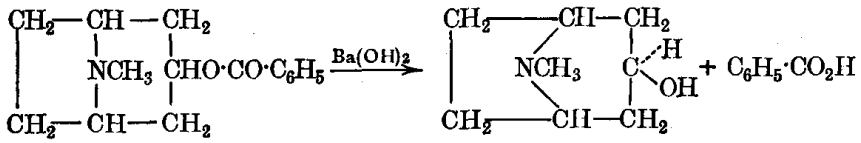
Hardegger *et al.* (1955) have correlated (−)-cocaine with L-glutamic acid and have shown that the formula represents the absolute configuration of L(−)-cocaine.

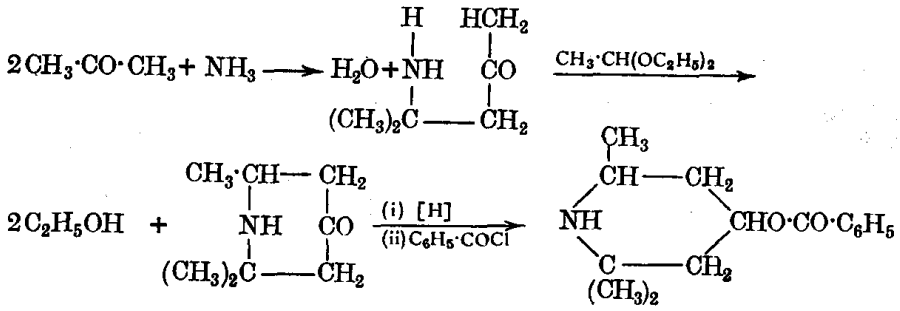
§23a. **Tropacocaine,** $C_{15}H_{19}O_2N$, m.p. 49°, occurs in Java coca leaves. When heated with barium hydroxide solution, tropacocaine is hydrolysed to *ψ*-tropine and benzoic acid; thus the alkaloid is benzoyl-*ψ*-tropine.



tropacocaine ψ-tropine

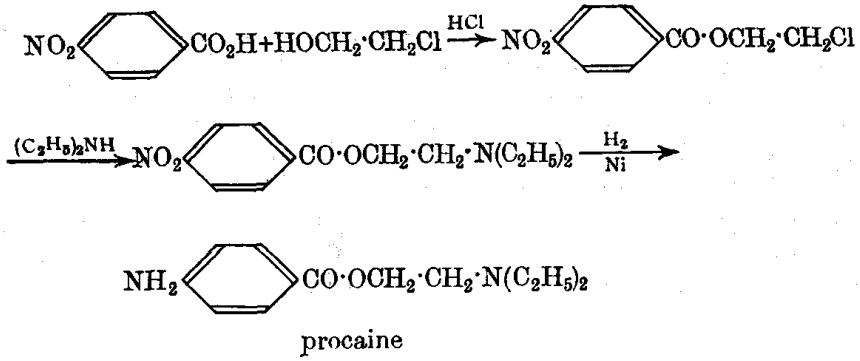
§23b. **Cocaine substitutes.** Cocaine is a very good local anæsthetic, but has certain disadvantages. The anæsthetic properties are lost if either the benzoyl group or the methyl ester group is removed; removal of the *N*-methyl group has no effect. A number of synthetic drugs have now been introduced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

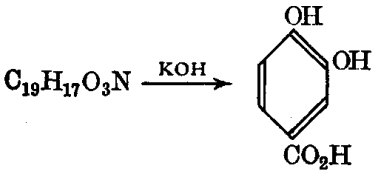


procaine

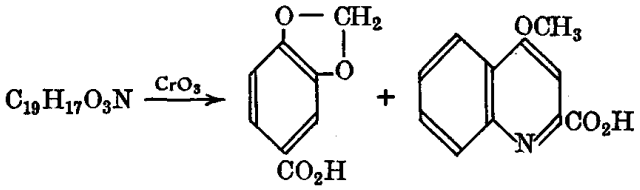
QUINOLINE GROUP

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

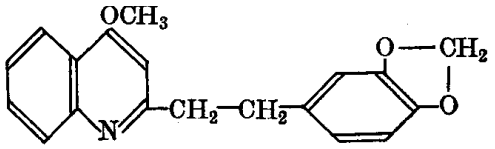
Cusparine, $C_{19}H_{17}O_3N$, m.p. 90–91°, has been shown to contain one methoxyl group (Zeisel method), and when fused with potassium hydroxide, protocatechuic acid is obtained.



