1.13 QUININE

1.13.1 Isolation:

It is obtained from the barks of cinchona bark, contains thirty alkaloids but its antimalarial activity is due to quinine, quinidine, cinchonine and cinchonidine. It is Isolated by crushing the Bark into fine powder . Lime and caustic soda is added and extracted with petroleum ether. IT is then washed with dilute sulphuric acid and allowed to stand for several hours where the mixture of sulphates is recrystallized with quinine sulphate having maximum solubility. It is obtained by precipitation with alkali, washing and drying.

1.13.2 Constitution of Quinine:

Elemental analysis shows the molecular formula of the compound is $C_{20}H_{24}N_2O_2$.

Presence of two tertiary nitrogen atoms:

Quinine adds two molecules of methyl iodide to form a diquaternary salt, it is a ditertiary base.

$$C_{20}H_{24}N_2O_2 + 2CH_3I \longrightarrow C_{20}H_{24}N_2O_2.2CH_3I$$

Presence of **olefinic linkage:**

Quinine adds one molecule of bromine and absorbs one molecule of hydrogen in the presence of a catalyst indicating the presence of one ethylenic bond.

$$CH(Br)-CH(Br) \xleftarrow{Br_2} CH=CH \xrightarrow{H_2} CH_2-CH_2$$

Presence of **secondary alcoholic group:**

Quinine forms monoacetate and monobenzoate indicates that it must contain one –OH group. Quinine on oxidation gives ketone, quininone.

$$\underset{\text{Quinine}}{C_{20}H_{24}N_2O_2} \xrightarrow{CrO_3} \underset{\text{Quininone}}{C_{20}H_{22}N_2O_2}$$

Presence of **methoxyl group:**

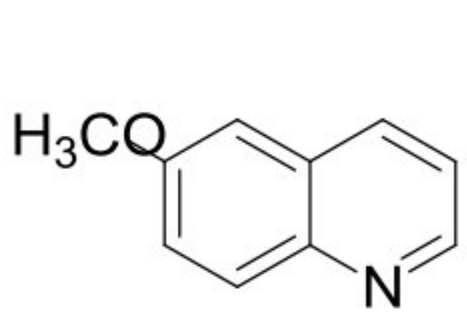
Quinine on heated with HCl, it eliminates as methyl chloride indicating the methoxyl group in quinine.

$$OCH_3 + HCl \xrightarrow{\triangle} CH_3Cl + OH$$

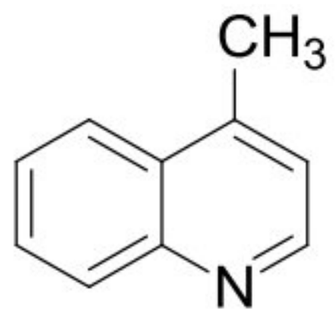
Presence of a **vinyl group:** On controlled oxidation with $KMnO_4$ it yields a monocarboxylic acid and formic acid which reveals the presence of vinyl group.

Presence of **quinoline group:**

Quinine on fusion with concentrated KOH, it yields a mixture of 6-methoxy quinoline and lepidine, indicating that quinoline nucleus is present in quinine.



6-methoxy quinoline



Lepidine

Presence of **meroquinone:**

Oxidation of quinine with chromic acid produces quininic acid.

$$C_{20}H_{24}N_2O_2 \xrightarrow{CrO_3} C_{11}H_9NO_3 + \text{Other Products}$$

Quinine — Quininic acid

$$C_{20}H_{24}N_2O_2 \xrightarrow{CrO_3} C_{11}H_9NO_3 + C_9H_{15}NO_2$$

Quinine — Quininic acid — Meroquinene

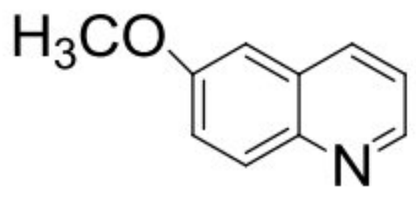
Controlled oxidation of quinine gives quininic acid and meroquinene.

a) Structure of quininic acid:

Molecular formula is $C_{11}H_9NO_3$

When quininic acid is heated with sodalime it undergoes decarboxylation yielding methoxyquinoline.

