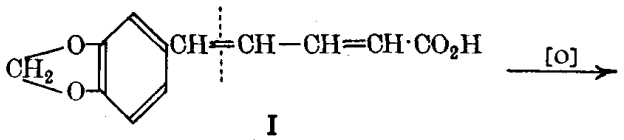
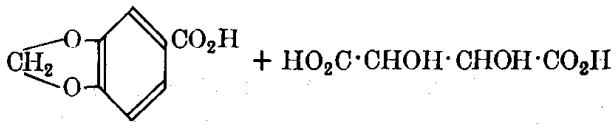
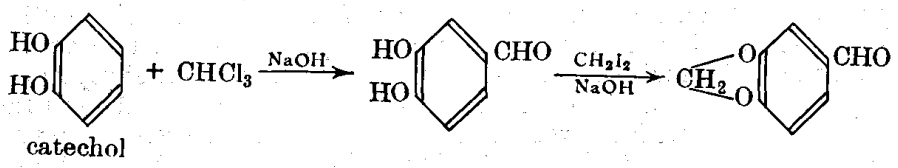
the structure of piperic acid, then all of the foregoing products of oxidation may be accounted for.



I

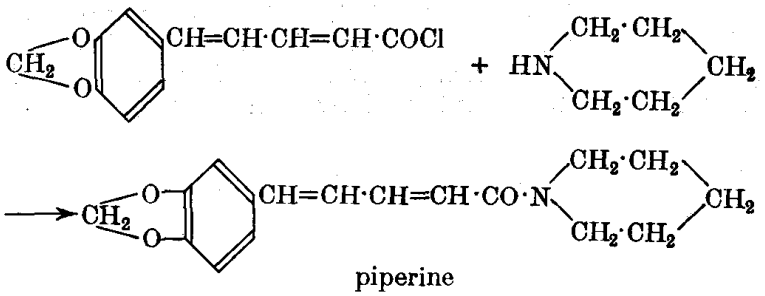


This has been confirmed by synthesis (Ladenburg *et al.*, 1894); piperonal (prepared *via* the Reimer–Tiemann reaction) is condensed with acetaldehyde in the presence of sodium hydroxide (Claisen–Schmidt reaction), and the product (a cinnamaldehyde derivative) is then heated with acetic anhydride in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

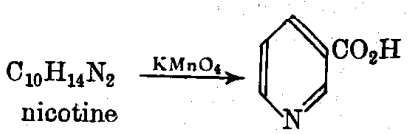


piperine

PYRROLIDINE-PYRIDINE GROUP

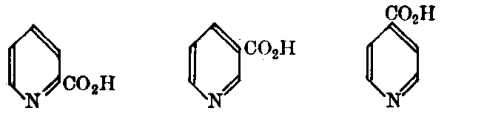
§21. Tobacco alkaloids. Many alkaloids have been isolated from the tobacco leaf, *e.g.*, nicotine, nicotimine (anabasine), nornicotine, etc.

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).



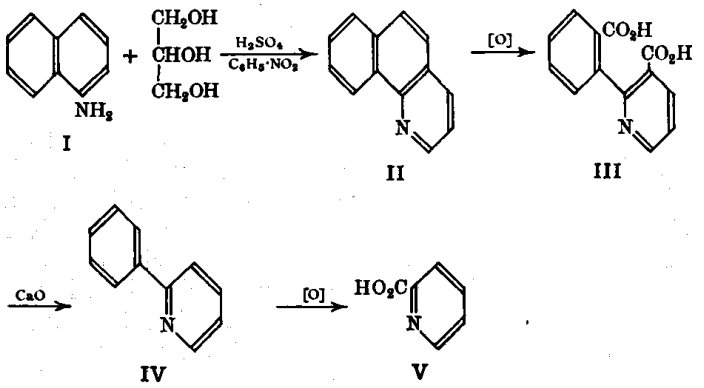
nicotine nicotinic acid

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

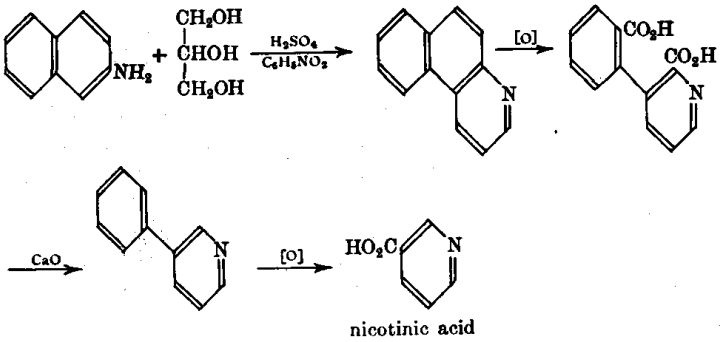


picolinic acid, m.p. 137° | nicotinic acid, m.p. 234-237° | *iso*nicotinic acid, m.p. 317°

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.



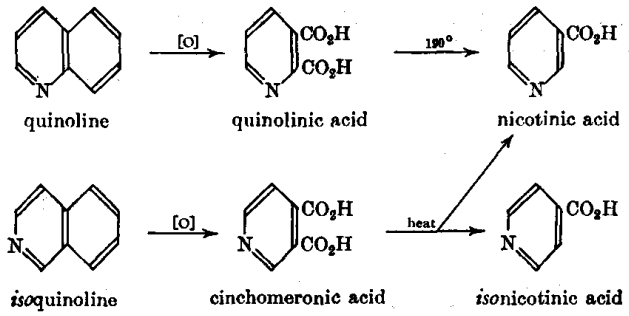
Nicotinic acid. This has been shown to be pyridine-3-carboxylic acid by a similar set of reactions, except that in this case the starting material is 2-naphthylamine.