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

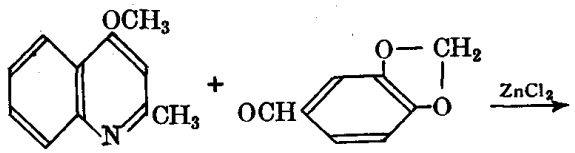


Consideration of this information led to the suggestion of the following structure for cusparine.



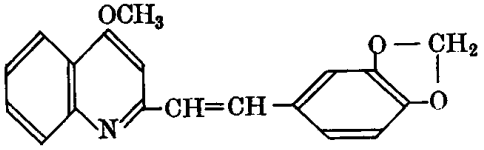
cusparine

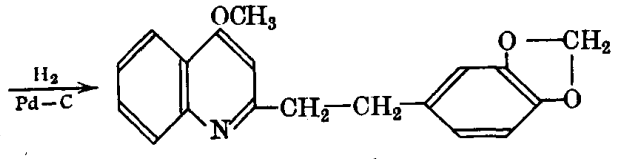
This has been confirmed by synthesis (Späth *et al.*, 1924).



4-methoxy-2-methylquinoline

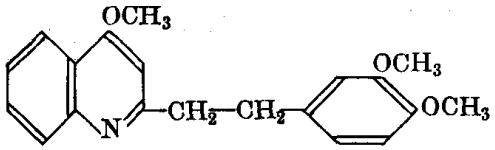
piperonal





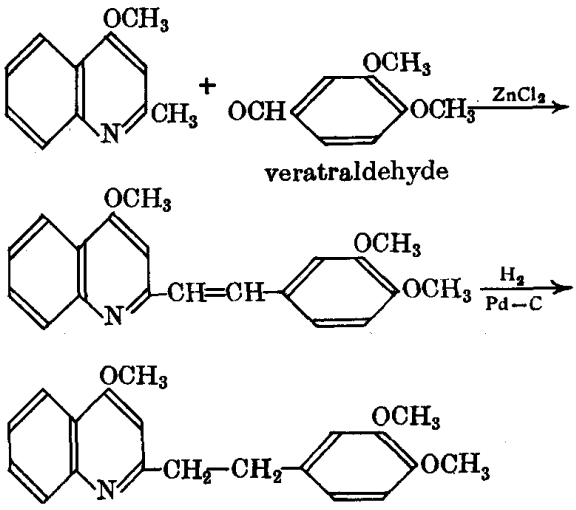
cusparine

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:



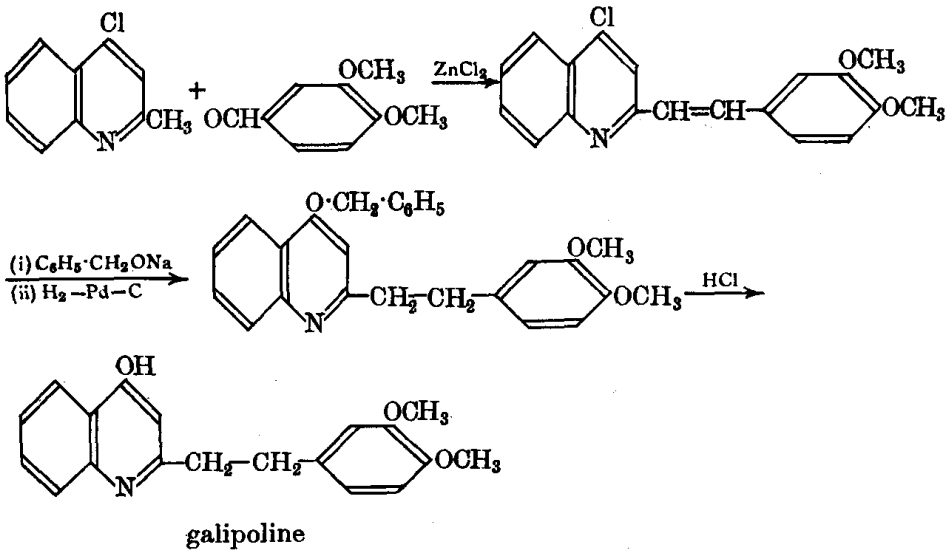
galipine

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).



