymmetric carbon atoms as cinchonine; thus the same number of pairs of enantiomorphs is possible. One pair is (±)-quinine, and another pair is (±)-*quinidine*; the configurations of C_3 and C_4 are the same in quinine, quinidine, cinchonine and cinchonidine, since all four give the *same* 8-oximino-3-vinylquinuclidine (see §25a).

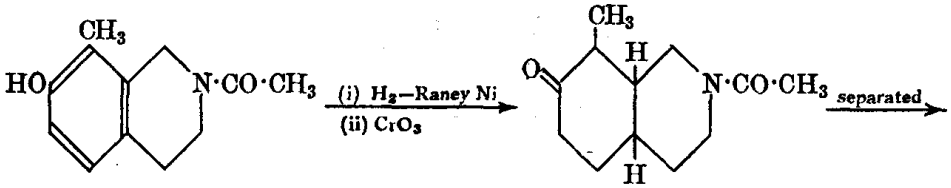
Rabe *et al.* (1918) carried out a partial synthesis of quinine starting from quinotoxine, which is prepared by heating quinine in acetic acid (*cf.* cinchotoxine). Woodward and Doering (1944) have synthesised (+)-quinotoxine, and so we now have a *total* synthesis of quinine. The following is Woodward and Doering's work up to (+)-quinotoxine, and from this to quinine is Rabe's work. *m*-Hydroxybenzaldehyde (I) is condensed with aminoacetal (II) and the product, 7-hydroxy*iso*quinoline (III), is treated with formaldehyde in methanol solution containing piperidine. The complex formed (IV) is converted into 7-hydroxy-8-methyl*iso*quinoline (V) by heating with methanolic sodium methoxide at 220°. V, on catalytic reduction (platinum) followed by acetylation, gives *N*-acetyl-7-hydroxy-8-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (VI), which, on further catalytic reduction by heating with a Raney nickel catalyst under pressure and then followed by oxidation with chromium trioxide, is converted into *N*-acetyl-7-keto-8-methyldecahydro*iso*quinoline (VII). VII is a mixture of *cis*- and *trans*-isomers; these were separated and the *cis*-isomer (VII*a*; see §11 vii. IV for conventions) then treated with ethyl nitrite in the presence of sodium ethoxide to give the homomeroquinene derivative VIII. This, on reduction, gives IX, which may now be written more conveniently as shown. Exhaustive methylation of IX, followed by hydrolysis, gives *cis*-(±)-homomeroquinene (X). X, after esterification and benzoylation, gives XI which, on condensation with ethyl quininate (XII), produces XIII. This, on heating with 16 per cent. hydrochloric acid, is hydrolysed and decarboxylated to (±)-quinotoxine (XIV). This was resolved *via* its dibenzoyltartrate (tartaric acid proved unsuccessful for resolution). The conversion of (±)-quinotoxine into quinine had already been accomplished by Rabe *et al.* (the equations for this conversion are also given below).



