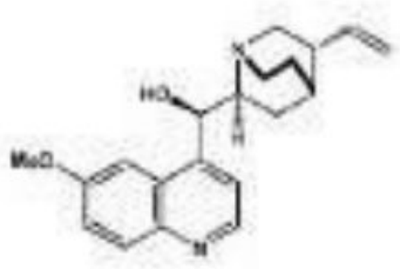
Quinine

Powdered dried bark of the cinchona tree, a native of South America, was made into a drink and used by the Quechua Indians of Peru to treat fevers.

"Discovered" by Jesuit priests in the 1620s, Barnabé de Cobo takes cinchona bark to Europe in 1632 to treat malaria.

Quinine isolated in 1820 by Pierre Joseph Pelletier and Joseph Caventou



First Total Synthesis (1943) RB Woodward and WE von Doering

108

QUININE

Quinine belongs to the quinoline group of alkaloids and is known as a cinchona alkaloid. It has long been used medicinally as an antimalarial. Its structure is established as follows :

(*i*) Its molecular formula is $C_{20}H_{24}O_2N_2$ (m.p. 177°).

(*ii*) Both the nitrogens are tertiary, since quinine adds on two molecules of methyl iodide to form a diquaternary salt, $C_{20}H_{24}O_2N_2.2CH_3I$.

(*iii*) It has one hydroxy group, since it forms monoacetate and monobenzoate. Quinine on oxidation with chromium trioxide gives a ketone, quinone $C_{20}H_{22}N_2O_2$, so the hydroxy group is secondary. It also contains one methoxy group.

(*iv*) It has one ethylenic double bond, since quinine adds on one molecule of hydrogen, bromine or halogen acid. Further, the ethylenic double bond is present as vinyl group, since quinine on oxidation, gives a monocarboxylic acid and formic acid (Scheme 2.29).

$$\underset{\text{Quinine}}{C_{19}H_{21}O_2N_2[-CH=CH_2]} \xrightarrow[KMnO_4]{[O]} \underset{\text{Monocarboxylic acid}}{C_{19}H_{21}O_2N_2[-COOH]} + \underset{\text{Formic acid}}{HCOOH}$$

(Scheme 2.29)

(*v*) Vigorous oxidation of quinine with chromic acid gives quininic acid $C_{11}H_9NO_3$ and a compound, designated as the 'second half', and called meroquinene, $C_9H_{15}NO_2$ (Scheme 2.30).

$$\underset{\text{Quinine}}{C_{20}H_{24}O_2N_2} \xrightarrow[CrO_3]{[O]} \underset{\text{Quininic acid}}{C_{11}H_9NO_3} + \underset{\text{Meroquinene}}{C_9H_{15}NO_2}$$

(Scheme 2.30)

109

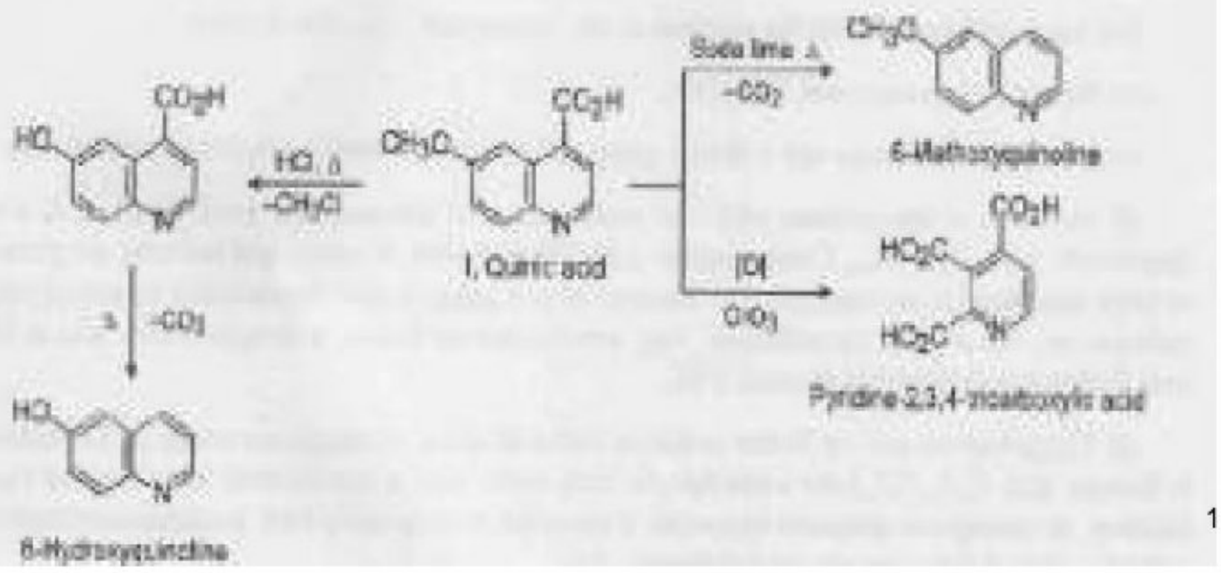
Thus the structure of quinine depends on the structure of quininic acid and meroquinene.