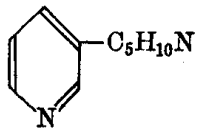
nicotinic acid

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

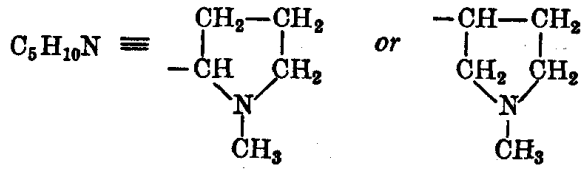
An alternative proof for the orientations of these three acids is based on the structures of quinoline and *iso*quinoline (which have been established by synthesis). Oxidation of quinoline with alkaline permanganate gives quinolinic acid which, by its method of preparation, must be pyridine-2 : 3-dicarboxylic 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.



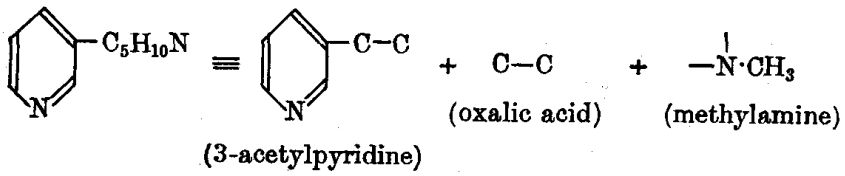
Returning to the structure of nicotine, since nicotinic acid is a product of oxidation, the alkaloid therefore contains a pyridine nucleus with a complex side-chain in the 3-position. Thus we may write the formula of nicotine as



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:

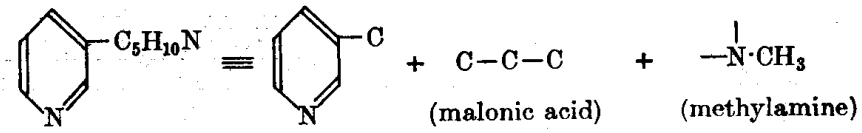


The correct structure of nicotine was obtained by Pinner (1892, 1893). Treatment of nicotine with bromine in acetic acid gives, among other products, the hydrobromide perbromide, $C_{10}H_{10}ON_2Br_2 \cdot HBr \cdot Br_2$, which, when treated with aqueous sulphurous acid, is converted into dibromocotinine, $C_{10}H_{10}ON_2Br_2$. 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:

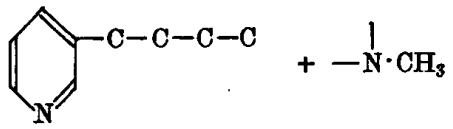


(3-acetylpyridine)

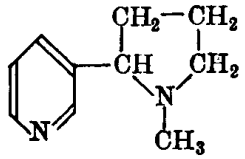
Now bromine, in the presence of hydrobromic acid, converts nicotine into dibromoticonine, $C_{10}H_8O_2N_2Br_2$, which, on heating with barium hydroxide solution at 100°, forms nicotinic acid, malonic acid and methylamine. Hence the structure of nicotine must also account for the following skeleton structures:



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

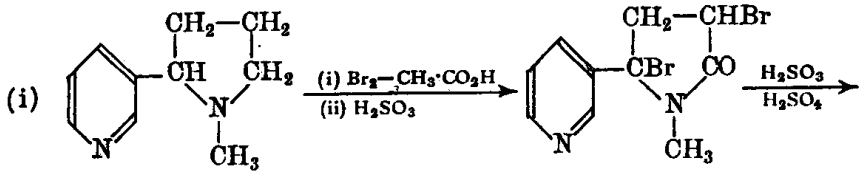


The problem now is: Where is the position of the *N*-methyl group? Nicotine behaves as a ***di-tertiary base***, and forms two isomeric " methyl iodide addition products ". Thus the nitrogen atom in the side-chain must be of the type —C—N(CH$_3$)—C—. Furthermore, it is extremely difficult to reduce nicotine 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.

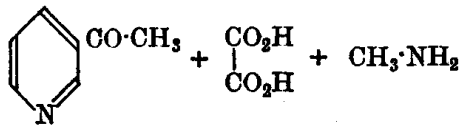


nicotine

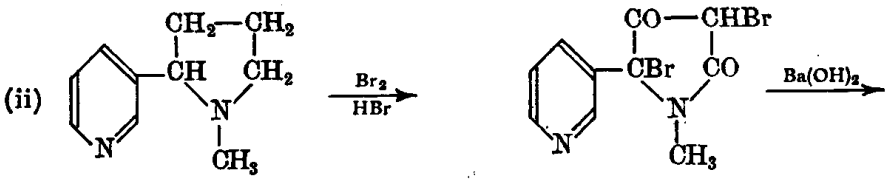
On this basis, Pinner's work may be formulated:



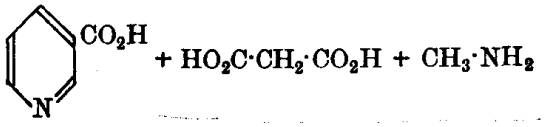
dibromocotinine



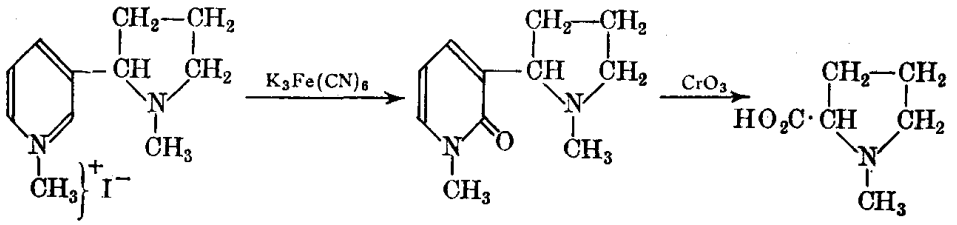
3-acetylpyridine



dibromoticonine

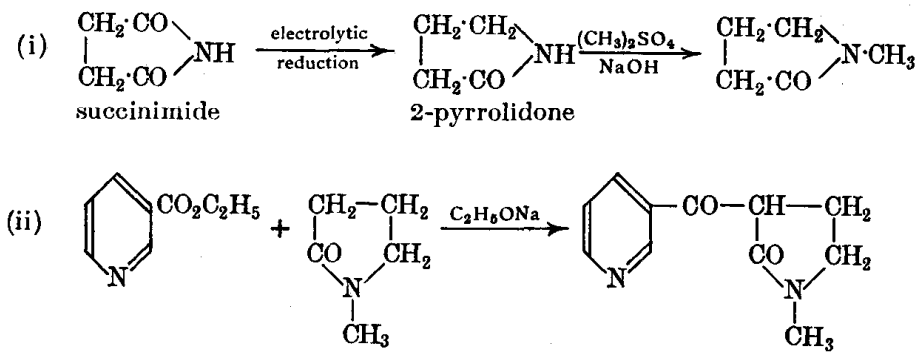


The most direct analytical evidence for the presence of the pyrrolidine nucleus has been given by Karrer (1925, 1926); nicotine hydriodide forms nicotine *iso*methiodide when warmed with methyl iodide and this, on oxidation with potassium ferricyanide, is converted into nicotone which, on oxidation with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



nicotine *iso*methiodide — nicotone — hygrinic acid

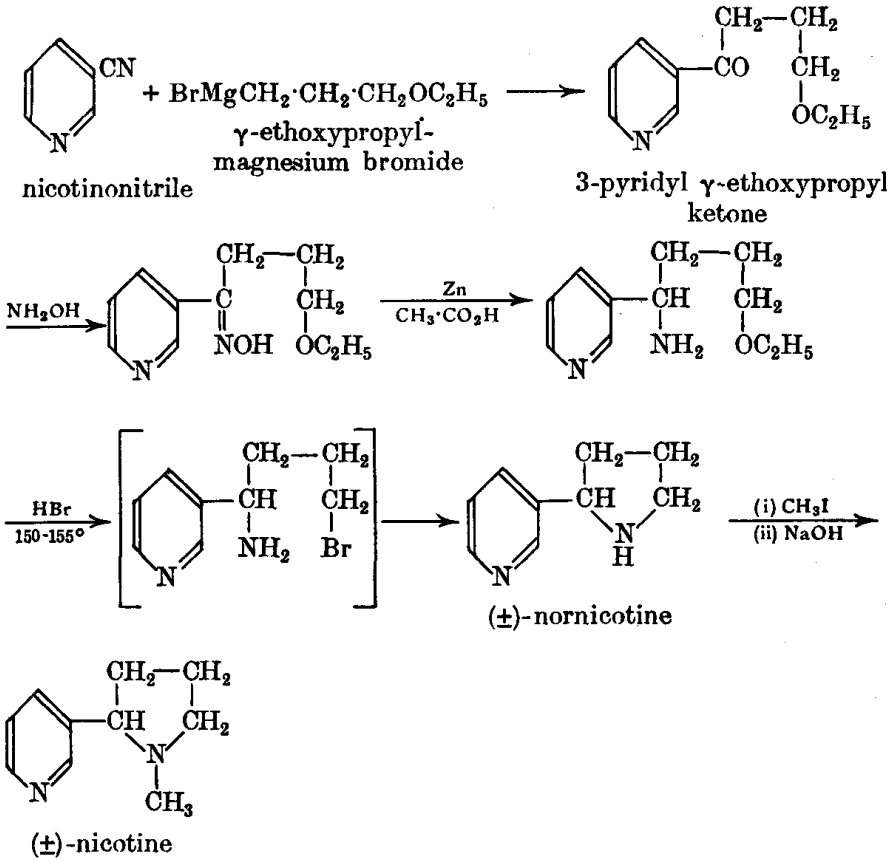
Pinner's formula for nicotine has been confirmed by synthesis, *e.g.*, *Späth and Bretschneider* (1928).



(±)-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).

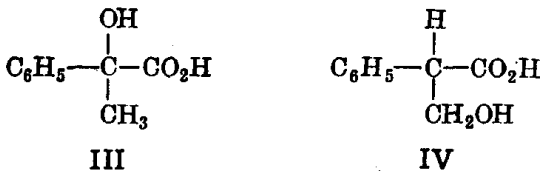
Atropine, $C_{17}H_{23}O_3N$, m.p. 118°, occurs in deadly nightshade (*Atropa belladonna*) together with hyoscyamine. Hyoscyamine is optically active (lævorotatory), but readily racemises to atropine when warmed in an ethanolic alkaline solution; thus atropine is (±)-hyoscyamine.