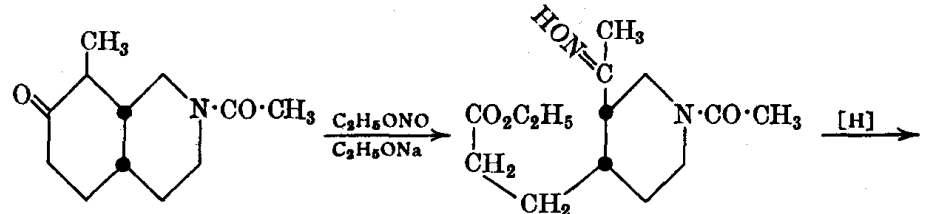
I III



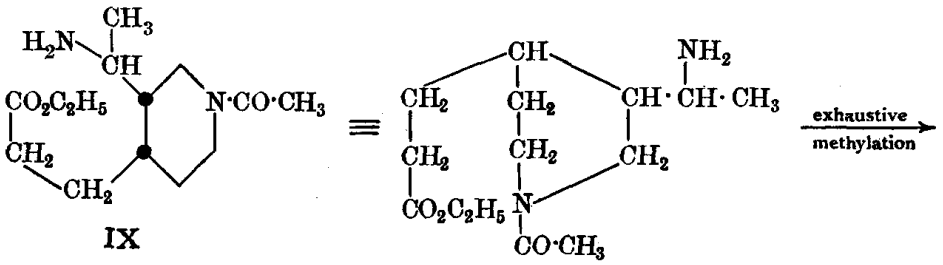
IV V



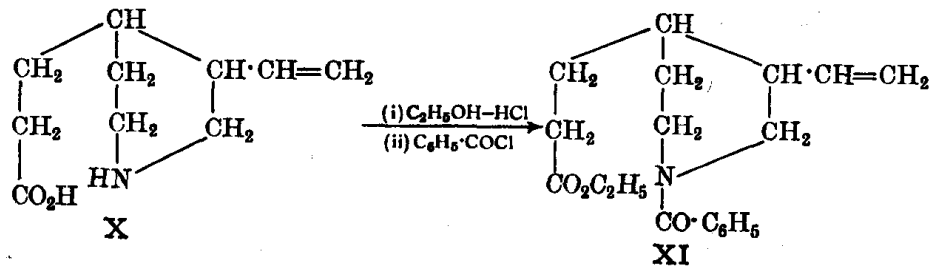
VI VII



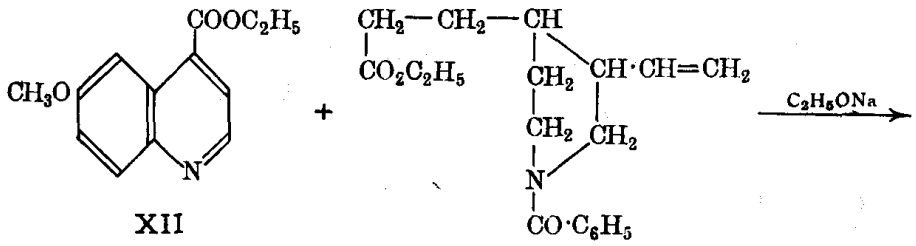
VII*a* VIII



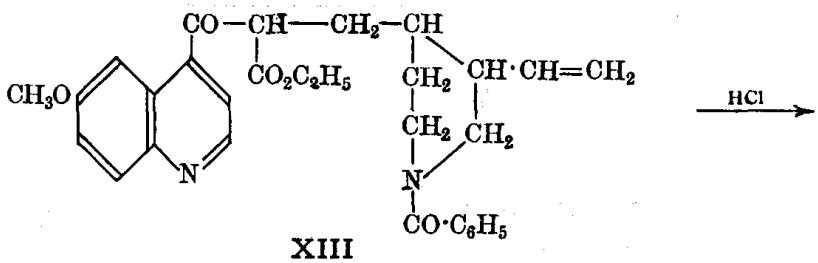
IX IX



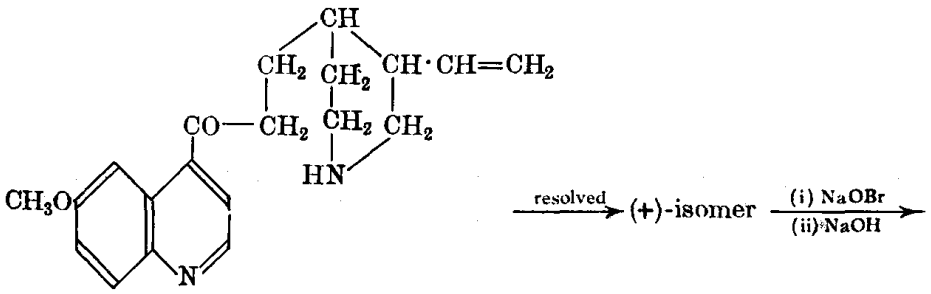
X XI



XII + XI

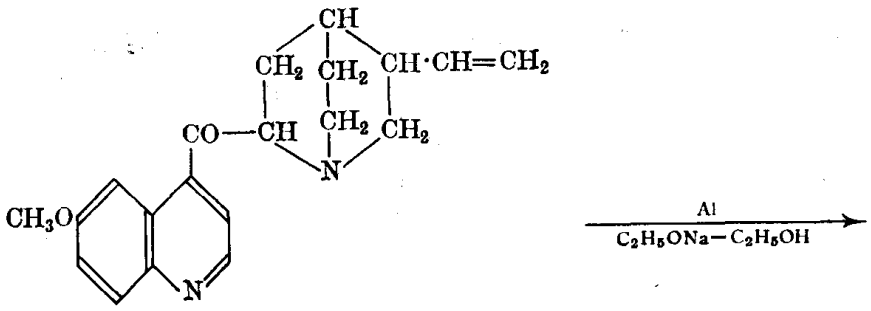


XIII

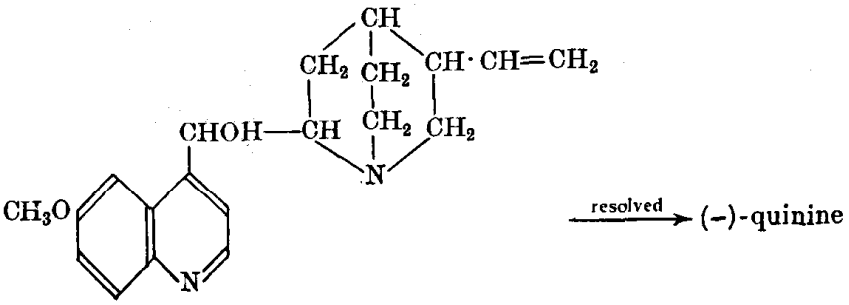


XIV

(±)-quinotoxine



(+)-quininone



(±)-quinine

ISOQUINOLINE GROUP

Opium alkaloids. Many alkaloids have been isolated from opium, and they are divided into two groups according to the nature of their structure:

(i) iso*Quinoline group, e.g.*, papaverine, laudanosine, etc.
(ii) *Phenanthrene group, e.g.*, morphine (see §27).