(vi) Structure of cuininic acid $C_{10}H_9NO_3$ is established as follows.

(a) Quininic acid on heating with soda lime undergoes decarboxylation to a methoxyquinoline, identified as 6-methoxyquinoline. Thus, quininic acid has a quinoline nucleus.

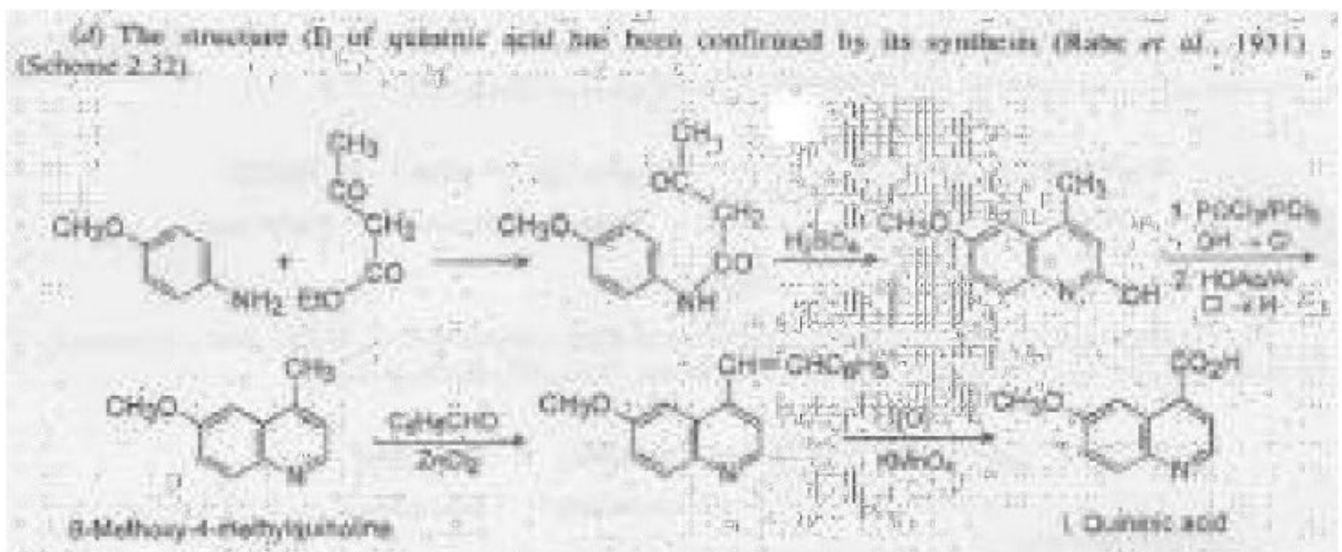
(b) Oxidation of quininic acid with chromic acid gives pyridine 2, 3, 4-tricarboxylic acid. This shows the presence of methoxy group in benzene ring (of quinoline) and carbonyl group at position-4.