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,

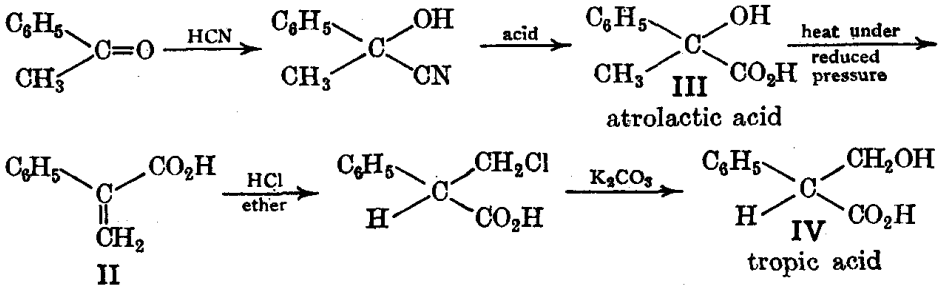
$C_6H_5\cdot CH{=}CH\cdot CO_2H$ (I) $\qquad$ $C_6H_5\cdot C(=CH_2)\cdot CO_2H$ (II)

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



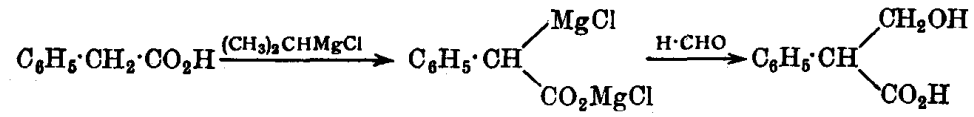
III IV

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.

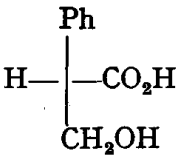


III is atrolactic acid, and its dehydration to II confirms the structure of atropic acid. It should also be noted that the addition of hydrogen chloride takes place contrary to Markownikoff's rule (see unsaturated acids, Vol. I); had the addition been in accordance with the rule, then atrolactic acid 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.

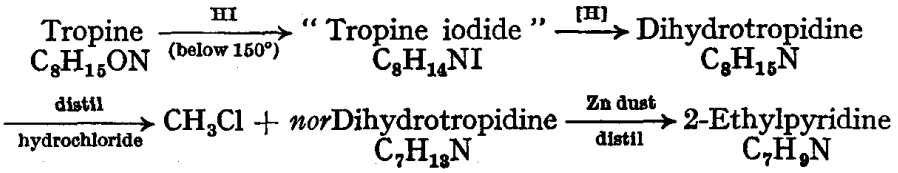
Blicke *et al.* (1952) have synthesised tropic acid by boiling phenylacetic acid with *iso*propylmagnesium chloride in ethereal solution, and then treating the product, a Grignard reagent, with formaldehyde.



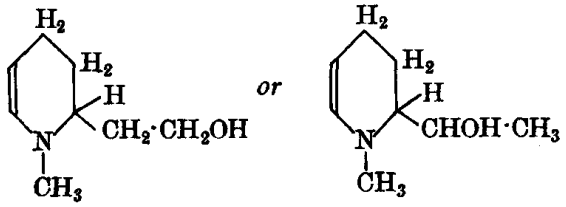
Fodor *et al.* (1961) have established the absolute configuration of (—)-tropic acid by its correlation with (—)-alanine. According to the Cahn–Ingold–Prelog convention (§5c. II), natural tropic acid is (*S*)-(—)-tropic acid.



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:



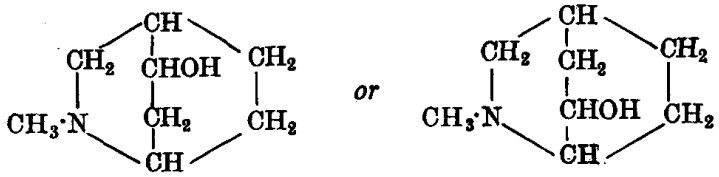
"Tropine iodide" is formed by the replacement of the alcoholic group in tropine by an iodine atom, which is then replaced by hydrogen to form dihydrotropidine (tropane). The formation of methyl chloride indicates the presence of an *N*-methyl group, and the isolation of 2-ethylpyridine shows the presence 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.

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

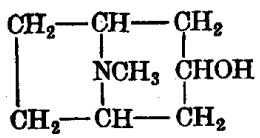
Tropinic acid is a dicarboxylic acid, and since there is no loss of carbon in its formation, the hydroxyl group in tropine must therefore be in a ring system. Thus Ladenburg's formula is untenable, and so Merling proposed the following structures for tropine:



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

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

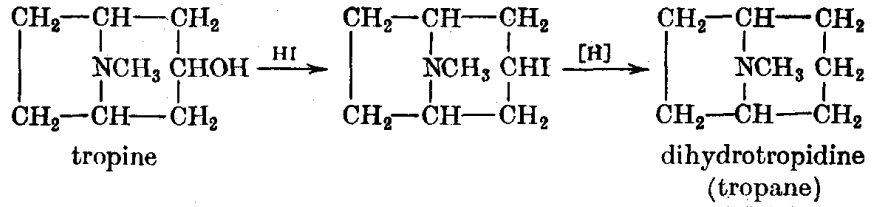
Tropinone behaved as a ketone; thus tropine is a secondary alcohol (*cf.* Merling's formula). Willstätter (1897) also showed that tropinone forms a dibenzylidene derivative with benzaldehyde, and a di-oximino derivative when treated with amyl nitrite and hydrochloric acid. Thus tropinone contains the ·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):

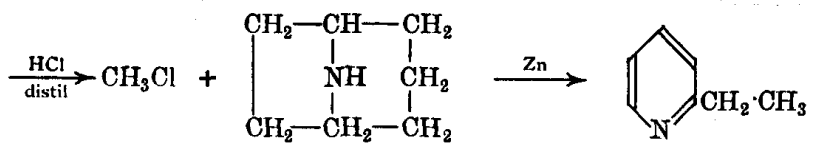


Not only did this fit the facts best, but it was also supported by the following evidence: (i) Exhaustive methylation of tropine gives tropilidene (*cyclo*-heptatriene), C_7H_8. (ii) Exhaustive methylation of tropinic acid gives an unsaturated dicarboxylic acid which, on reduction, forms pimelic acid.