$C_{11}H_9NO_3$ (Quininic acid) $\xrightarrow{\text{sodalime}}$

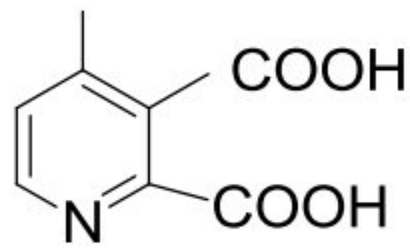


6-Methoxy quinoline

When quininic acid is oxidised with chromic acid it yields pyridine 2,3,4 tricarboxylic acid indicating that the methoxyl group is a substituent in the benzene ring of quinoline and COOH is at position 4.

Reaction:

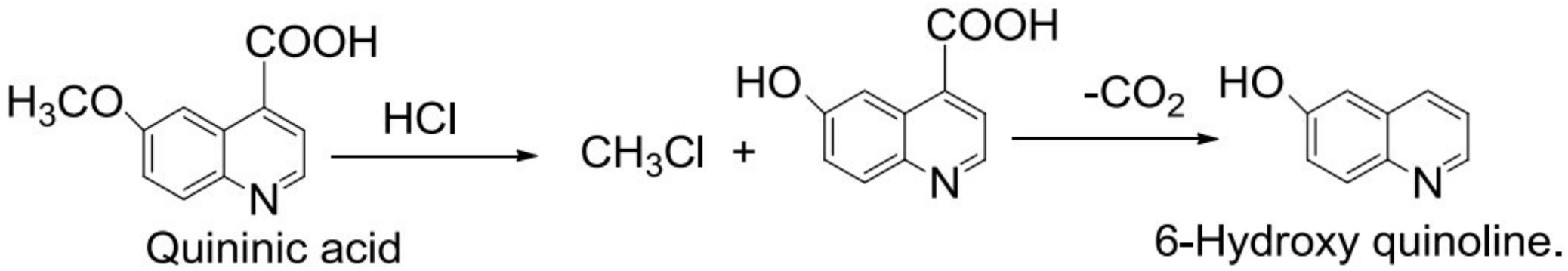
$C_{11}H_9NO_3$ (Quininic acid) $\xrightarrow{CrO_3}$



Pyridine 2,3,4-tricarboxylic acids

To ascertain the position of methoxy group , quininc acid is heated with HCl to yield demethylated product which on decarboxylation yields 6-hydroxy quinoline.

Reactions:

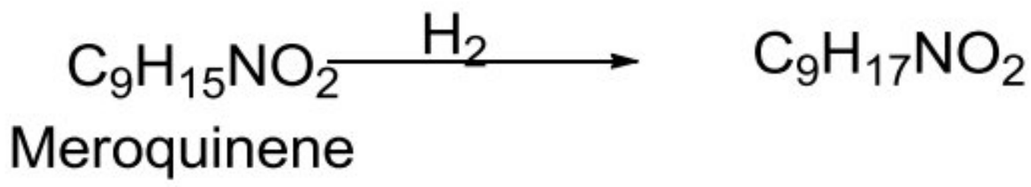


b) Structure of Meroquinene:

Molecular formula of Meroquinene is $C_9H_{15}NO_2$.

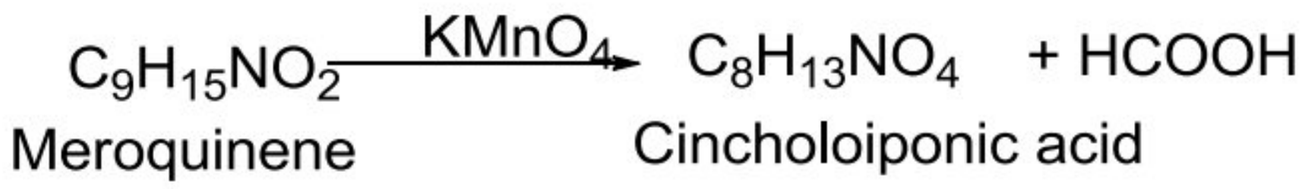
It forms monosodium salt as well as ester it represents the presence of –COOH group.

Merquinene is reduced with hydrogen suggesting the presence of one ethylenic bond, indicates the presence of side chain in the molecule.