(c) Quininic acid on heating with hydrochloric acid undergoes demethylation and decarboxylation to give 5-hydroxyquinoline, a known product. Thus quininic acid is 6-methoxycinchoninic acid (I)



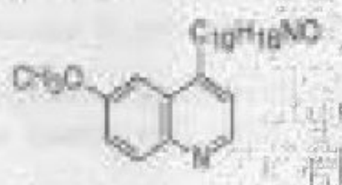
110

(d) The structure (I) of quininic acid has been confirmed by its synthesis (Rabe *et al.*, 1931) (Scheme 2.32).



In the above synthesis the direct oxidation of methyl group of 6-methoxy-4-methylquinoline to quinonic acid (I) is extremely difficult (direct oxidation of methyl group is accompanied by the oxidation of the benzene ring to give pyridine-2,3,4-tricarboxylic acid).

On the basis of above, quinine may be represented by its partial structure as



Partial structure of Quinine

111

The main problem is to find the structure of the 'second half', *i.e.*, meroquinene.

(*vii*) Structure of meroquinene, $C_9H_{15}NO_2$.

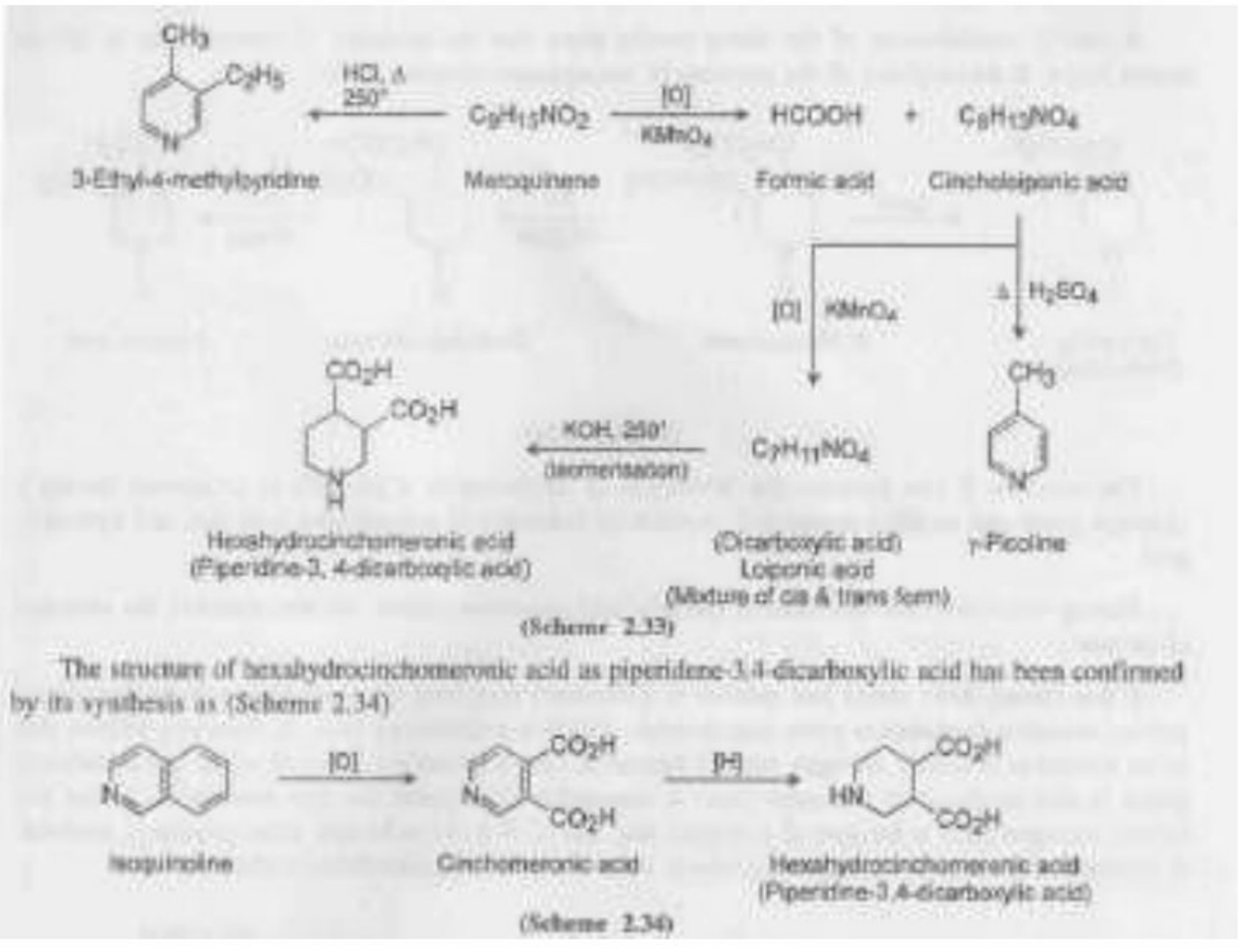
(*a*) Meroquinene contains one carboxyl group and one double bond as shown by routine tests.