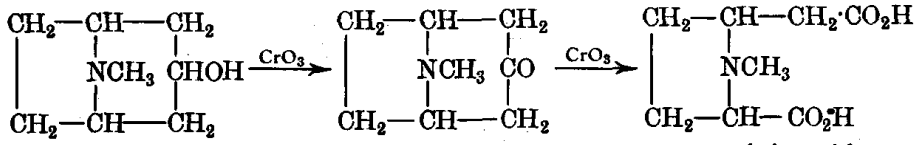
All the foregoing reactions of tropine can be readily explained on the Willstätter formula.

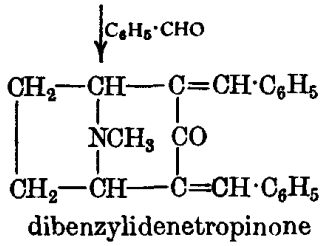
Formation of 2-ethylpyridine from tropine.



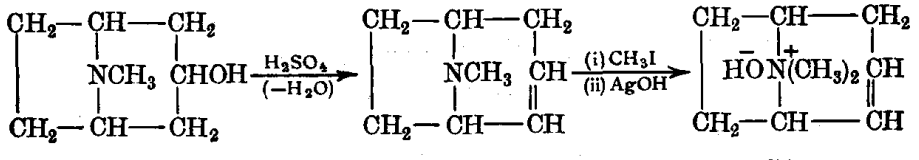


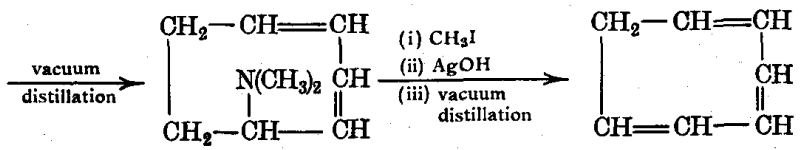
Formation of tropinone and tropinic acid from tropine.



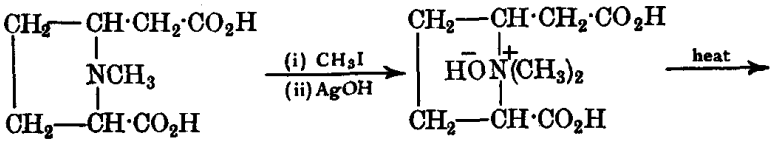


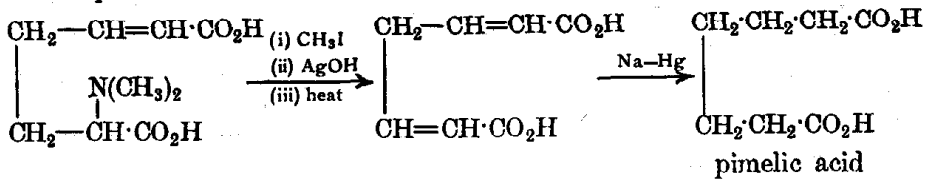
Formation of tropilidene from tropine.





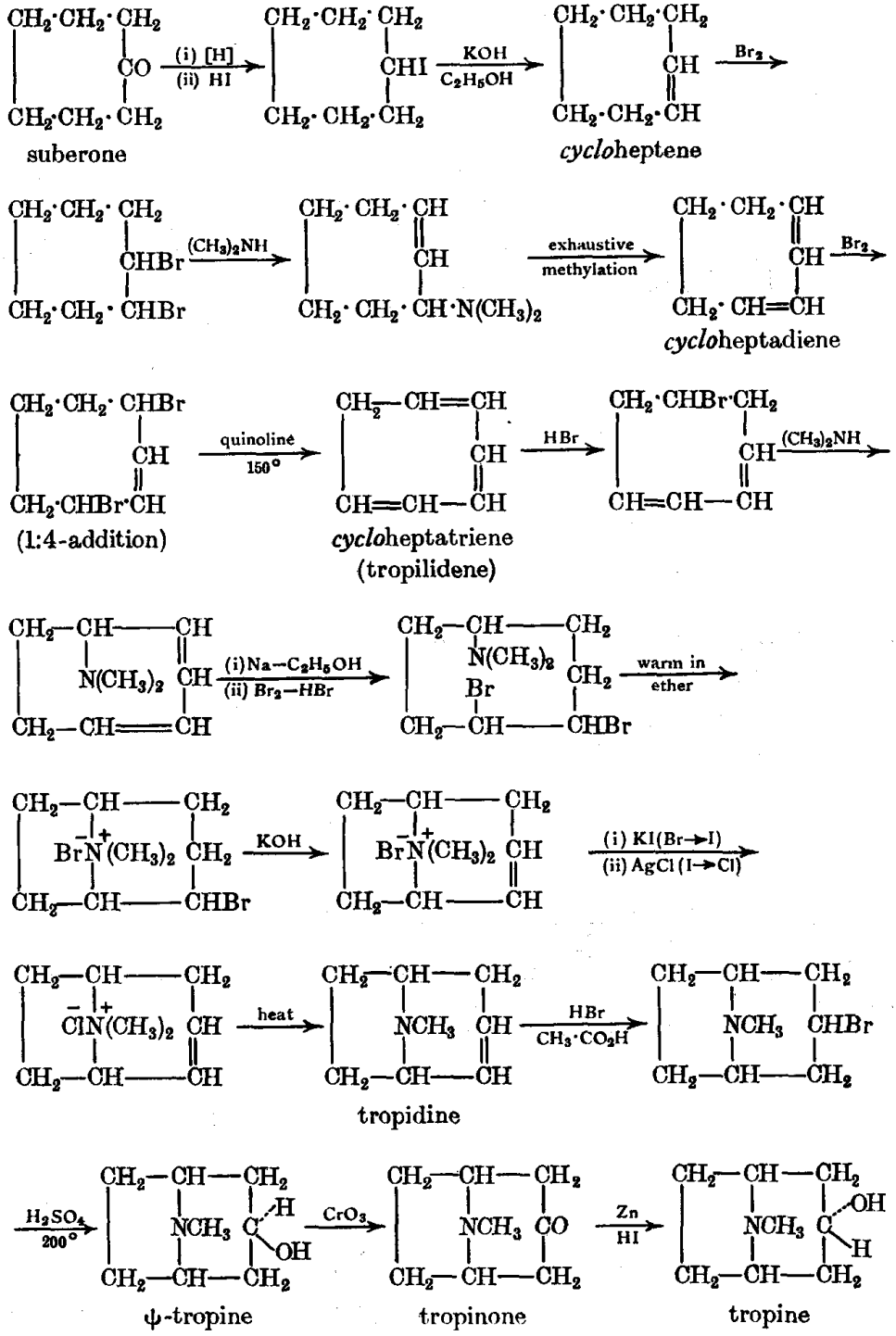
Formation of pimelic acid from tropinic acid.