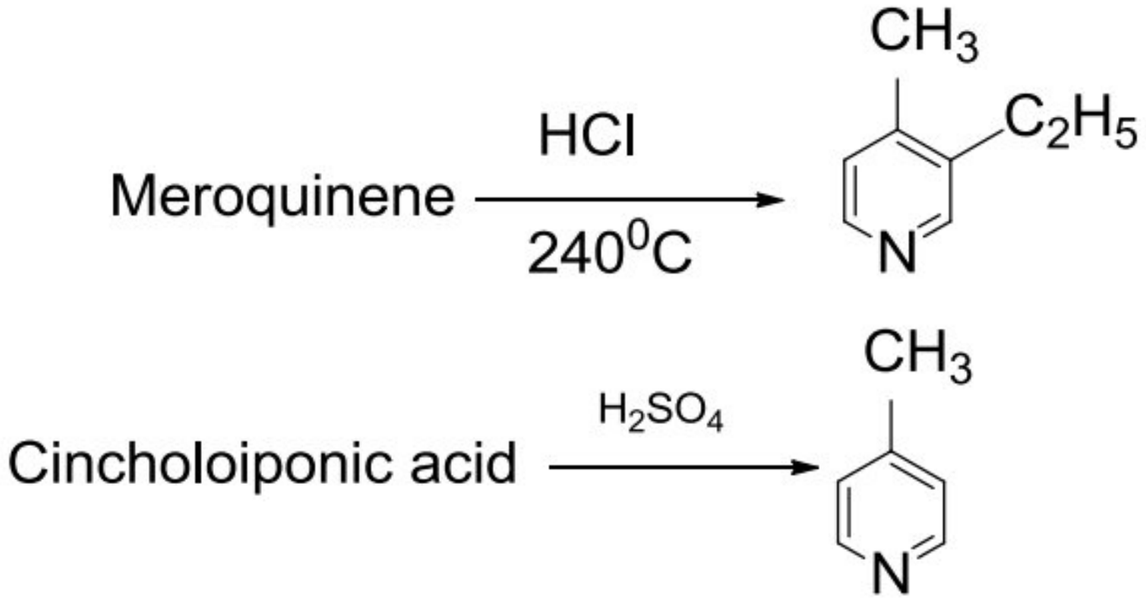
Meroquinene is benzoylated, acetylated and nitosated indicating the presence of secondary amino group .

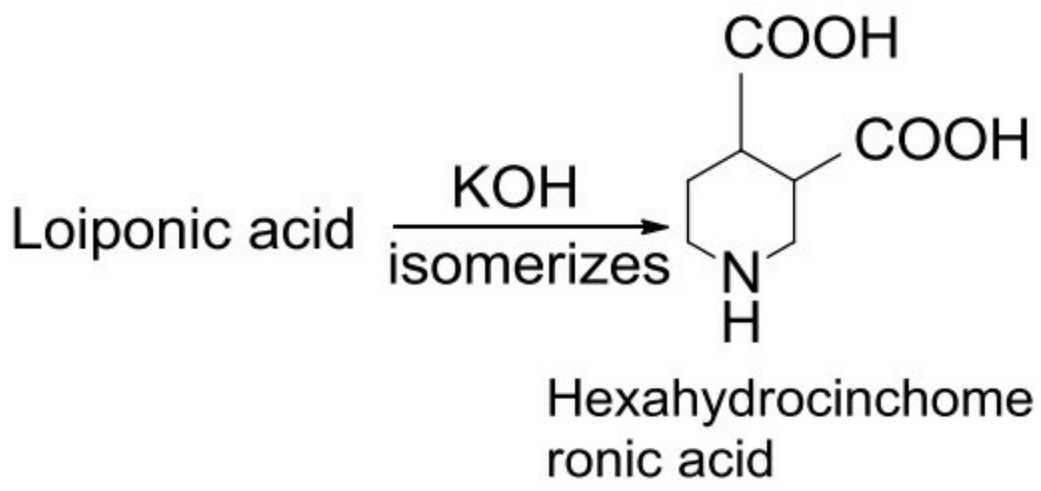
Meroquinene is oxidised with acidified $KMnO_4$, it yields a cincholoiponic acid and formic acid., indicates the presence of $–CH=CH_2$ group in the side chain.



When cincholoiponic acid is oxidised with acid $KMnO_4$ it yields loiponic acid, $C_7H_{11}NO_4$. It is a carboxylic acid with a methylene group indicate that cincholoiponic acid contains $–CH_2COOH$.