(*b*) Oxidation of meroquinene with cold acidic potassium permanganate gives formic acid, and a dicarboxylic acid, $C_8H_{13}NO_4$, Cincholoiponic acid. The formation of formic acid indicates the presence of vinyl side chain in meroquinene. The presence of this group is also demonstrated by ozonolysis of meroquinene, which gives formaldehyde. Also meroquinene on heating with hydrochloric acid at 240° gave 3-ethyl-4-methylpyridine (Scheme 2.33).

(*c*) Cincholoiponic acid on further oxidation with cold acidic permanganate results in the formation of loiponic acid, $C_7H_{11}NO_4$ (also a dicarboxylic acid) which exist in two isomeric forms (cis and trans). However, on heating with potassium hydroxide, it isomerises to more stable form, hexahydrocinchomeronic acid (piperidene-3,4-dicarboxylic acid) (Scheme 2.33).

Loiponic acid or its isomerised product contains one methylene less than its precursor, cincholoiponic acid. This suggests that the later contains a side chain $-CH_2CO_2H$.

(*d*) Furthermore, cincholoiponic acid on treatment with concentrated sulphuric acid gives γ-picoline. This suggests that the additional $-CH_3$ group is present at position 4 in cincholoiponic acid (Scheme 2.33).

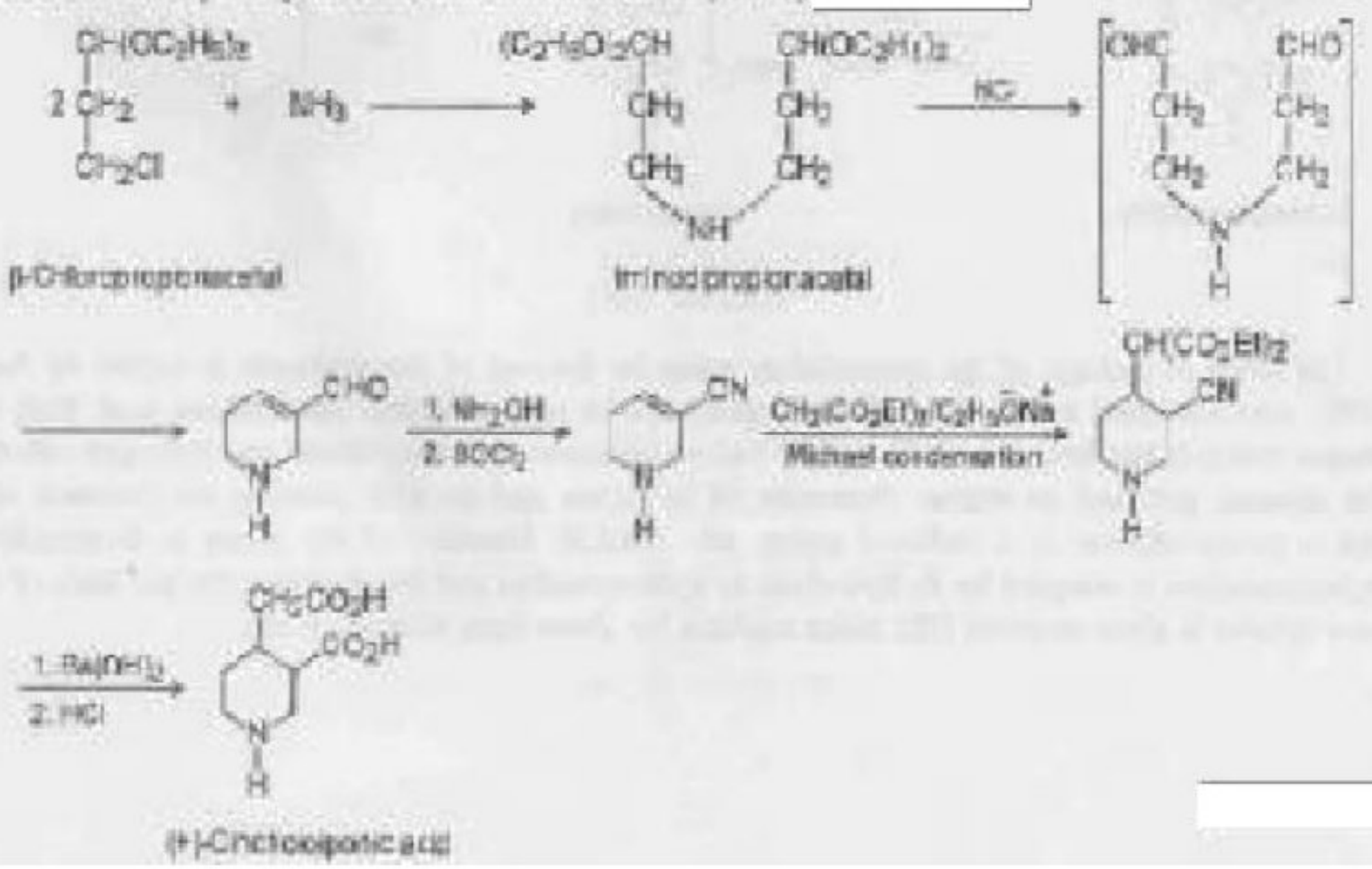


(Scheme 2.33)

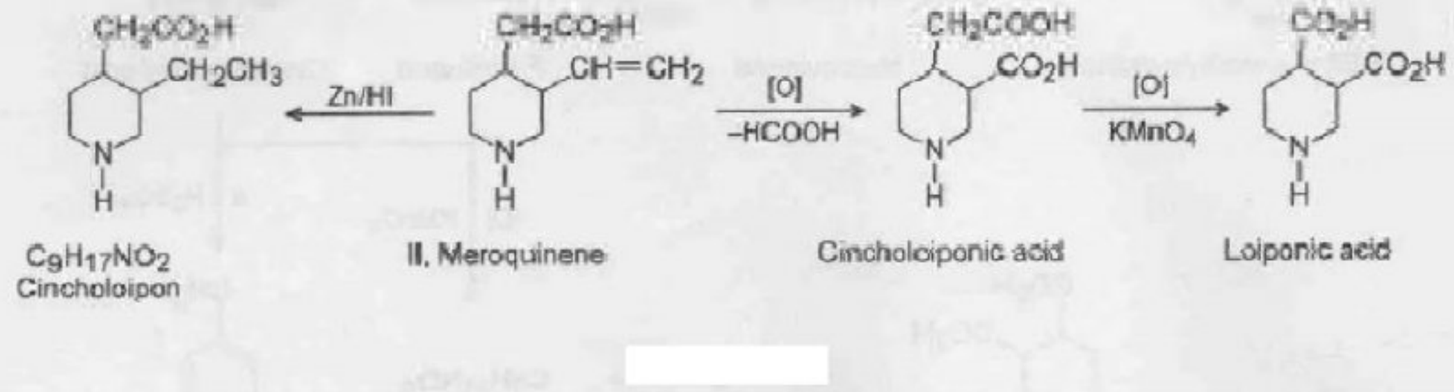
The structure of hexahydrocinchomeronic acid as piperidene-3,4-dicarboxylic acid has been confirmed by its synthesis as (Scheme 2.34)