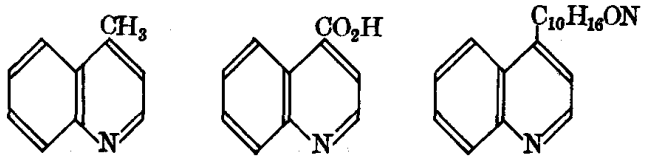
galipoline

§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

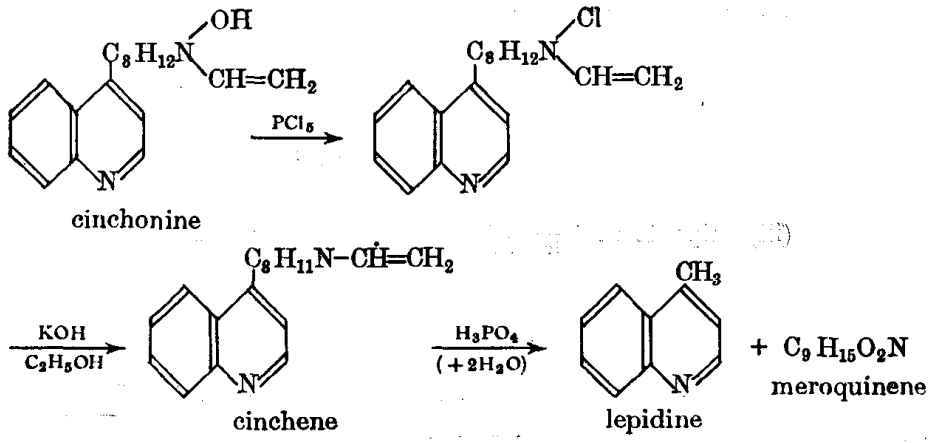
contains a quinoline nucleus with a side-chain in position 4 (III); this side-chain was referred to by Skraup as the " second-half " of the molecule. The hydroxyl group in cinchonine must be in this " second-half ", since if it were not, then a hydroxy derivative or a carboxy derivative (since the hydroxyl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

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

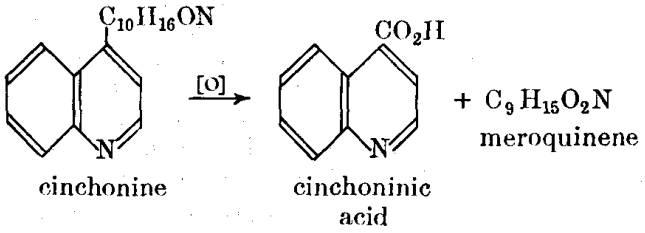
$$C_{19}H_{22}ON_2 + 4[O] \xrightarrow{KMnO_4} \underset{\text{cinchotenine}}{C_{18}H_{20}O_3N_2} + H{\cdot}CO_2H$$

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).

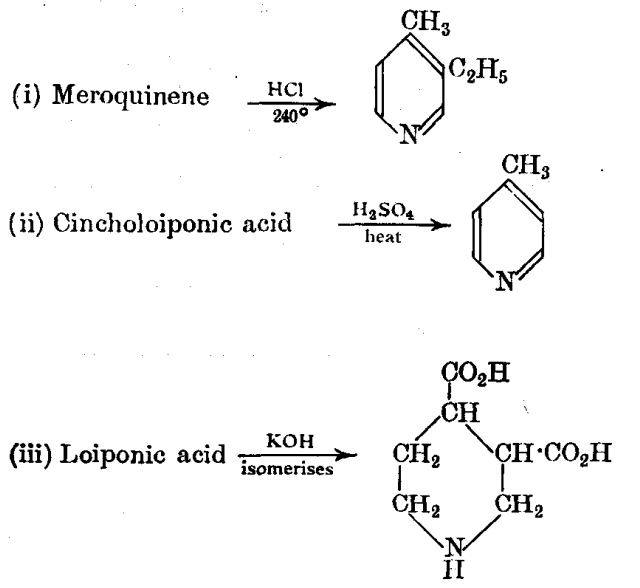


Thus the key to the structure of the " second-half " is the structure of meroquinene. The routine tests showed that meroquinene contains one carboxyl group and one double bond; the presence of the latter indicates that the $-CH=CH_2$ side-chain is still present in meroquinene. Oxidation of meroquinene 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 $-CH_2{\cdot}CO_2H$.

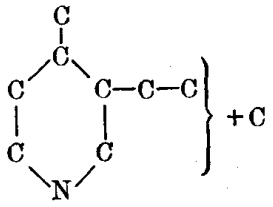
The reactions of the above three acids indicated that they were all secondary bases; that they all contained a piperidine ring is shown by the following reactions.