§26. Papaverine, $C_{20}H_{21}O_4N$, m.p. 147°, is one of the optically inactive alkaloids; it does not contain any asymmetric carbon atom. The structure of papaverine was established by Goldschmiedt and his co-workers (1883–1888). Since papaverine adds on one molecule of methyl iodide to form a quaternary iodide, the nitrogen atom in the molecule is in the tertiary state. The application of the Zeisel method shows the presence of four methoxyl groups; the demethylated product is known as papaveroline.

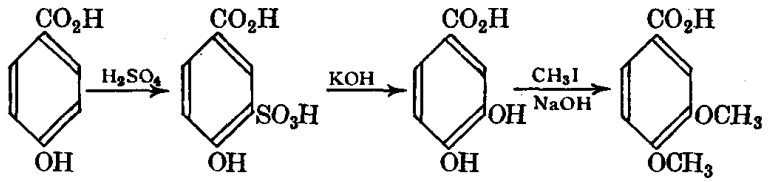
$$\underset{\text{papaverine}}{C_{20}H_{21}O_4N} + 4HI \longrightarrow 4CH_3I + \underset{\text{papaveroline}}{C_{16}H_{13}O_4N}$$

When oxidised with cold dilute permanganate, papaverine is converted into the secondary alcohol papaverinol, $C_{20}H_{21}O_5N$. This, on more vigorous oxidation with hot dilute permanganate, is oxidised to the ketone papaveraldine, $C_{20}H_{19}O_5N$ (it is the formation of this *ketone* that shows that papaverinol is a *secondary* alcohol). Finally, the prolonged action of hot permanganate oxidises papaveraldine to papaverinic acid, $C_{16}H_{13}O_7N$. This acid is a dibasic acid and still contains the keto group present in its precursor—it forms an oxime, etc.; papaverinic acid also contains two methoxyl groups. The foregoing reactions lead to the conclusion that papaverine contains a methylene group.

$$\underset{\text{papaverine}}{(C_{19}H_{19}O_4N)CH_2} \xrightarrow{[O]} \underset{\text{papaverinol}}{(C_{19}H_{19}O_4N)CHOH} \xrightarrow{[O]} \underset{\text{papaveraldine}}{(C_{19}H_{19}O_4N)CO}$$

When oxidised with hot concentrated permanganate, papaverine (or the oxidised products mentioned above) is broken down into smaller fragments, *viz.*, veratric acid, metahemipinic acid, pyridine-2 : 3 : 4-tricarboxylic acid and 6 : 7-dimethoxy*iso*quinoline-1-carboxylic acid. Let us now consider the evidence for the structures of these compounds.

Veratric acid. When decarboxylated, veratric acid forms veratrole. Since this is *o*-dimethoxybenzene, veratric acid is therefore a dimethoxybenzoic acid. The position of the carboxyl group with respect to the two methoxyl groups (in the *ortho*-position) is established by the following synthesis.

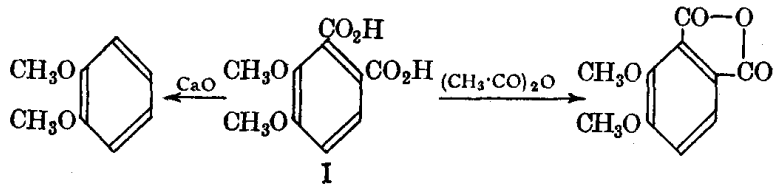


veratric acid

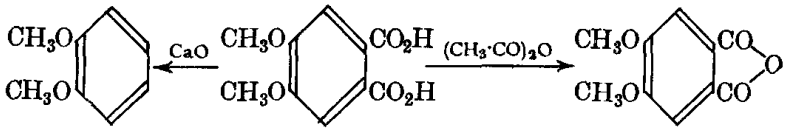
Thus veratric acid is 3 : 4-dimethoxybenzoic acid.

Metahemipinic acid. This is a dicarboxylic acid, and when decarboxylated by heating with calcium oxide, veratrole is formed; thus metahemipinic acid contains two methoxyl groups in the *ortho*-position. Furthermore, since the acid forms an anhydride when heated with acetic anhydride, the two carboxyl groups must be in the *ortho*-position. Thus metahemipinic acid is either I or II. Now metahemipinic acid forms only *one* monoester; II permits the formation of only one monoester, but I can give rise to two

different monoesters. Thus II is metahemipinic acid; I is actually hemipinic acid (this isomer was known before metahemipinic acid).

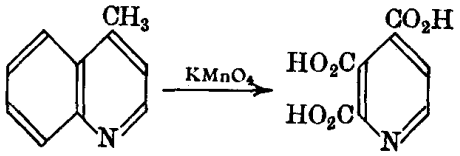


I
hemipinic acid



II
metahemipinic acid

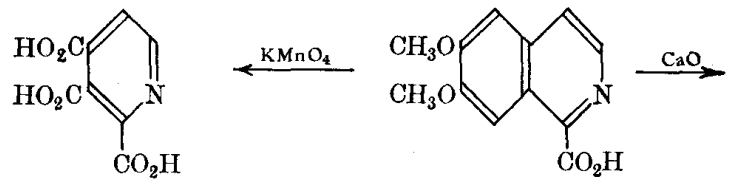
Pyridine-2 : 3 : 4-tricarboxylic acid. The routine tests showed that this contains three carboxyl groups, and since decarboxylation gives pyridine, the acid must be a pyridinetricarboxylic acid. The positions of the three carboxyl groups are established by the fact that this pyridinetricarboxylic acid is produced when lepidine (4-methylquinoline) is oxidised.