(Scheme 2.34)

Or the basis of the above cincholoiponic acid is represented as shown below. This structure has been confirmed by its synthesis (Wolf and Lasmisoh; 1970)



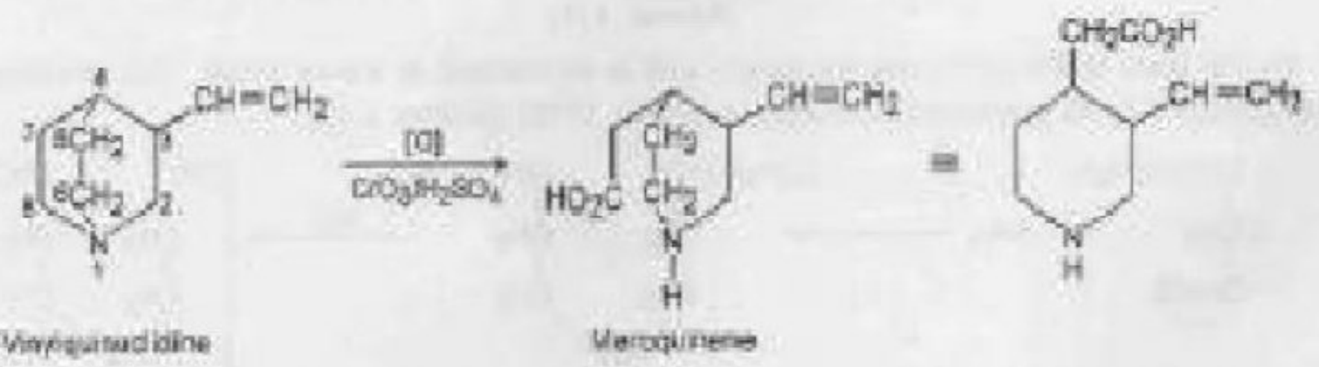
A careful consideration of the above results show that the structure of meroquinene is (II) as shown below. It also explains all the reactions of meroquinene



The structure II also explains the formation of cincholoipon, $C_9H_{17}NO_2$ (a compound having a carboxyl group and an ethyl group) and obtained by reduction of meroquinene with zinc and hydriodic acid.