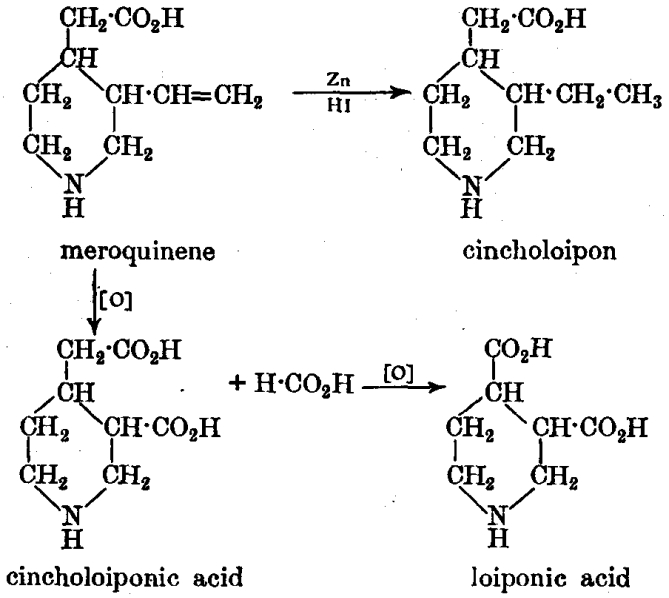
hexahydrocinchomeronic acid

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

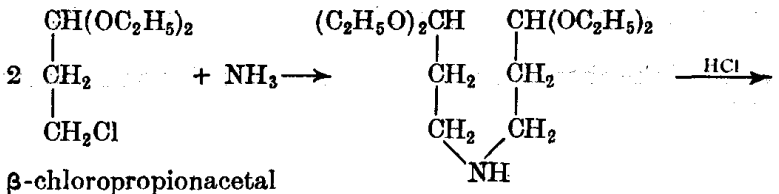
Consideration of the above results shows that a possible skeleton structure of meroquinene is:



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:

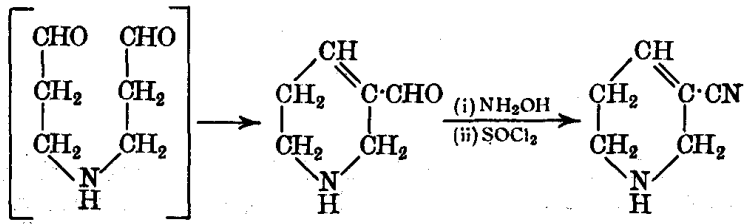


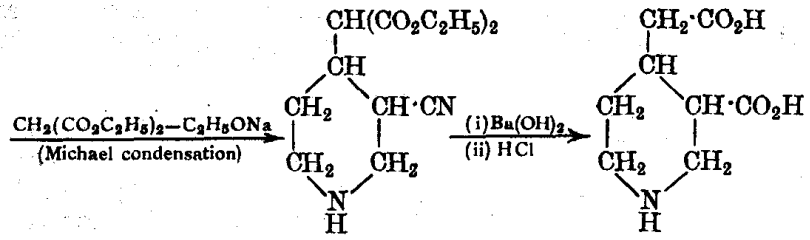
This formula for meroquinene is supported by the synthesis of cincholoiponic acid (Wohl *et al.*, **1907**; *cf.* §17) (see next page).



β-chloropropionacetal

iminodipropionacetal

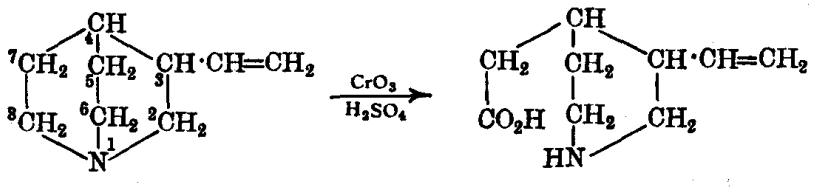




(±)-cincholoiponic acid

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.

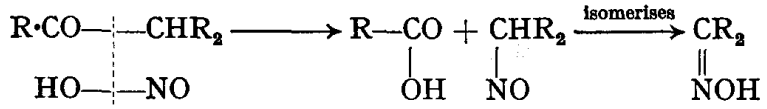
Since meroquinene is obtained from cinchonine by oxidation, the carbon atom of the carboxyl group in meroquinene will be the point of linkage to the " quinoline-half " at which scission of the " second-half " occurs. Since cinchonine is a di-tertiary base, the " second-half " therefore contains a tertiary 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:



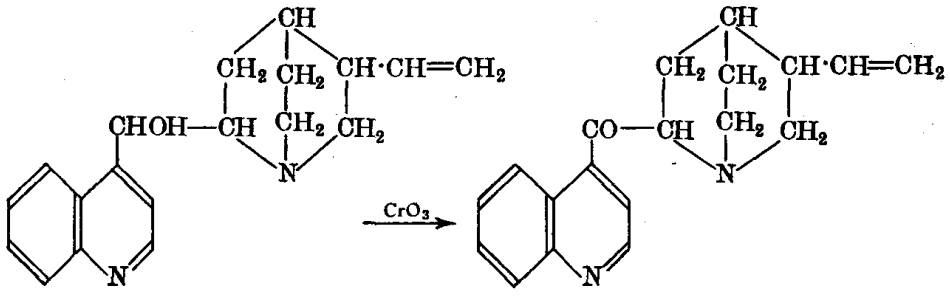
3-vinylquinuclidine meroquinene

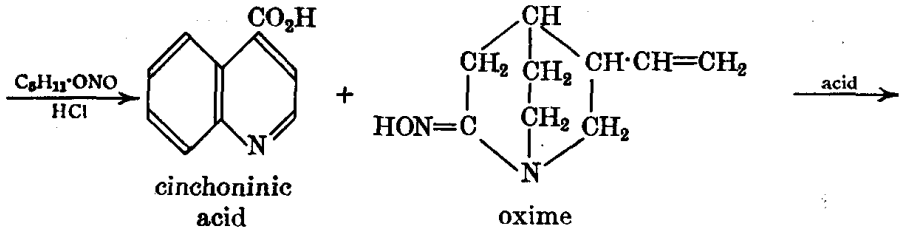
Thus, in cinchonine, the " quinoline-half " must be joined *via* its side-chain at position 4 to the " quinuclidine-half " at position 8. The remaining problem is to ascertain the position of the secondary alcoholic group in the " second-half ". Rabe *et al.* (1906, 1908) converted cinchonine into the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

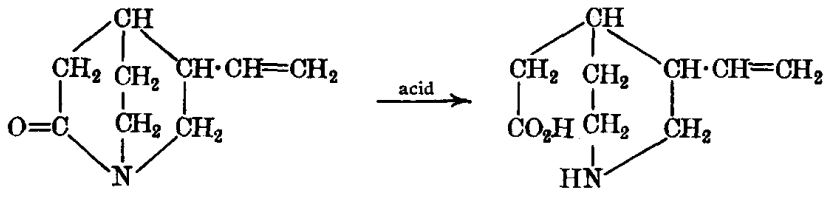
nitrite and hydrogen chloride, gives cinchoninic acid and an oxime. The formation of an acid and an oxime indicates the presence of the group —CO·CH—, *i.e.*, a methyne group adjacent to a carbonyl group:



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.

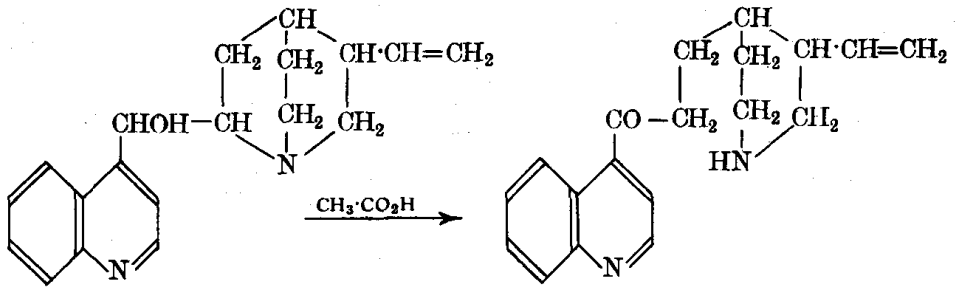






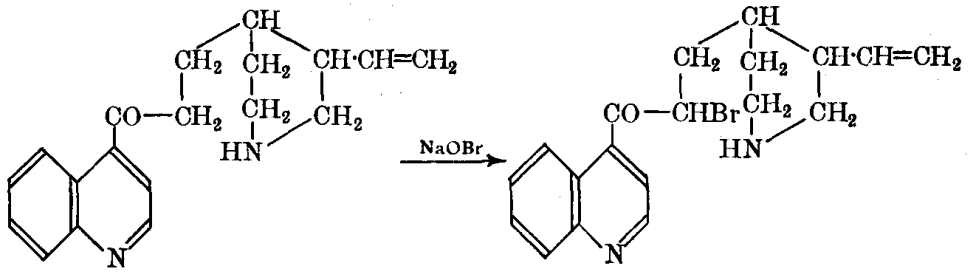
The above structure of cinchonine contains four dissimilar asymmetric carbon atoms, *viz.*, 3, 4, 8, and the carbon atom of the CHOH group (see 3-vinylquinuclidine for numbering). One pair of enantiomorphs is (±)-cinchonine, and another pair is (±)-*cinchonidine*; the configurations of C_3 and C_4 are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