lepidine

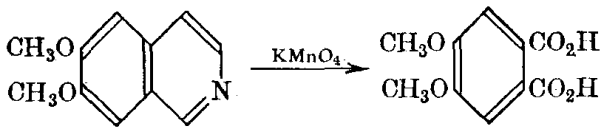
pyridine-2:3:4-tricarboxylic acid

6 : 7-Dimethoxy*iso*quinoline-1-carboxylic acid. The usual tests showed that this compound contains one carboxyl group and two methoxyl groups. On oxidation, this acid forms pyridine-2 : 3 : 4-tricarboxylic acid; when decarboxylated, the acid forms a dimethoxy*iso*quinoline which, on oxidation, gives metahemipinic acid; thus the structure is established.



pyridine-2:3:4-tricarboxylic acid

6:7-dimethoxy-*iso*quinoline-1-carboxylic acid

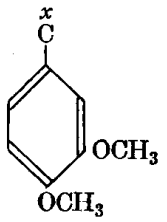


metahemipinic acid

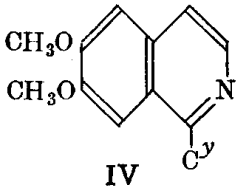
We may now deduce the structure of papaverine as follows:

(i) The isolation of veratric acid indicates the presence of group III in papaverine.

(ii) The isolation of 6 : 7-dimethoxy*iso*quinoline-1-carboxylic acid indicates the presence of group IV in the molecule.



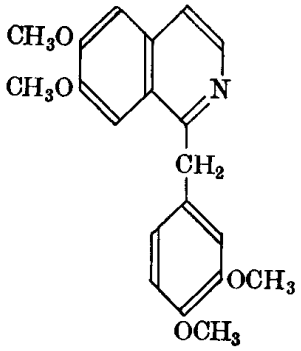
III



IV

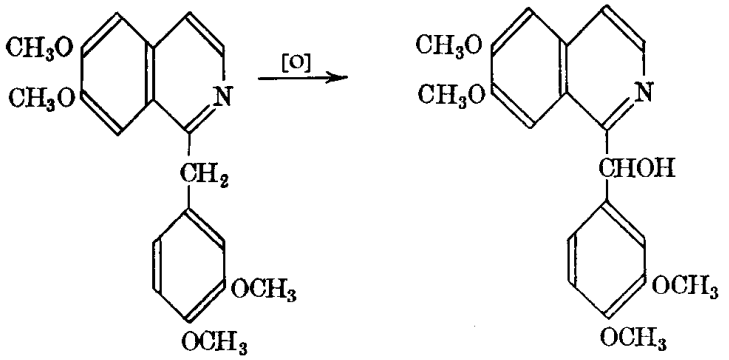
The presence of these two groups also accounts for the isolation of the other two fragments.

(iii) The total carbon content of III (9 carbon atoms) and IV (12 carbon atoms) is 21 carbon atoms. But papaverine contains only 20. There is, however, a —CH_2— group present, and if we assume that C^x and C^y are one and the same carbon atom, *viz.*, the carbon atom of the CH_2 group, then the following structure of papaverine accounts for all the facts:

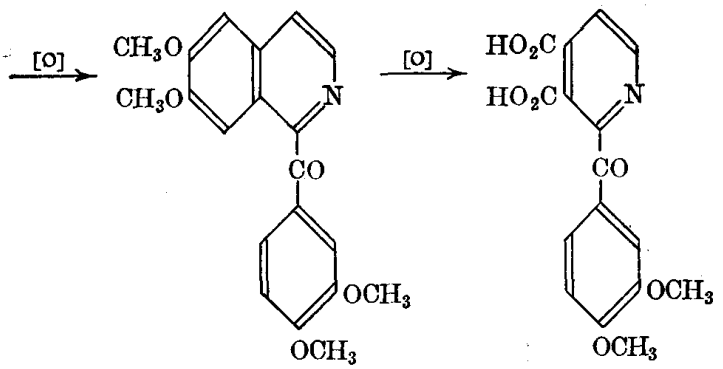


papaverine

Thus, with this formula, we can formulate the oxidation of papaverine as follows:



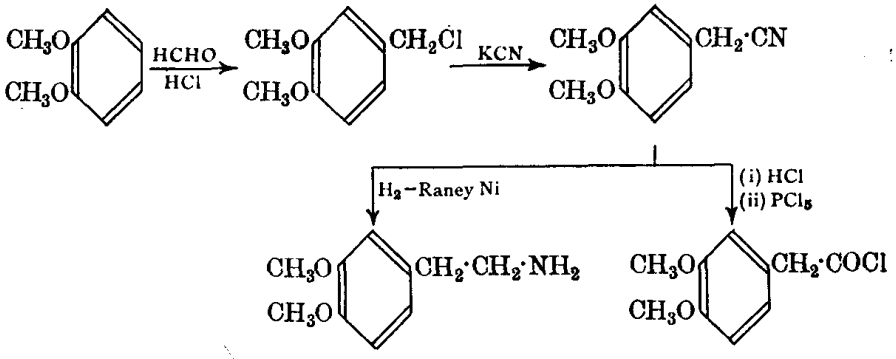
papaverine papaverinol



papaveraldine papaverinic acid

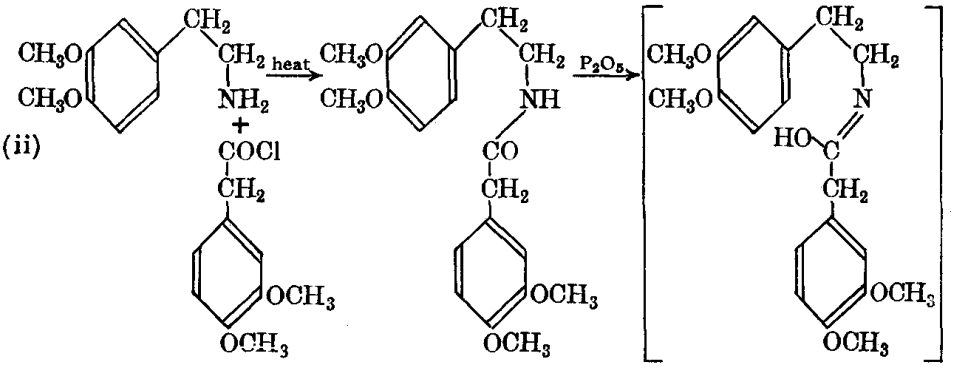
This structure for papaverine has been confirmed by synthesis. The first synthesis was by Pictet and Gams (1909), but Bide and Wilkinson (1945) carried out a simpler one, and it is this that is described here.

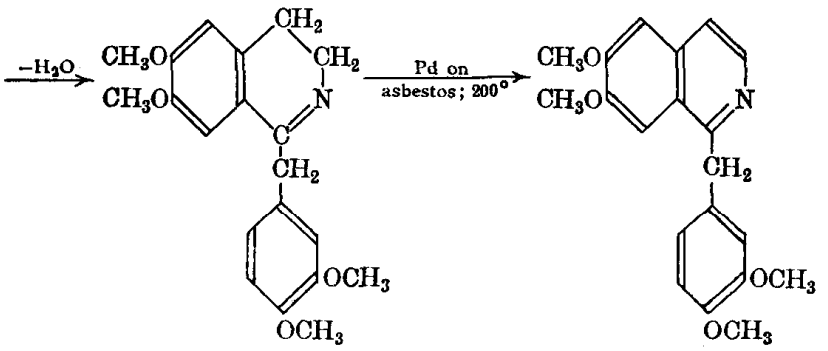
(i)



homoveratrylamine homoveratroyl chloride

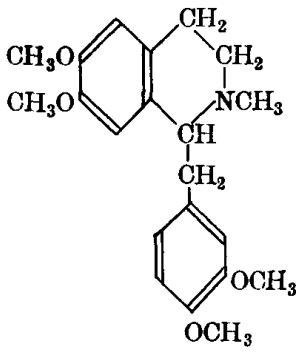
(ii)



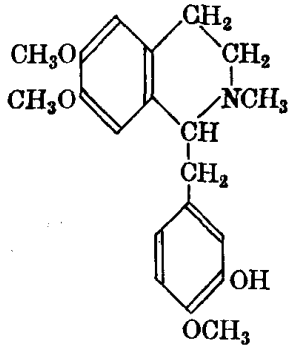


papaverine

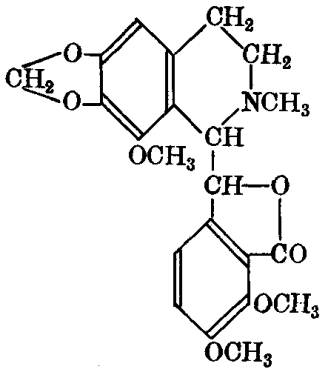
§26a. Some other alkaloids of the *iso*quinoline group are:



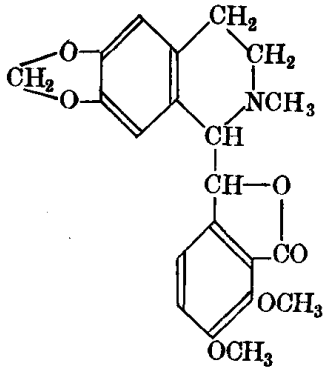
laudanosine



laudanine



narcotine



hydrastine

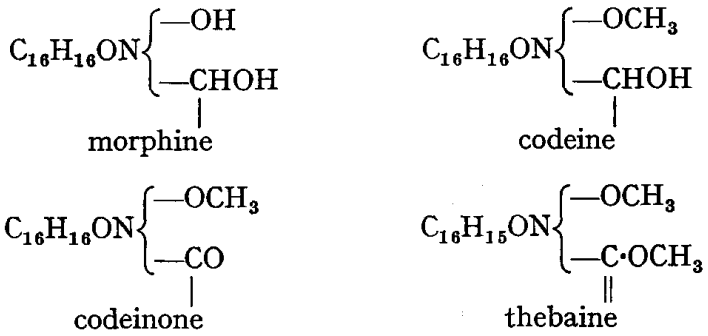
PHENANTHRENE GROUP

§27. Morphine, codeine and thebaine. These are three important opium alkaloids which contain the phenanthrene nucleus.