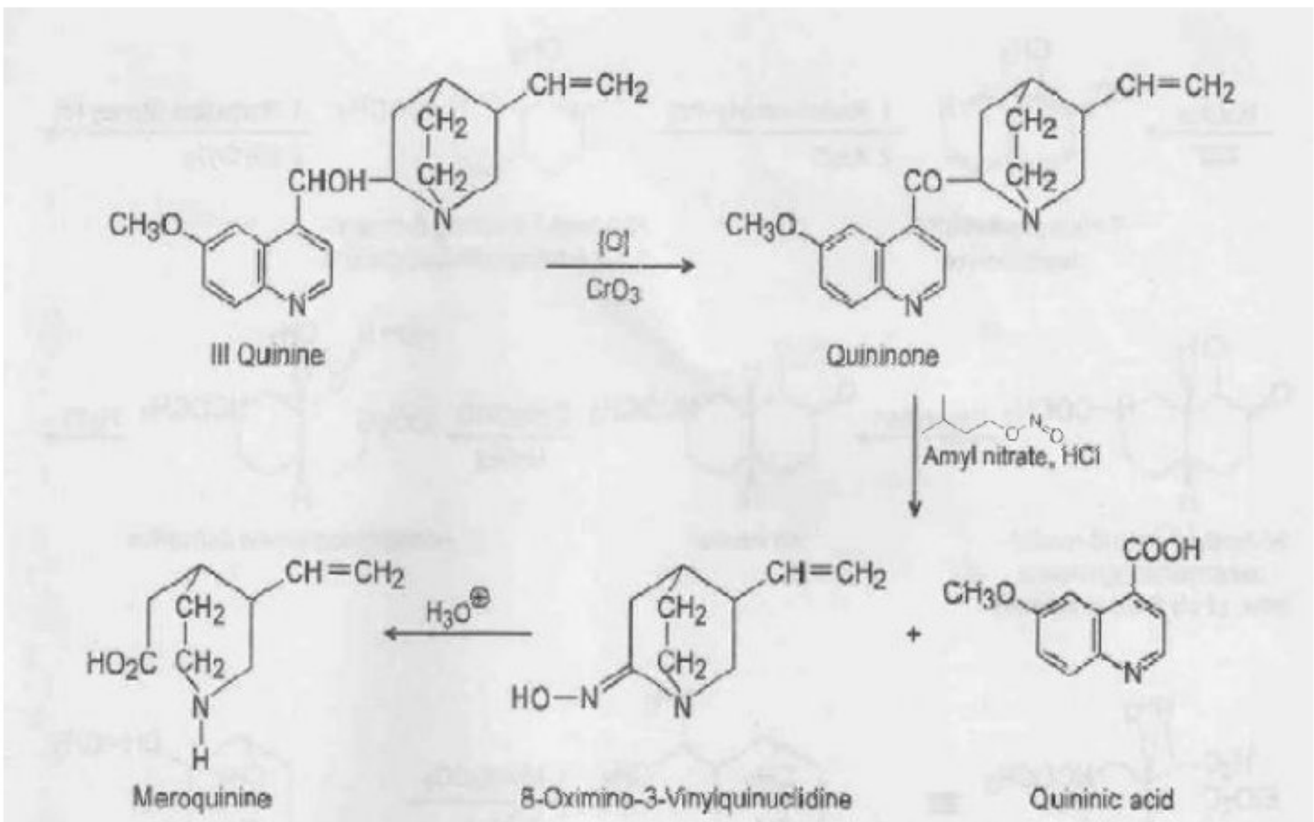
Having established the structures of quininic acid and meroquinene, we now establish the structure of quinine.

It has already been stated that quinine is a ditertiary base (and does not have a N-methyl group) and on oxidative degradation gives meroquinene, which is a secondary base. It, therefore follows that in its formation a tertiary nitrogen atom is converted into a secondary nitrogen atom, and a carboxyl group is also produced at the same time. A reasonable explanation for this observation is that the tertiary nitrogen atom is the part of a bridged ring, one C–N bond is broken when quinine is oxidised. A junction of this type is shown in a synthetic compound, 3-vinylquinuclidine