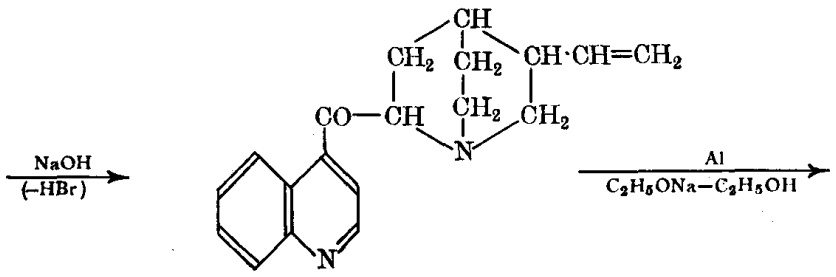


cinchonine cinchotoxine

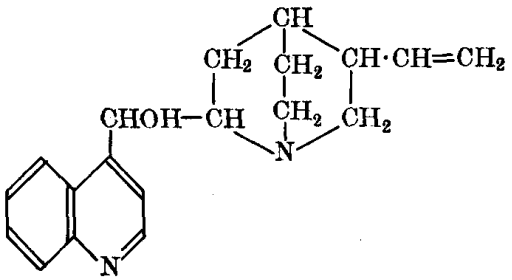
This isomerisation is an example of the *hydramine fission* (see §7). The conversion of cinchotoxine into cinchonine was carried out as follows:



cinchotoxine



cinchoninone



(±)-cinchonine

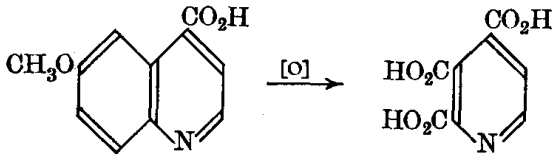
§25b. (—)-Quinine, $C_{20}H_{24}O_2N_2$, m.p. 177°, is used as a febrifuge and as an antimalarial. Since quinine adds on two molecules of methyl iodide to form a di-quaternary salt, it is therefore a di-tertiary base. When heated with hydrochloric acid, quinine eliminates one carbon atom as methyl chloride; 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.

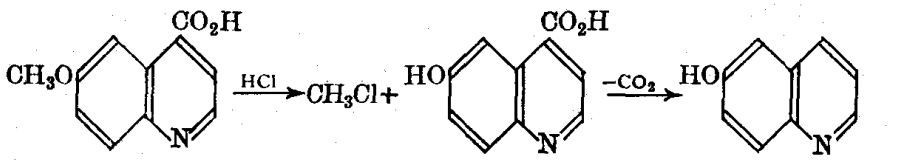
$$\underset{\text{quinine}}{C_{20}H_{24}O_2N_2} \xrightarrow[H_2SO_4]{CrO_3} \underset{\text{quininic acid}}{C_{11}H_9O_3N}$$

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



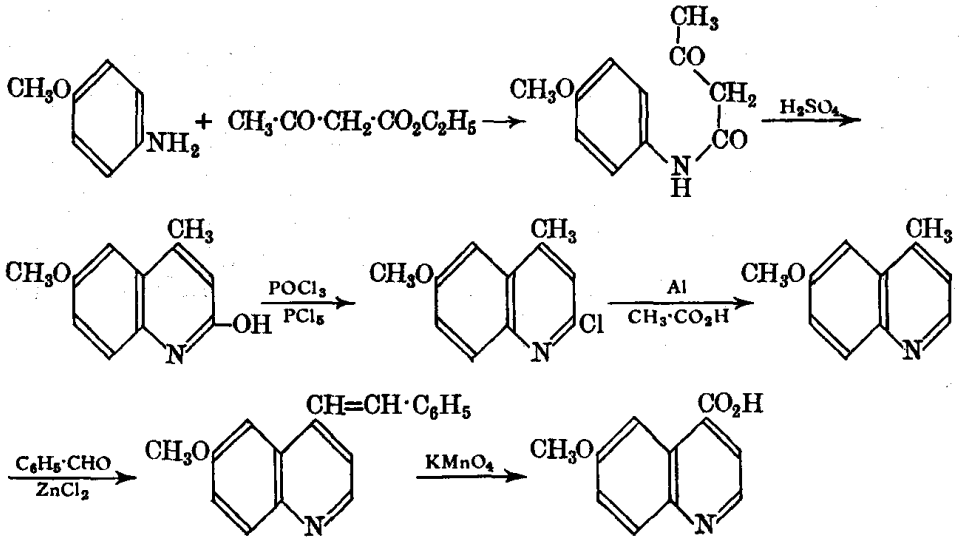
quininic acid pyridine-2:3:4-tricarboxylic acid

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



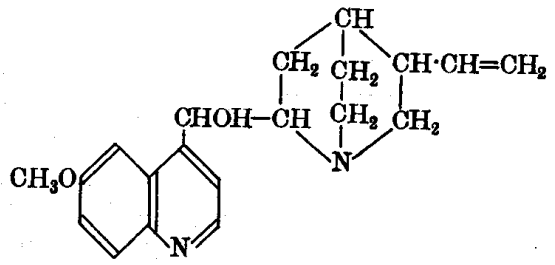
quininic acid 6-hydroxyquinoline

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).