(−)-*Morphine*, $C_{17}H_{19}O_3N$, m.p. 254°, is the chief alkaloid in opium, and was the first alkaloid to be isolated (Sertürner, 1806). The usual tests show that the nitrogen atom is in the tertiary state, and since morphine forms a diacetate and a dibenzoate, two hydroxyl groups are therefore present in the molecule. Morphine gives the ferric chloride test for phenols, and dissolves in aqueous sodium hydroxide to form a *monosodium* salt, and this is reconverted into morphine by the action of carbon dioxide; thus *one* of the hydroxyl groups is phenolic (Matthiessen *et al.*, 1869). The second hydroxyl group is secondary alcoholic, as is shown by the following reactions. Halogen acids convert morphine into a monohalogeno derivative, one hydroxyl group being replaced by a halogen atom. When heated with methyl iodide in the presence of aqueous potassium hydroxide, morphine is methylated to give (−)-*codeine*, $C_{18}H_{21}O_3N$, m.p. 155° (Grimaux, 1881). Since codeine is no longer soluble in alkalis, it therefore follows that it is only the *phenolic* hydroxyl group in morphine that has been methylated. Furthermore, codeine can be oxidised by chromic acid to *codeinone*, a ketone (Hesse, 1884). Thus the hydroxyl group in codeine (and this one in morphine) is secondary alcoholic, and so codeine is the monomethyl (phenolic) ether of morphine.

(−)-*Thebaine*, $C_{19}H_{21}O_3N$, m.p. 193°, produces two molecules of methyl iodide when heated with hydriodic acid (Zeisel method); hence thebaine is a dimethoxy derivative. When heated with sulphuric acid, thebaine

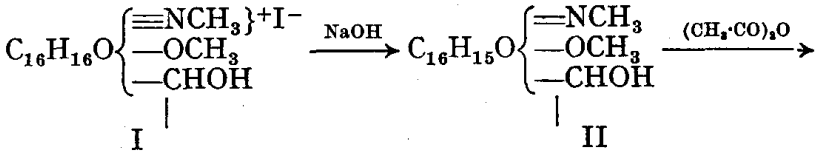
eliminates one methyl group as methyl hydrogen sulphate, and forms codeinone (Knorr, 1906). The formation of a *ketone* led Knorr to suggest that thebaine is the methyl ether of the *enolic* form of codeinone. The foregoing work can thus be summarised by assigning the following formulæ to the compounds described:



So far, we have accounted for the functional nature of two of the oxygen atoms; the unreactivity of the third oxygen atom suggests that it is probably of the ether type (Vongerichten, 1881).

All three alkaloids are tertiary bases (each combines with one molecule of methyl iodide to form a methiodide). When heated with hydrochloric acid at 140° under pressure morphine loses one molecule of water to form *apomorphine*, $C_{17}H_{17}O_2N$. Codeine, under the same conditions, also gives apomorphine (and some other products). Thebaine, however, when heated with dilute hydrochloric acid, forms *thebenine*, $C_{18}H_{19}O_3N$ (a secondary base), and with concentrated hydrochloric acid, morphothebaine, $C_{18}H_{19}O_3N$ (a tertiary base). Thus in the formation of thebenine from thebaine, a tertiary nitrogen atom is converted into a secondary one. For this change to occur, the tertiary nitrogen must be of the type $>N\cdot R$, where the nitrogen is in a ring system; had the nitrogen been in the group $—NR_2$, then the formation of a *primary* base could be expected.

When morphine is distilled with zinc dust, phenanthrene and a number of bases are produced (Vongerichten *et al.*, 1869). This suggests that a phenanthrene nucleus is probably present, and this has been confirmed as follows. When codeine methiodide, I, is boiled with sodium hydroxide solution, α-methylmorphimethine, II, is obtained and this, on heating with acetic anhydride, forms methylmorphol, III, and ethanoldimethylamine, IV (some of II isomerises to β-methylmorphimethine).



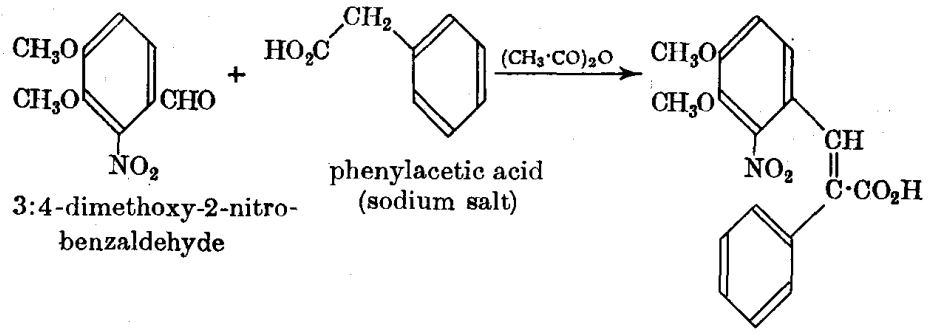
I II

$$C_{15}H_{12}O_2 + (CH_3)_2N\cdot CH_2\cdot CH_2OH$$

III IV

The structure of methylmorphol (III) was ascertained by heating it with hydrochloric acid at 180° under pressure; methyl chloride and a dihydroxyphenanthrene, *morphol*, were obtained. Oxidation of diacetylmorphol gives a diacetylphenanthraquinone; thus positions 9 and 10 are free. On further oxidation (permanganate), the quinone is converted into phthalic acid; therefore the two hydroxyl groups are in the same ring. Since the fusion of morphine with alkali gives protocatechuic acid, this shows that both