The three acids reveals the presence of a piperidine ring as shown by the following reactions.



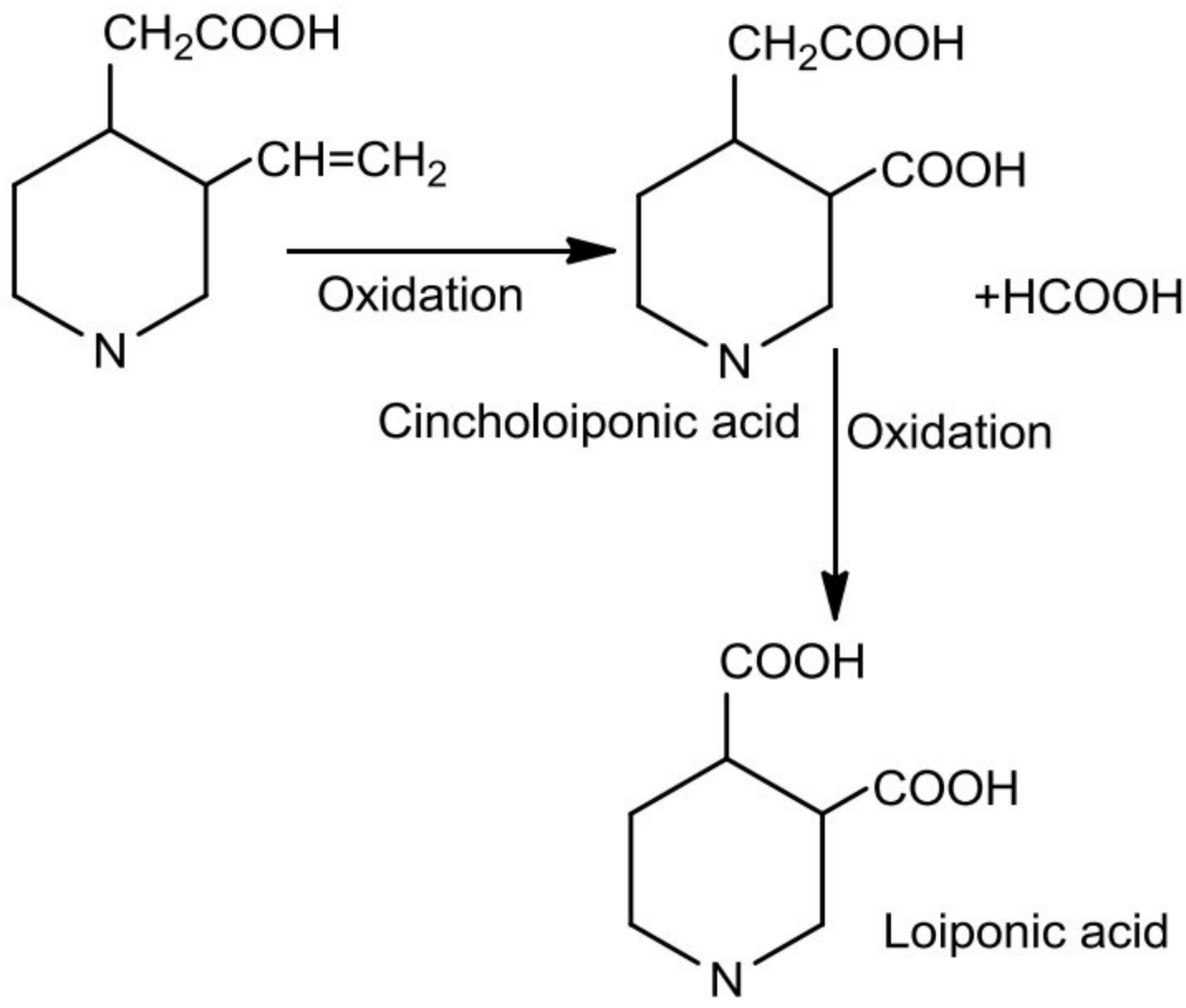


Thus the skeleton of meroquinine will be,

The position of remaining carbon can be at any one of the three positions,

1.As N- methyl group- since all the three acids are secondary bases it is been ruled out.

Since meroquinine contains a side chain of $-CH=CH_2$, the possibility of one carbon in the side chain will leads to the presence of allyl group. This allyl group would result in propyl group not an ethyl group. Carbon can be attached to COOH at 4 position. The reactions of meroquinine can be explained by this structure.

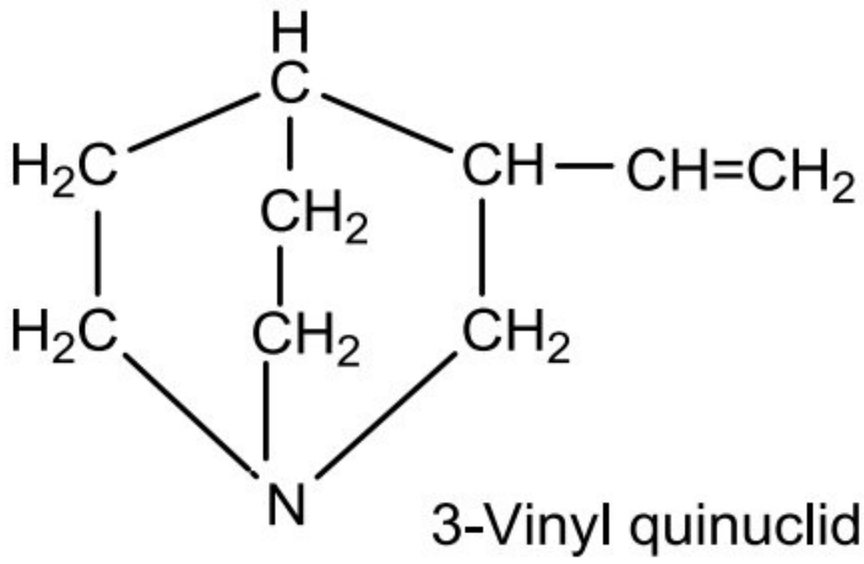


c) Point of linking between quininic acid and meroquinine:

In quinine molecule, the carboxylic groups are not present. Quininic acid and meroquinine contains free carboxylic acid group indicating that the two fragments are linked through this –COOH group.

Quinine is a di tertiary base while meroquinine is a secondary base indicating that the tertiary nitrogen is converted to –NH and at the same time –COOH group is produced. It is possible only when the nitrogen is in a condensed ring system.

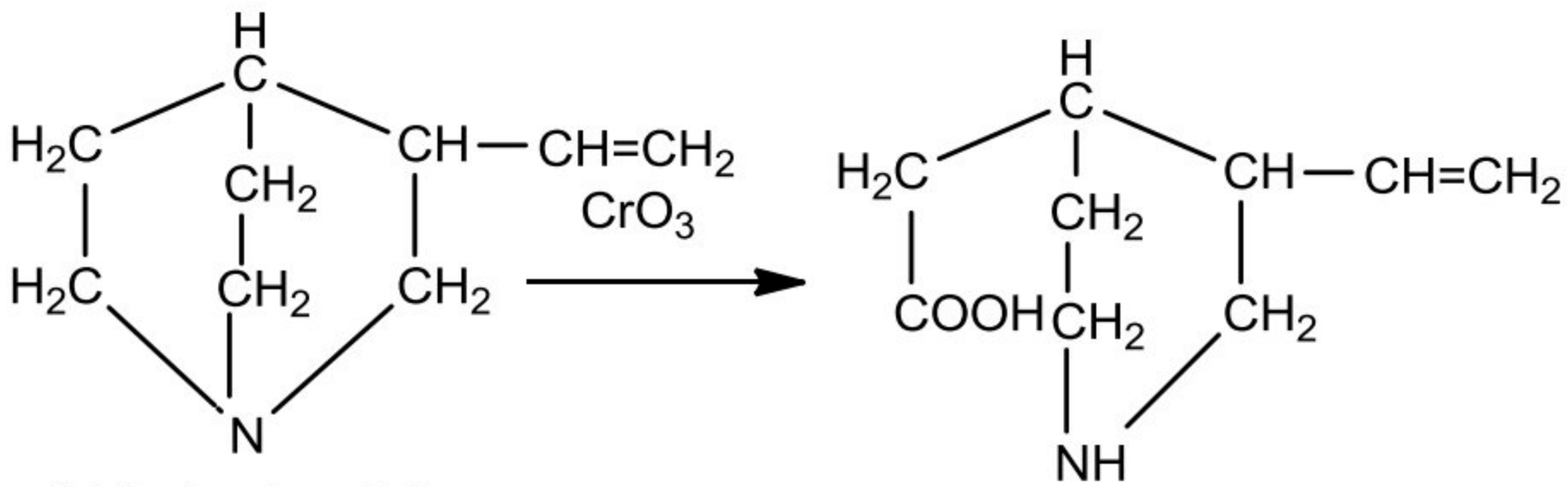
A possible structure could be:



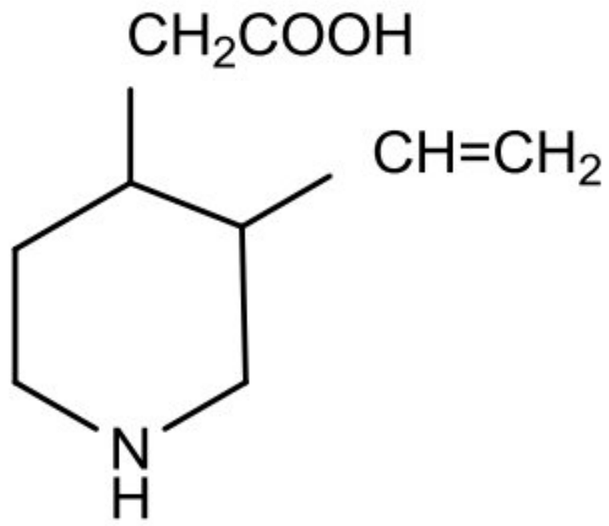
3-Vinyl quinuclidine

When 3-Vinyl quinuclidine is oxidised with CrO_3 one C-N bond is cleaved thus producing an secondary nitrogen and a COOH group.

Reaction:



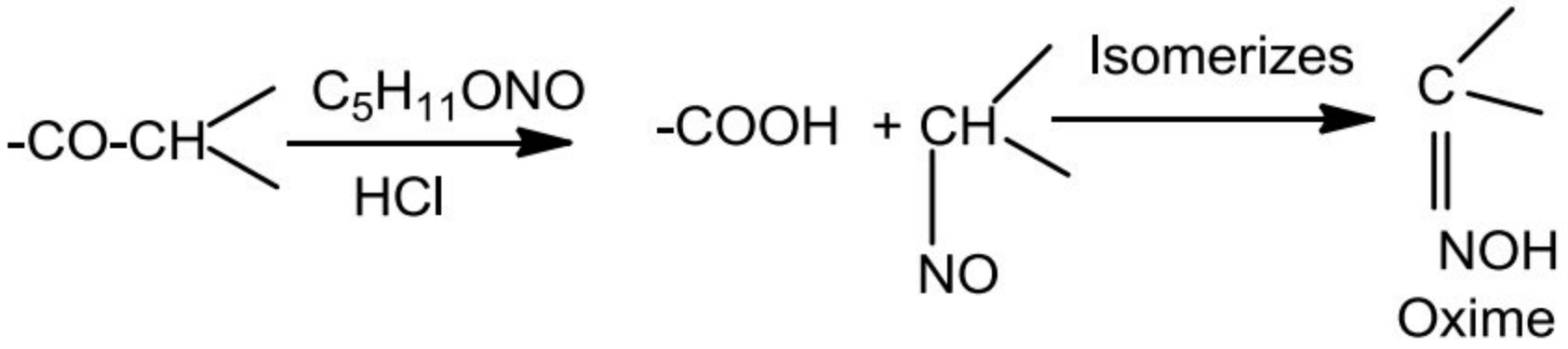
Structure of Meroquinine:



In quinine molecule, the quinoline fraction is joined at position 4 to the quinuclidine at position-8.

d) Position of secondary alcoholic group:

Quinine is oxidised to quninone, on treating with amyl nitrite and HCl yields quininic acid and an oxime. The formation of acid and an oxime reveals the presence of –COCH- (ie a methylene group is adjacent to carbonyl group).



The above reaction is ascertained by its hydrolysis to meroquinine and hydroxyl amine. It follows that both quinoline and quinuclidine units are linked by –CHOH groups.

Thus the **structure of quinine is,**