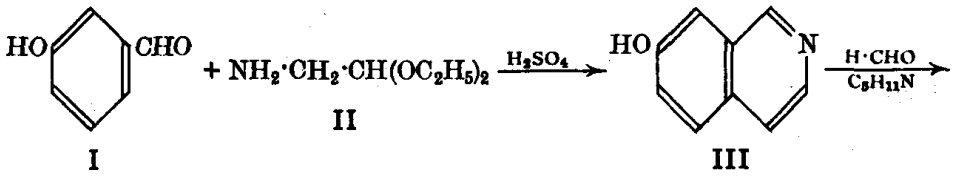
Thus, on the basis of the foregoing evidence, the structure of quinine is:



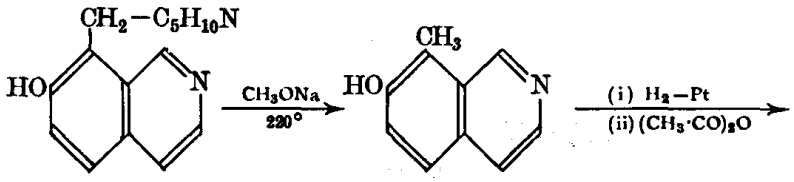
quinine

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).

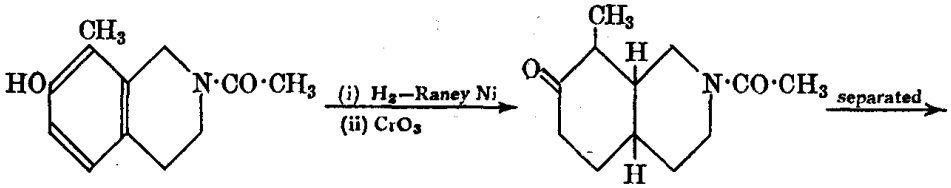
Rabe *et al.* (1918) carried out a partial synthesis of quinine starting from quinotoxine, which is prepared by heating quinine in acetic acid (*cf.* cinchotoxine). Woodward and Doering (1944) have synthesised (+)-quinotoxine, and so we now have a *total* synthesis of quinine. The following is Woodward 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).



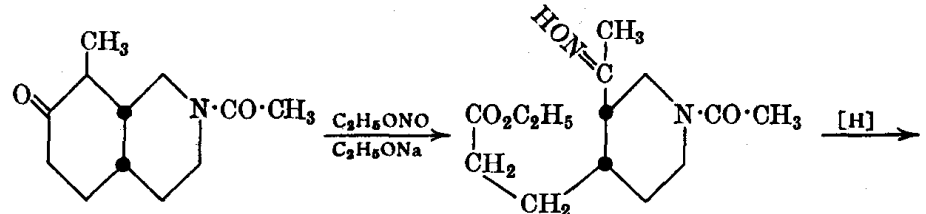
I III



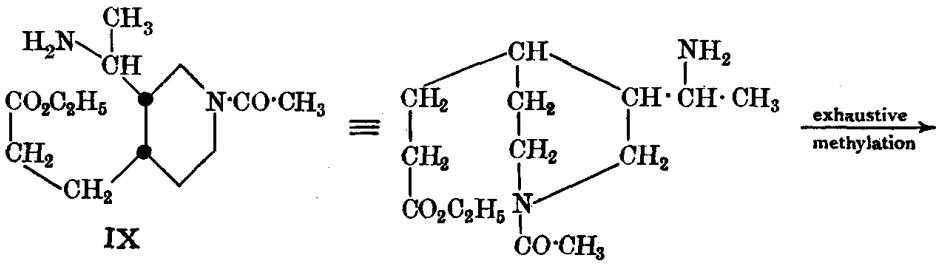
IV V



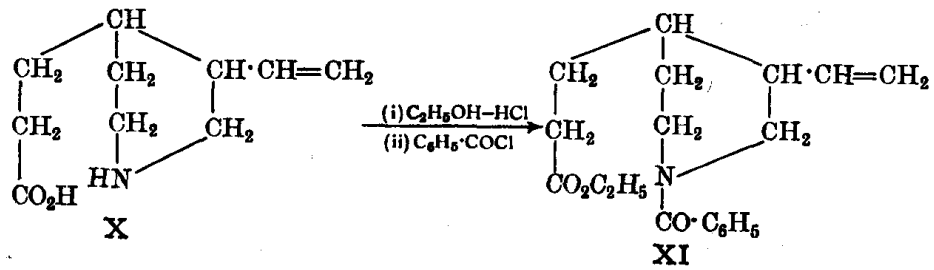
VI VII



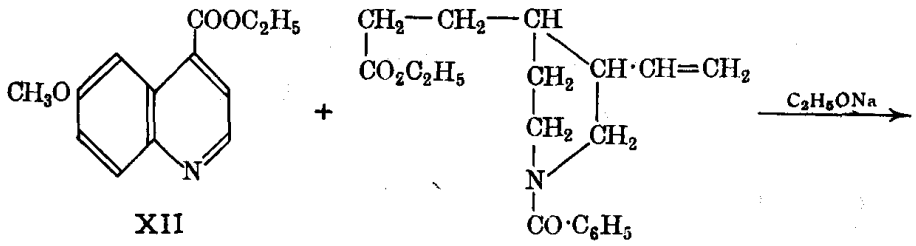
VII*a* VIII



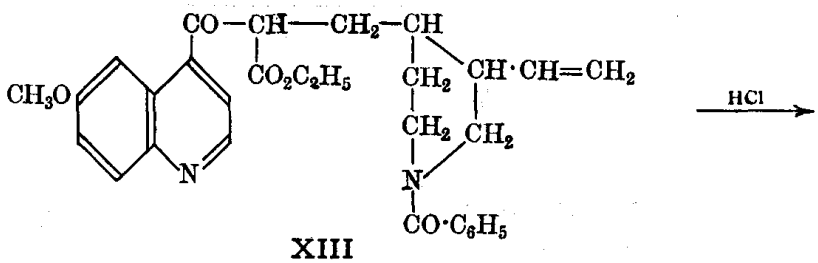
IX IX



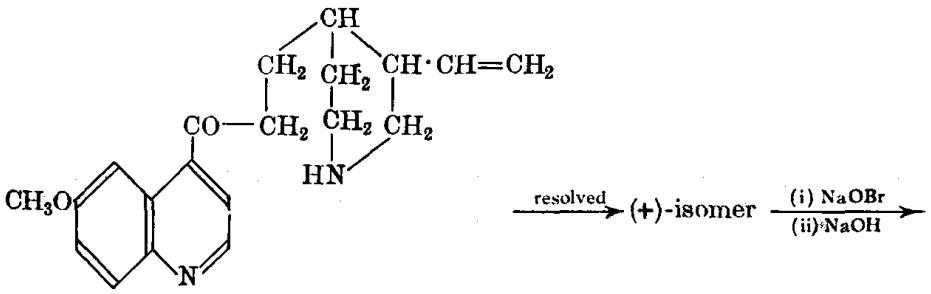
X XI



XII + XI

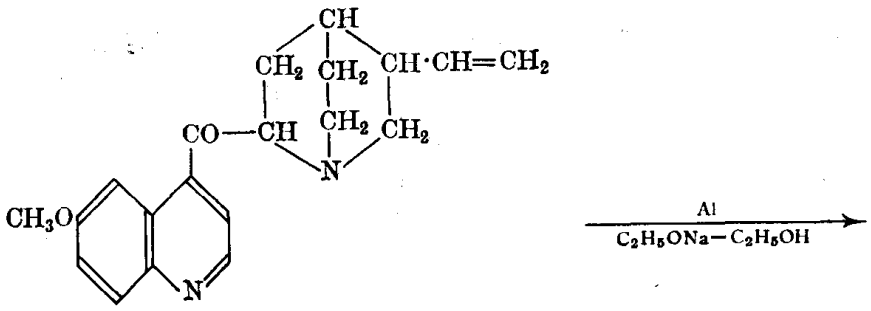


XIII

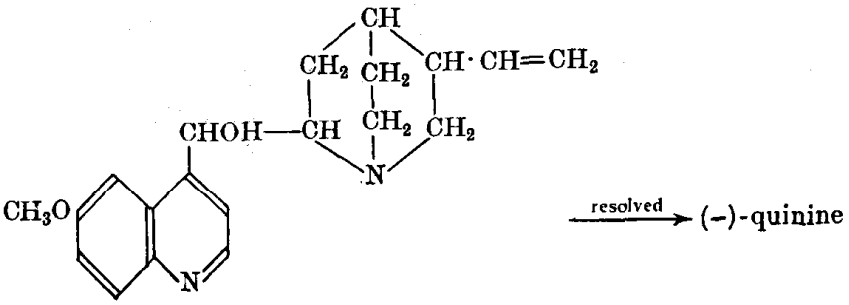


XIV

(±)-quinotoxine



(+)-quininone



(±)-quinine