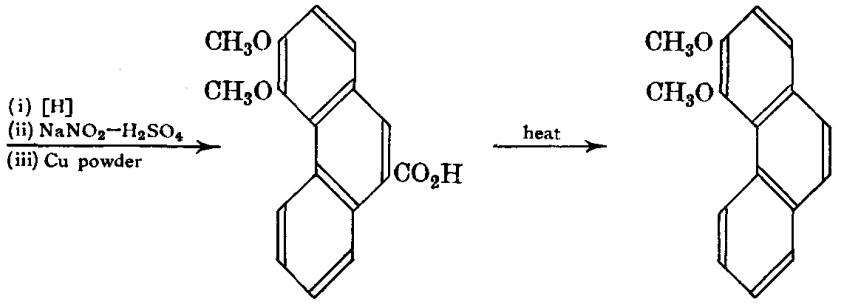
hydroxyl groups in morphol are in the *ortho*-position. Finally, Pschorr *et al.* (1900) showed by synthesis that dimethylmorphol is 3 : 4-dimethoxyphenanthrene (*cf.* Pschorr synthesis, §2 vi*a*. X).



3:4-dimethoxy-2-nitrobenzaldehyde

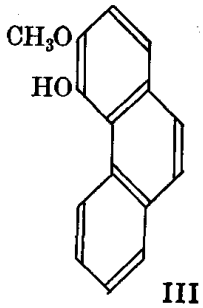
phenylacetic acid (sodium salt)

3:4-dimethoxy-2-nitro-α-phenylcinnamic acid



dimethylmorphol

Then Pschorr *et al.* (1902) synthesised methylmorphol (III), and showed it to be 4-hydroxy-3-methoxyphenanthrene (in this synthesis Pschorr used 3-acetoxy-4-methoxy-2-nitrobenzaldehyde).



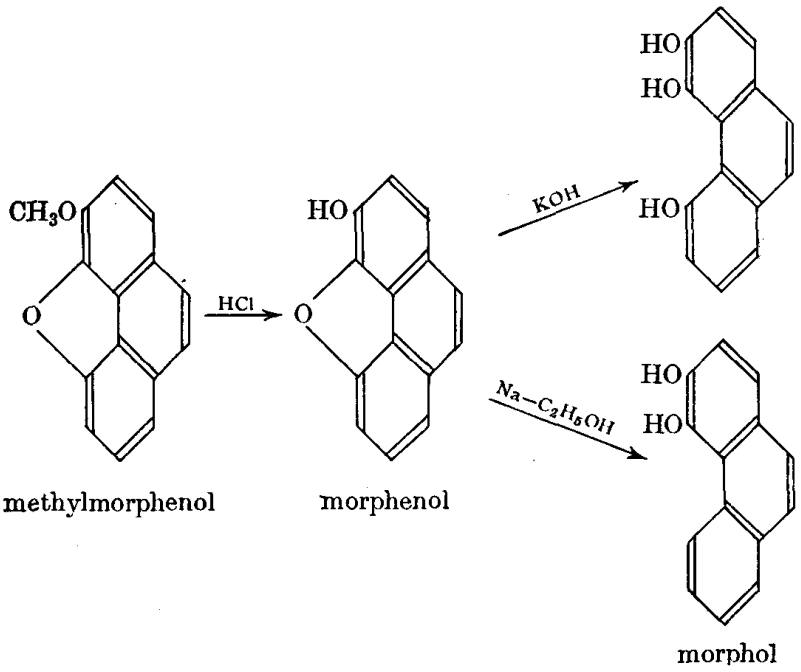
III

methylmorphol

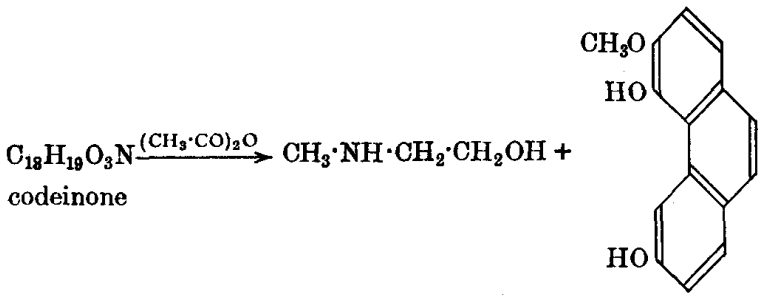
The formation of ethanoldimethylamine (IV) from α-methylmorphimethine indicates that there is a $>NCH_3$ group in codeine (only *one* methyl iodide molecule adds to codeine to form codeine methiodide; it has also been shown above that this nitrogen is in a heterocyclic ring).