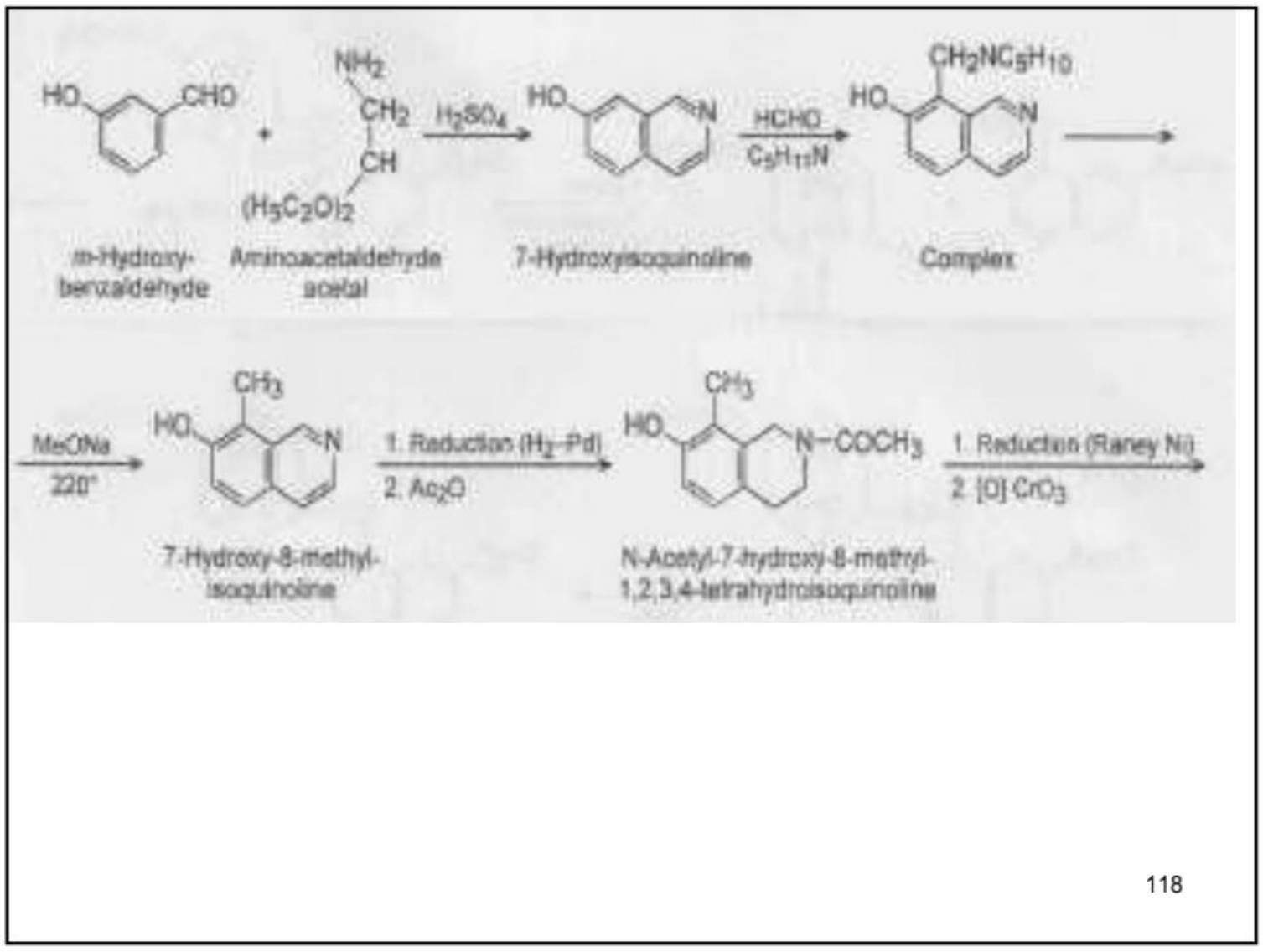
The point of linkage of the quinuclidine group to the rest of the molecule is settled by Rabe (1908), who converted quinine into a ketone, quininone by mild oxidation with chromic acid. Both the nitrogen atoms in this ketone are still tertiary and on treatment with amyl nitrite and hydrogen chloride gave quininic acid and an oxime. Formation of an oxime and an acid indicates the presence of a methine group adjacent to a carbonyl group, viz. –COCH. Structure of the oxime as 8-oximino-3-vinylquinuclidine is assigned by its hydrolysis to hydroxylamine and meroquinene. On the basis of the above quinine is given structure (III) which explains the above facts

116



The structure of quinine as (III) has finally been confirmed by its synthesis. A partial synthesis (Rabe *et al.*, 1918) starts from quinotoxine, which was obtained by heating quinine in acetic acid. Quinotoxine was synthesised by Woodward and Doering (1944). Thus a total synthesis of quinine has been achieved.

117



118