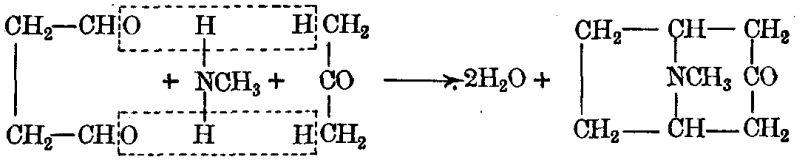
The structure of tropine has been confirmed by synthesis, one by Willstätter (1900–1903), and the other by Robinson (1917).

Willstätter's synthesis.

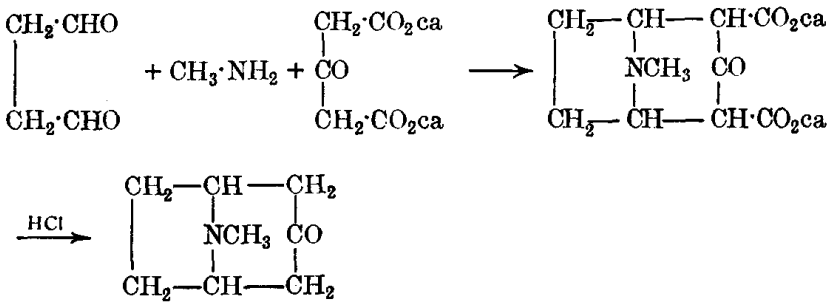


Robinson's synthesis.

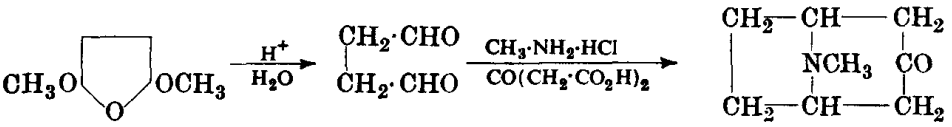
When a mixture of succinaldehyde, methylamine and acetone is allowed to stand in water for thirty minutes, tropinone is produced in very small yield.



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):

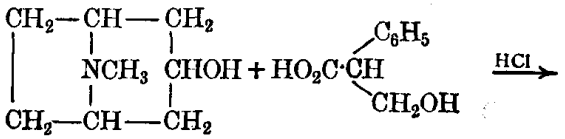


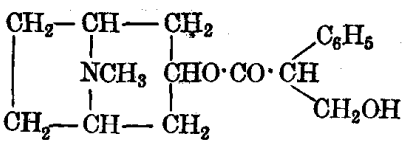
Schöpf *et al.* (1935) have obtained a yield of 70–85 per cent. by carrying out Robinson's synthesis at a *p*H of 7. Elming *et al.* (1958) have also synthesised tropinone using methylamine hydrochloride, acetonedicarboxylic acid and generating succinaldehyde *in situ* by the action of acid on 2,5-dimethoxytetrahydrofuran:



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

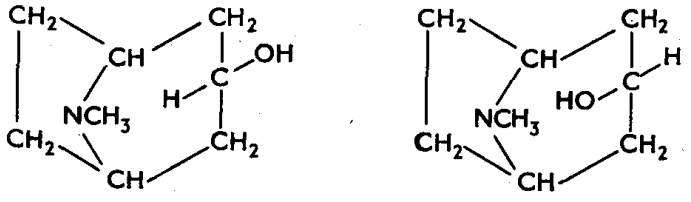


FIG. 14.1.

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).

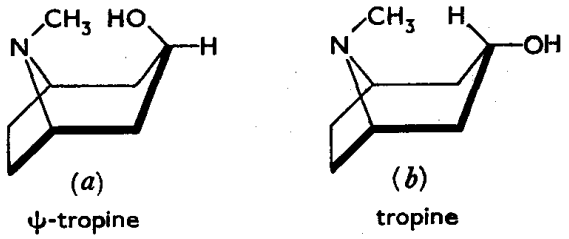


FIG. 14.2.

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.

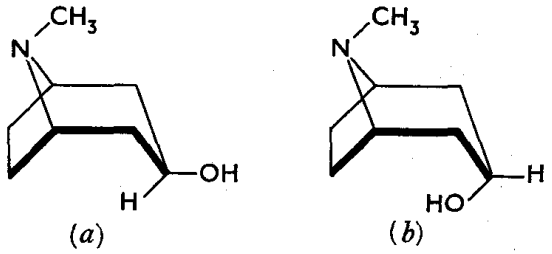
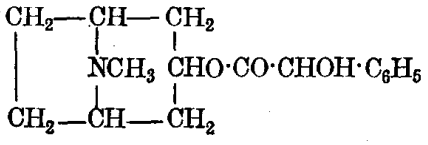


FIG. 14.3.

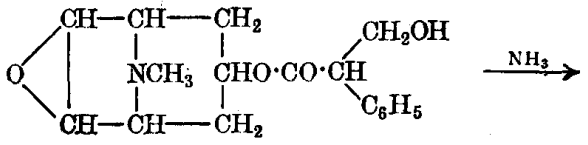
If these be the configurations, then it is difficult to explain Fodor's work (which involves rearrangements), and also the fact that there is intramolecular hydrogen bonding in *ψ*-tropine. Sparke (1953) has suggested that the chair form can readily change into the boat form; this would then explain 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.

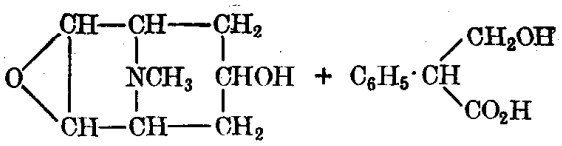


homatropine

§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.

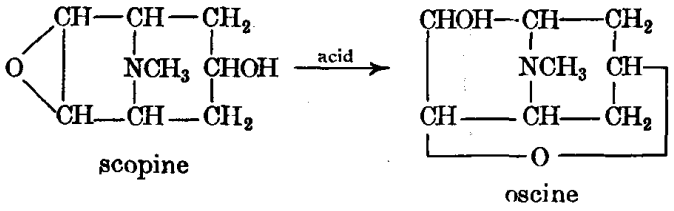


hyoscine



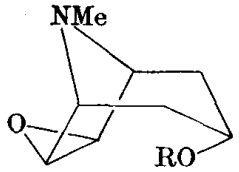
scopine tropic acid

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.

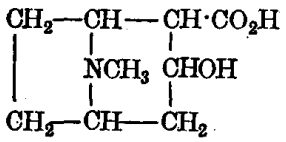
$$\underset{\text{benzoylecgonine}}{C_{16}H_{19}O_4N} + H_2O \xrightarrow{Ba(OH)_2} \underset{\text{ecgonine}}{C_9H_{15}O_3N} + C_6H_5{\cdot}CO_2H$$

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.*,

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

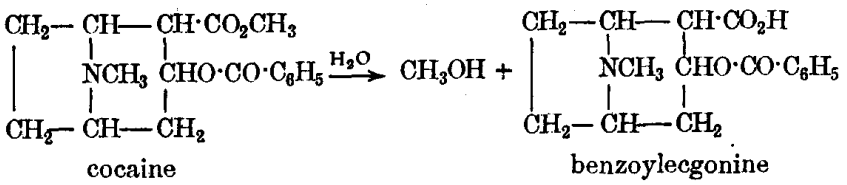
From these results, it follows that ecgonine contains the tropane structure and that the alcoholic group must be in the same position as in tropine (§22). Now in the formation of tropinone from ecgonine, a carboxyl group is lost (as we have seen, ecgonine contains a carboxyl group). Thus the carboxyl 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:

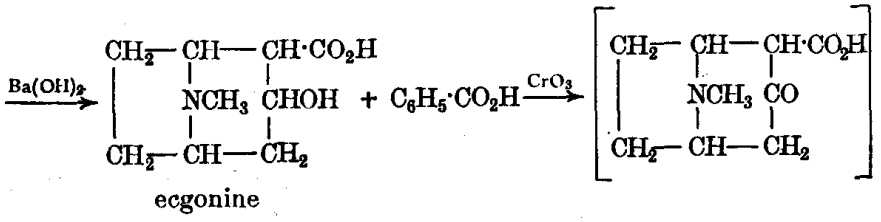


ecgonine

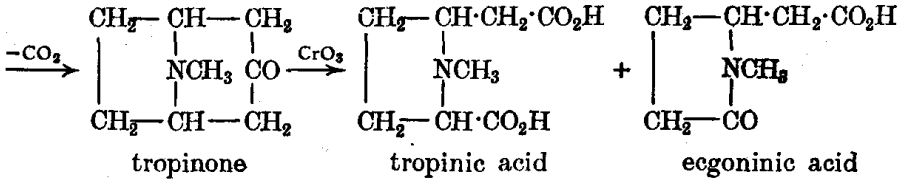
On this basis, the foregoing reactions may therefore be written:



cocaine benzoylecgonine

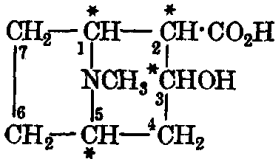


ecgonine



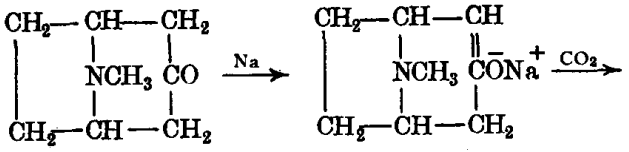
tropinone tropinic acid ecgoninic acid

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

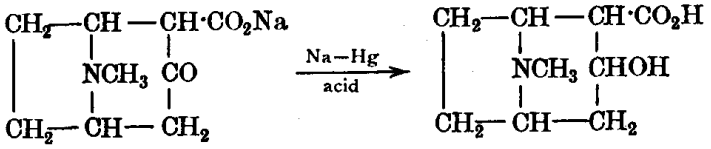


asymmetric carbon atoms present (*), and so there are $2^4 = 16$ optically active forms (eight pairs of enantiomorphs) possible (*cf.* tropine, §22). Since, however, only the *cis* fusion of the nitrogen bridge is possible in practice, C_1 and C_5 therefore have only one configuration (the *cis*-form),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

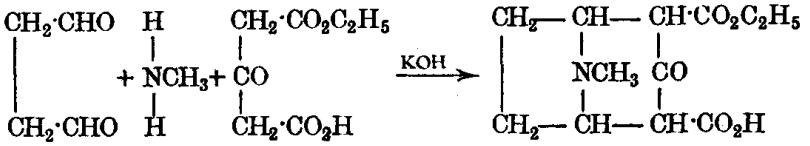


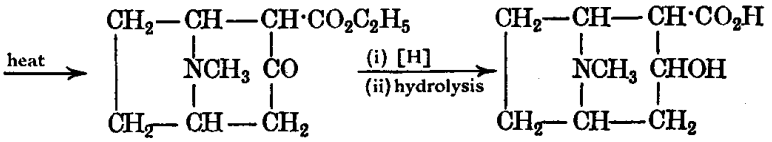
tropinone



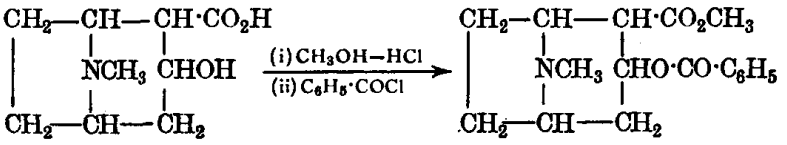
sodium tropinonecarboxylate — a (±)-ecgonine

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





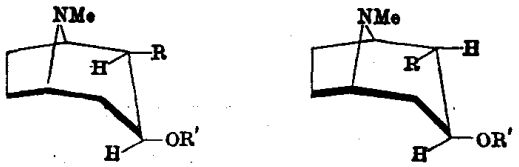
The final product was shown to be a mixture of three racemates, (±)-ecgonine, (±)-ψ-ecgonine and a third pair of enantiomorphs (Willstätter *et al.*, 1923). The racemic ecgonine was resolved, and the (—)-form esterified with methanol and then benzoylated; the product was (—)-cocaine.



(—)-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.

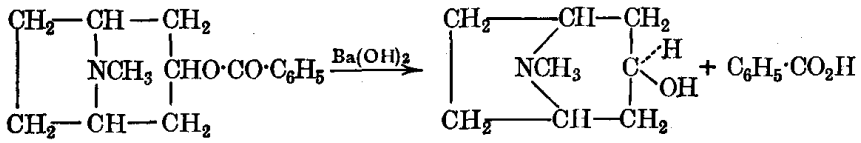
Fodor *et al.* (1953, 1954) and Findlay (1953, 1954) have established the conformations of ecgonine and ψ-ecgonine (R = CO_2H; R′ = H) and the corresponding cocaines (R = CO_2Me; R′ = COPh) (*cf.* §22):



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.

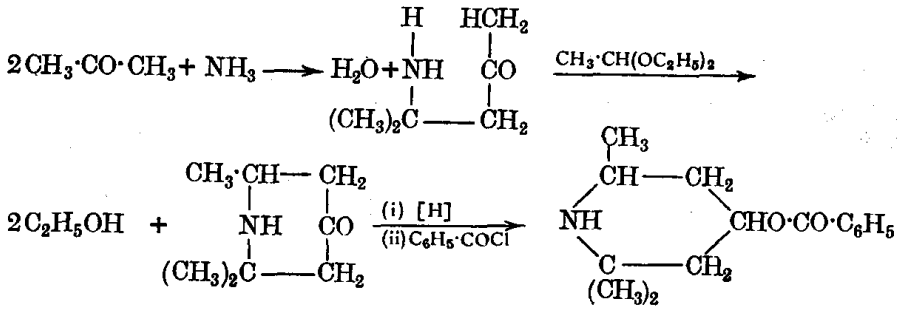
§23a. **Tropacocaine,** $C_{15}H_{19}O_2N$, m.p. 49°, occurs in Java coca leaves. When heated with barium hydroxide solution, tropacocaine is hydrolysed to *ψ*-tropine and benzoic acid; thus the alkaloid is benzoyl-*ψ*-tropine.



tropacocaine ψ-tropine

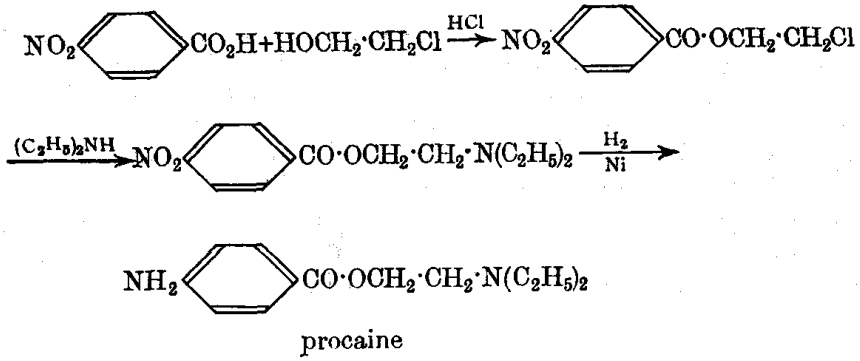
§23b. **Cocaine substitutes.** Cocaine is a very good local anæsthetic, but has certain disadvantages. The anæsthetic properties are lost if either the benzoyl group or the methyl ester group is removed; removal of the *N*-methyl group has no effect. A number of synthetic drugs have now been introduced 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.