When β-methylmorphimethine is heated with water, the products obtained are trimethylamine, ethylene and *methylmorphenol* (Vongerichten, 1896). Demethylation of this compound with hydrochloric acid produces *morphenol*, a compound which contains one phenolic hydroxyl group and an inert

oxygen atom. On fusion with potassium hydroxide, morphenol gives 3 : 4 : 5-trihydroxyphenanthrene (Vongerichten *et al.*, 1906). The structure of this compound was shown by the synthesis of 3 : 4 : 5-trimethoxyphenanthrene, which was found to be identical with the product obtained by methylating the trihydroxyphenanthrene obtained from morphenol (Pschorr *et al.*, 1912). Furthermore, the reduction of morphenol with sodium and ethanol gives morphol (Vongerichten, 1898). These results can be explained by assuming that morphenol has a structure containing an ether linkage in positions 4 : 5 (of the phenanthrene nucleus).

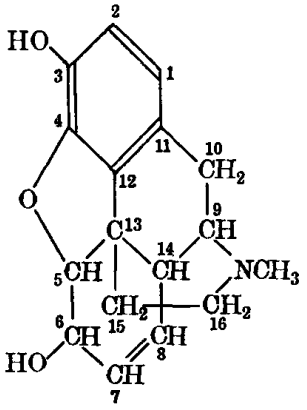


Codeinone, on heating with acetic anhydride, gives ethanolmethylamine and the diacetyl derivative of 4 : 6-dihydroxy-3-methoxyphenanthrene.

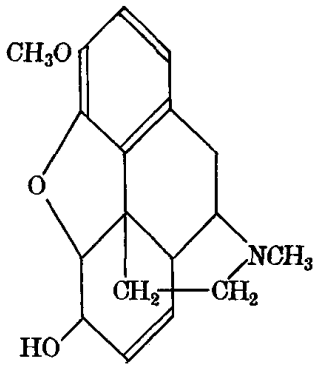


The position 3 of the methoxyl group and the position 4 of the hydroxy group have already been accounted for; the hydroxyl group in the 6-position must therefore be produced from the oxygen of the keto group in codeinone.

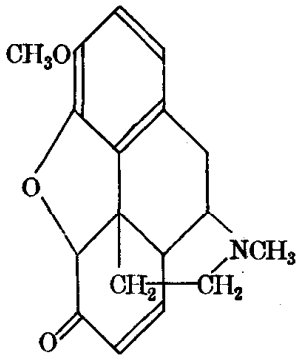
Based on the foregoing evidence, and a large amount of other experimental work, Gulland and Robinson (1923, 1925) have proposed the following structures.



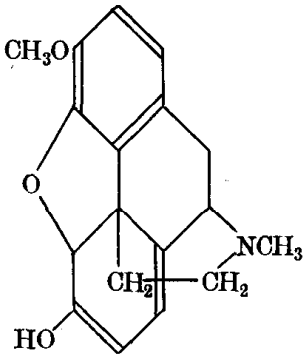
morphine



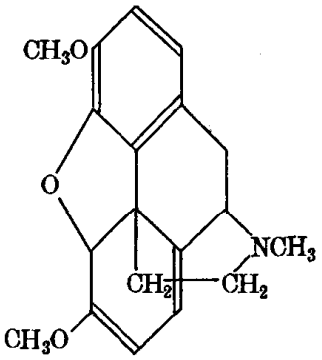
codeine



codeinone
(*keto form*)



codeinone
(*enol form*)



thebaine

Gates *et al.* (1956) have now synthesised morphine.

§28. Biosynthesis of alkaloids. As more and more structures of alkaloids were elucidated, it became increasingly probable that the precursors in the biosynthesis of alkaloids were amino-acids and amino-aldehydes and amines derived from them. A particularly interesting point is that the consideration of biosynthesis has led to deductions in structure, *e.g.*, Woodward (1948) proposed a biosynthesis of strychnine, and from this Robinson (1948) deduced the structure of emetine which was later confirmed by the synthetic work of Battersby *et al.* (1950).

We have already seen (§18. XIII) how keto-acids may be converted into amino-acids, and *vice versa*. There are also enzymes which bring about the decarboxylation of amino-acids to amines and the decarboxylation of α-keto-acids to aldehydes. Thus amino-acids, amines and amino-aldehydes, together with formaldehyde (or its equivalent) are believed to be the units involved in the biosynthesis of alkaloids. The general technique has been to administer labelled precursors to plants and to isolate the alkaloid after some time has elapsed for the growth of the plant.

The following examples of biosynthesis illustrate the principles outlined above. Alkaloids containing a benzene ring are believed to be products of the shikimic acid route (§18. XIII); the amino-acids phenylalanine and tyrosine are the starting points for the biosynthesis of, *e.g.*, ephedrine, hordenine, mezcaline, etc. As an example, we may describe the biosynthesis of adrenaline (§12) from tyrosine; the route is possibly: