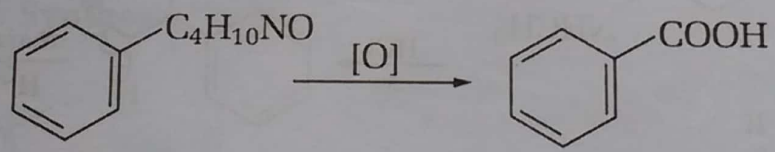
H

(±)-Coniine

4.5 EPHEDRINE

Ephedrine is an important constituent of genus Ephedra, alongwith five other structurally related alkaloids, namely norephedrine, ψ-ephedrine, Nor-ψ-ephedrine, methylephedrine and methyl ψ-ephedrine. It is considered one of the most important constituent of Chinese drug, Ma Huang. It raises blood pressure thus acting as a powerful stimulant which can be taken orally. It has been also used for the treatment of bronchial asthma, hey fever and to stop haemorrhage locally.

Ephedrine is a laeveortatory ($[\alpha]_D = -6.3°$), low melting white solid, m.p. 38°C. It was first isolated from ephedra in 1887 by Nagai *et. al.* It was found to have molecular formula $C_{10}H_{15}NO$ which gives DBE as 4. Oxidation of ephedrine with chromic acid yields benzoic acid indicating ephedrine to be a benzene derivative.

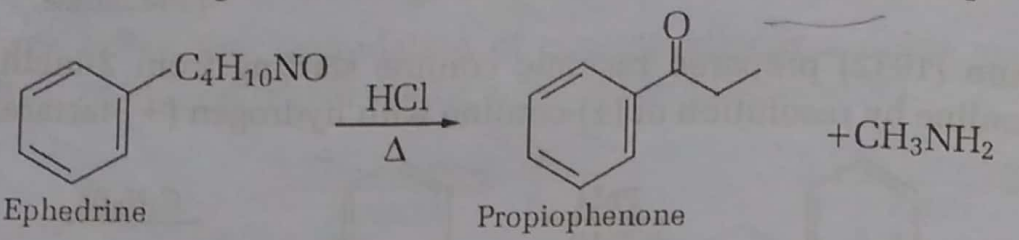


Ephedrine — Benzoic acid

Ephedrine was found to be a secondary amine having a secondary hydroxyl group. It forms a nitroso derivative when treated with nitrous acid and when heated with hydriodic acid at 150°C produces one molecule of methyl iodide showing that it has a $-NHCH_3$ group. Ephedrine forms a dibenzoyl derivative with benzoyl chloride which suggests that a hydroxyl group must be present in ephedrine (Benzoylation of $—NH–CH_3$ group also

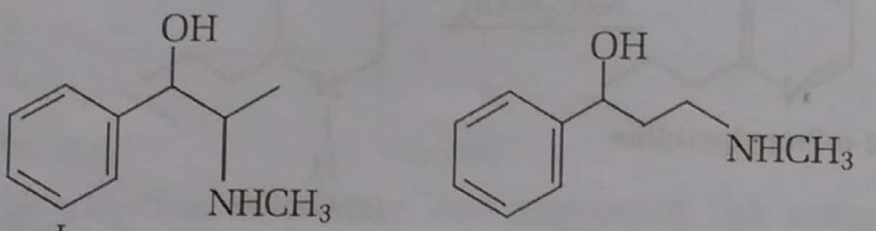
takes place). The nature of hydroxyl group was found to be secondary by its oxidation to a ketone.

The position of hydroxyl group in ephedrine was confirmed by heating it with concentrated hydrochloric acid, which yielded propiophenone and methylamine. The formation of methylamine again confirms the presence of —$NHCH_3$ group.



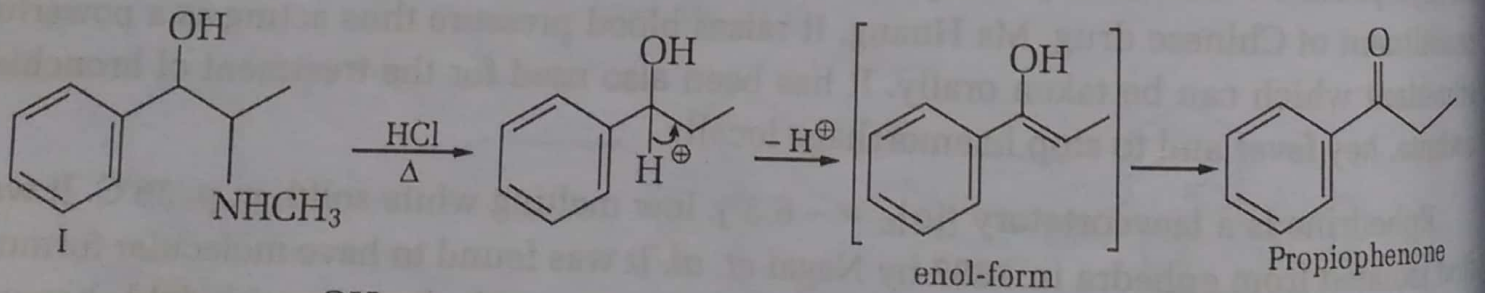
Ephedrine Propiophenone

The formation of propiophenone can be explained by following two structures, which have hydroxyl group at benzylic position and differ only in the position of —$NHCH_3$ group.

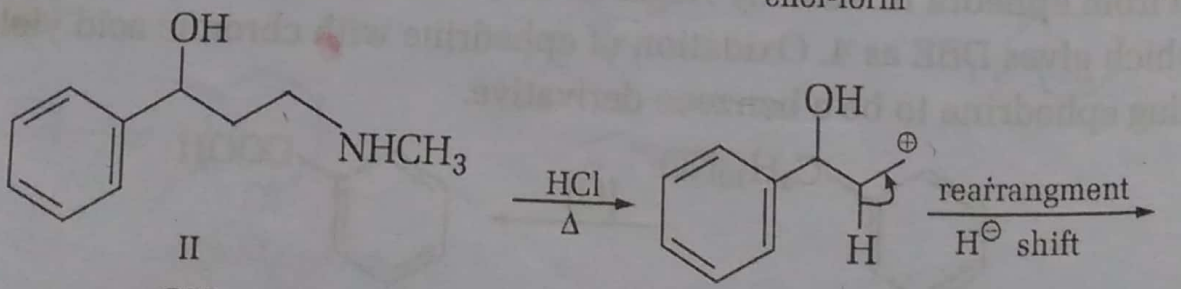


I II

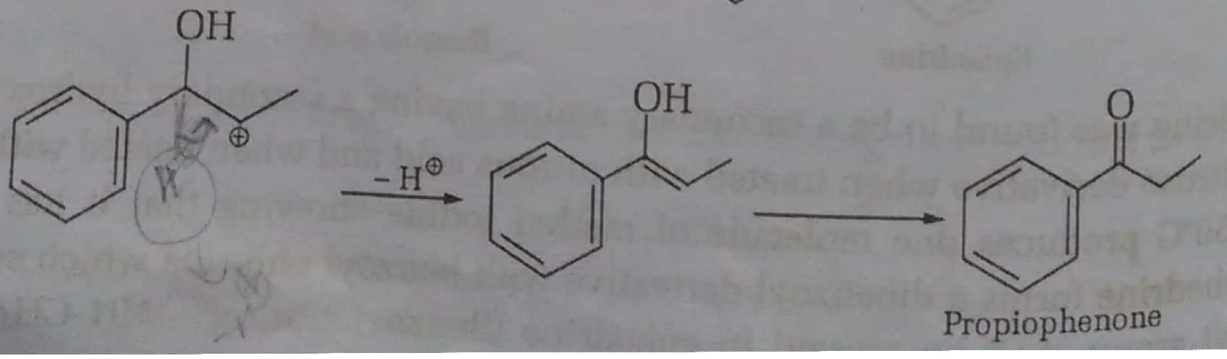
A compound having structure I produced propiophenone and methylamine when heated with hydrochloric acid which indicated that ephedrine may have structure I but since formation of propiophenone can also be explained from structure II, the assignment needed more evidence.



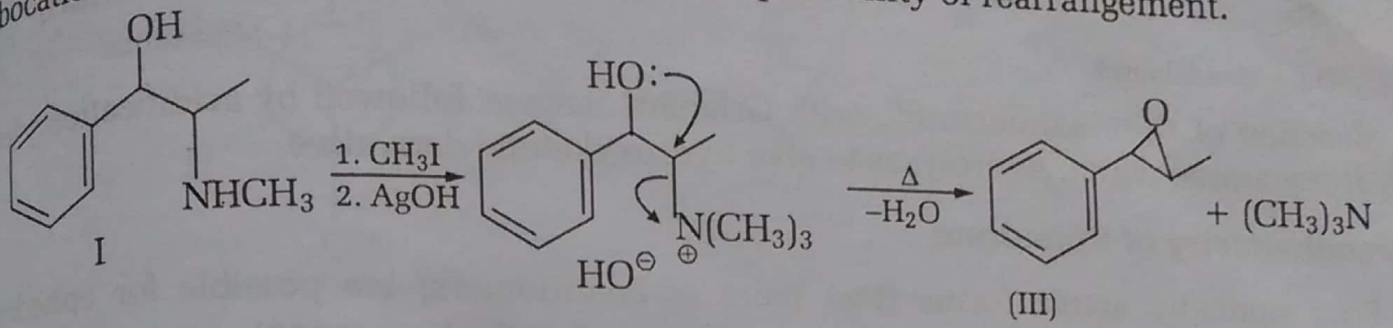
I



II



Evidence in support of the assignment was provided by Hofmann exhaustive methylation of ephedrine which yielded epoxide (III), which can only be expected from structure I. It must be noted that propiophenone was not obtained which means that carbocation is not an intermediate ruling out the possibility of rearrangement.



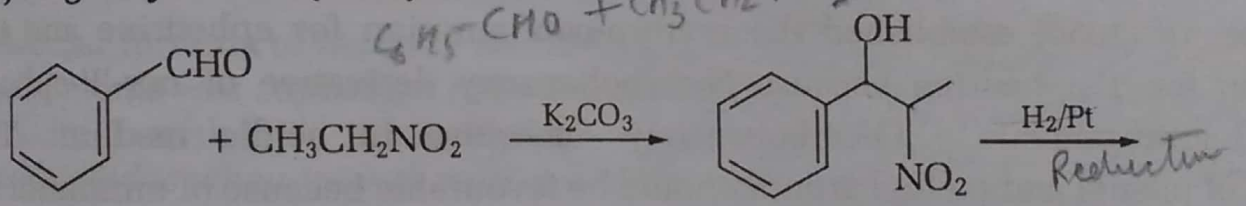
(III)

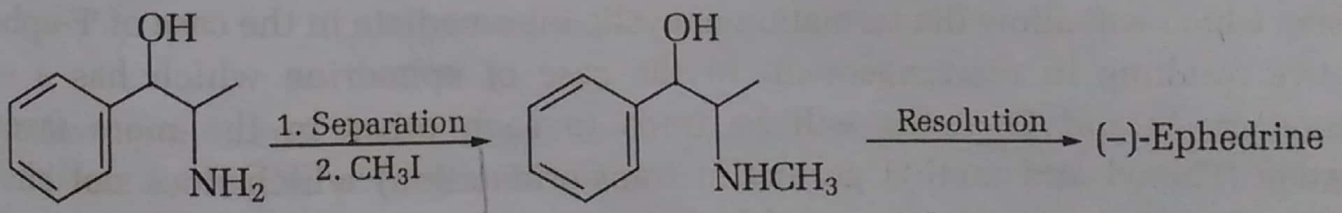
The above assignment is also supported by optical activity of ephedrine. Structure I has two chiral carbon atoms and replacement of hydroxyl with H atom should still give an optically active amine. Deoxyephedrine formed by replacement of hydroxyl group with H atom was found optically active confirming the structure of ephedrine as I.

Synthesis of Ephedrine

The structure of ephedrine was confirmed by synthesis. Few of several syntheses of (I) and (–)-ephedrine are given. The racemic mixture of ephedrine was resolved by mandelic acid whenever needed.

(1) Nagai Synthesis (1929).



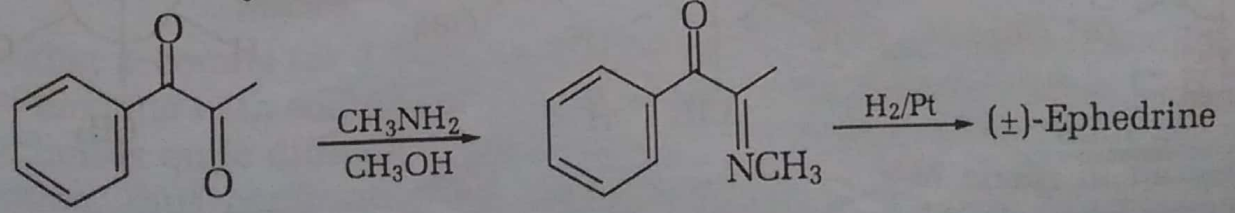


(±)-Ephedine

(±)-norephedrine

(±)-nor-ψ-ephedrine

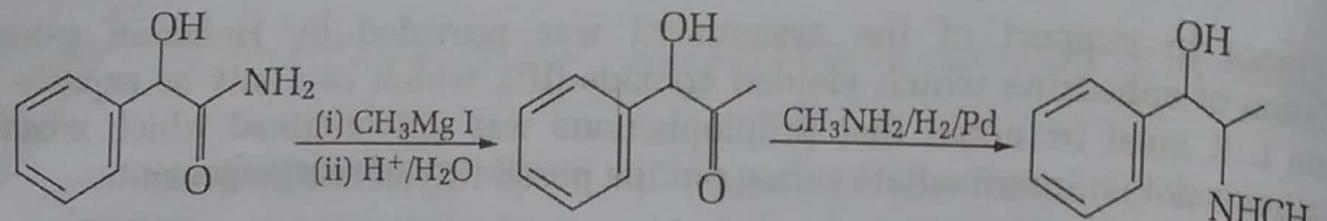
(2) Manske *et. al.* Synthesis (1929)



Phenylpropane-1,2-dione

(3) Freudenberg *et. al.* Synthesis (1932)

This synthesis relates the configuration of carbinol carbon atom to that of D-(–)-mandelic acid.

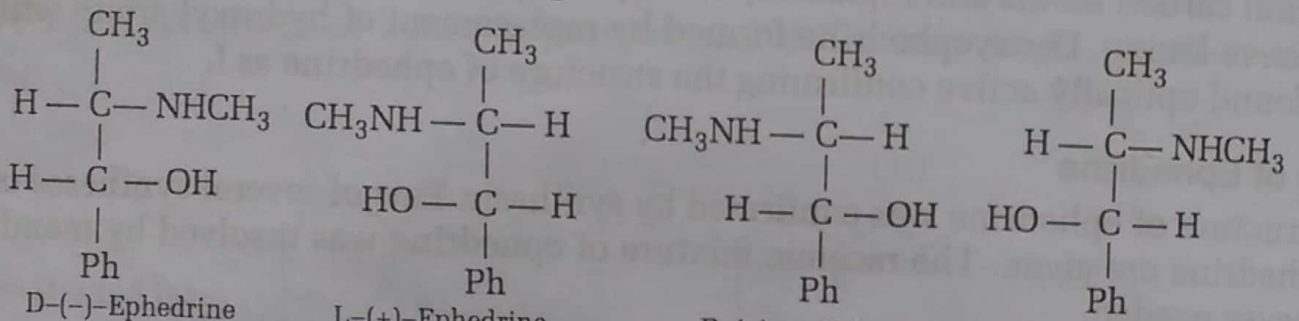


D-(–)-Mandelamide (–)-Ephedrine

Reaction of *D*(–)-mandelamide with Grignard reagent followed by acidification yield a hydroxylamine which hydrolyses to give hydroxyketone derivative.

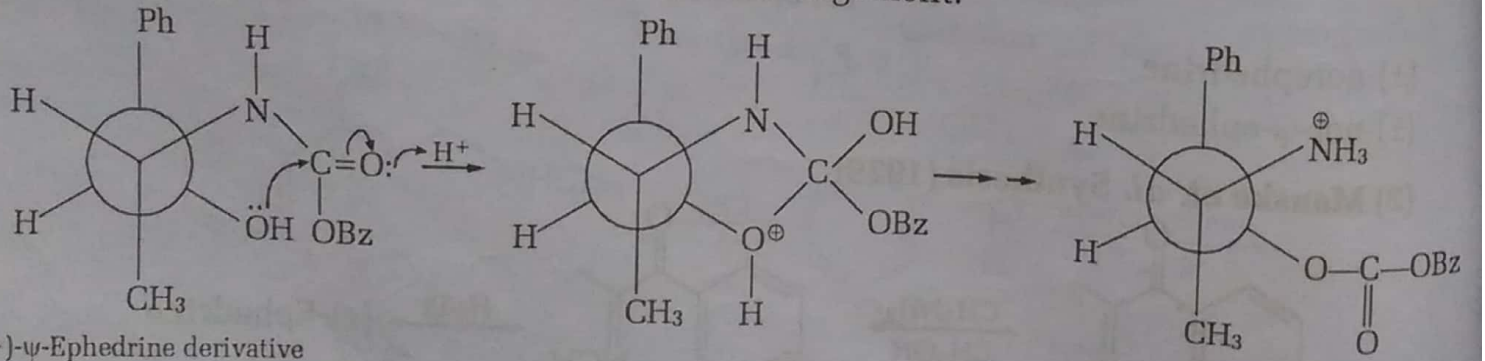
Stereochemistry of Ephedrine

Four optically active forms (two pairs of enantiomers) are possible for ephedrine because it has two dissimilar chiral carbon atoms. Freudenberg (1932) assigned following configurations to ephedrine and Ψ-ephedrine.



D-(–)-Ephedrine L-(+)-Ephedrine D-(–)-ψ-Ephedrine L-(+)-ψ-Ephedrine

Fodor *et. al.* (1950) established the erythro-configuration for ephedrine and threo-configuration for Ψ-ephedrine because N-carbobenzoxy derivative of nor-Ψ-ephedrine undergoes rearrangement to O-carbobenzoxy derivative in acidic medium. Trans-orientations of phenyl and methyl groups should be favourable because of minimum steric repulsion which will allow the formation of cyclic intermediate in the case of Ψ-ephedrine derivative resulting in rearrangement. In the case of ephedrine which has a erythro configuration, N and O atoms will be trans to each other in the more favourable orientation (Phenyl and methyl groups in trans-orientation) which does not allow the formation of cyclic intermediate needed for rearrangement.

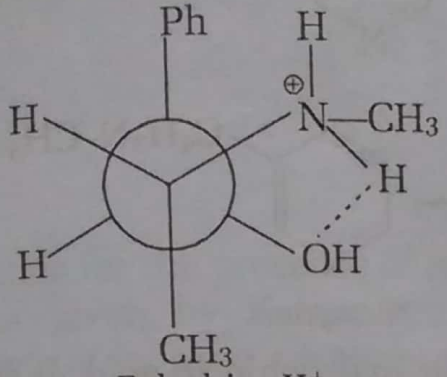


(+)-ψ-Ephedrine derivative

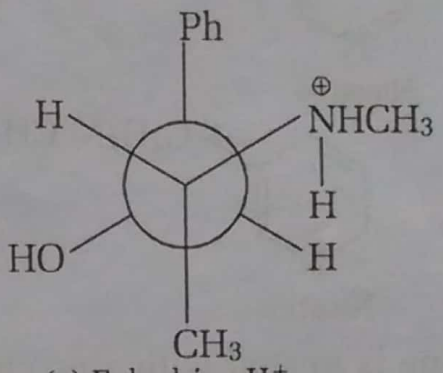
Basicity

ψ-Ephedrine is a stronger base (PK_a 9·22) than ephedrine (PK_a 9·14) which can be explained in terms of stabilities of their conjugate bases. Favourable orientation (phenyl and methyl groups trans-oriented) allows stabilization of conjugate base of ψ-Ephedrine by

intramolecular hydrogen bonding which would be strongly opposed by steric repulsion between phenyl and methyl groups in the case of ephedrine.



(+)-ψ-Ephedrine-H$^+$



(–)-Ephedrine-H$^+$

4.6 NICOTINE

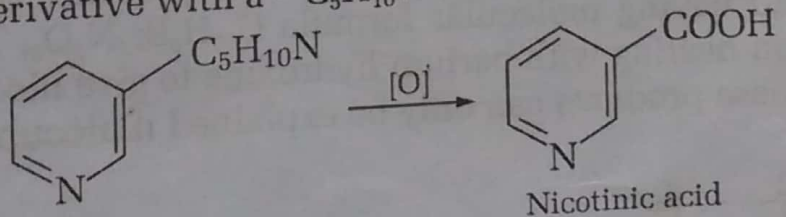
Nicotine is the best known alkaloid found in *nicotiana* species. Tobacco is its commercial source but it also occurs in several flowering (*e.g. sedum acre* L.) and vascular cryptogams (Pteridophyta), *e.g., Equisetum arvense* L. and *Lycopodium clavatum* L.). Though nicotine is distributed throughout the plant, the concentration in leaves is higher. It is highly toxic and increases blood pressure due to constriction of blood vessels.

Nicotine is a colourless, hygroscopic liquid (b.p. 247°C) which is miscible with water. Natural nicotine is laevorotatory ($[\alpha]_D = -169°$) but its salts are dextrorotatory. Physiologically (–)-nicotine is twice as active as (+)-nicotine.

Molecular formula of nicotine was determined to be $C_{10}H_{14}N_2$ (DBE = 5). The nature of both the N atoms was confirmed to be tertiary because nicotine formed a diquaternary salt (dimethiodide) with two molecules of methyl iodide. It also forms two isomeric monomethiodides when treated with one molar equivalent of methyl iodide.

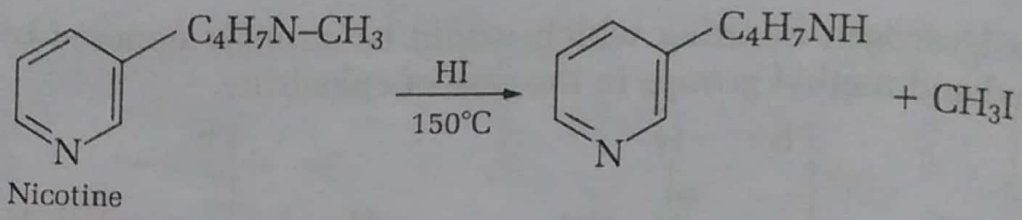
$$\underset{\text{Nicotine}}{C_{10}H_{14}N_2} + 2CH_3I \rightarrow \underset{\text{Dimethiodide of nicotine}}{[C_{10}H_{14}N_2.2CH_3]^{++}\ 2I^-}$$

Oxidation of nicotine with chromic acid gives pyridine-3-carboxylic acid (nicotinic acid) which confirms the presence of pyridine ring in nicotine. Thus, nicotine can be regarded as a pyridine derivative with a $-C_5H_{10}N$ side chain at C-3.

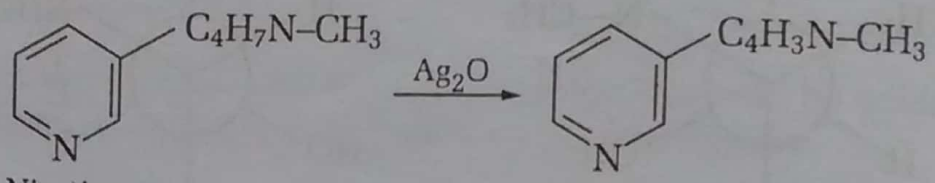


Nicotine Nicotinic acid

Pyridine ring accounts for 4 DBEs so side chain in nicotine must account for 1 DBE. Reduction of nicotine with sodium in alcohol yields a hexahydroderivative, $C_{10}H_{20}N_2$, and further reduction is quite difficult. The conversion of pyridine to piperidine can account for this reaction, thus confirming the saturated nature of side chain in nicotine and, therefore, it must be cyclic. Initially, nicotine was believed to be piperidyl pyridine but was proved incorrect. Heating nicotine with hydriodic acid at 150°C gave methyl iodide confirming the presence of $>N-CH_3$ group. Moreover, oxidation of nicotine with a mild oxidant like silver oxide yielded nicotyrine ($C_{10}H_{10}N_2$). These reactions ruled out the presence of a piperidine ring in nicotine.

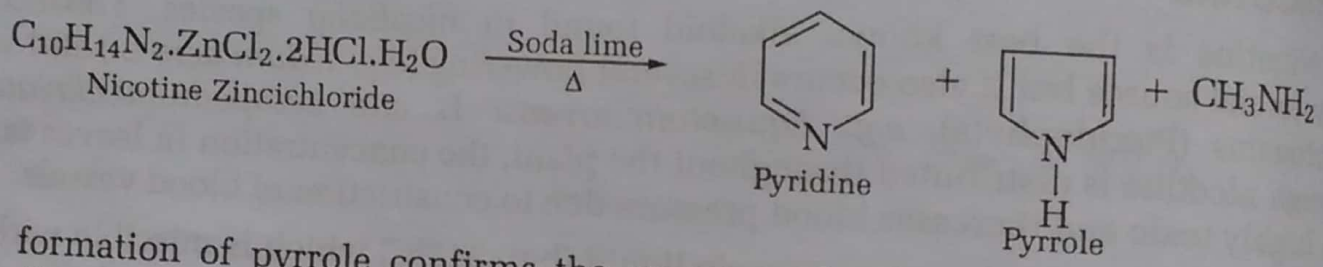


Nicotine



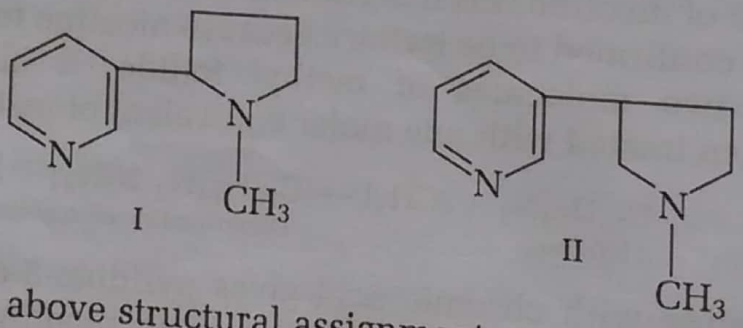
Nicotine Nicotyrine

When nicotine is treated with zinc chloride in hydrochloric acid, it forms an adduct named nicotine zincichloride which on distillation with soda lime decomposes to give pyridine, pyrrole and methylamine.



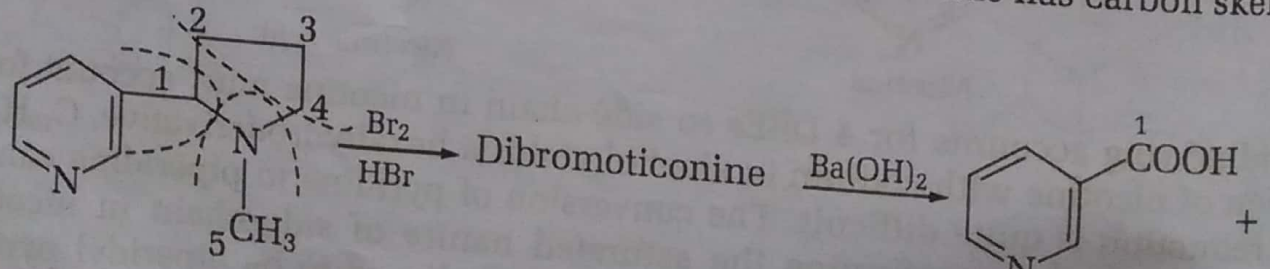
Nicotine Zincichloride Pyridine Pyrrole

The formation of pyrrole confirms the presence of a five membered N-containing heterocyclic ring (pyrrolidine) in nicotine. There are only two positions through which pyrrolidine ring may be attached to pyridine. Of the two probable structures (I and II), nicotine was found to have structure I.

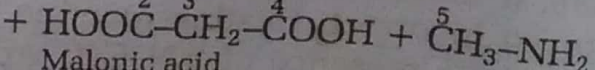


I II

First evidence for the above structural assignment was provided by Pinner (1893). He studied the reaction of nicotine with bromine in the presence of hydrobromic acid and obtained a compound having molecular formula $C_{10}H_8Br_2N_2O_2$, named dibromoticonine which decomposed on heating with barium hydroxide to give nicotinic acid, malonic acid and methylamine. These products can only be explained if nicotine has carbon skeleton of structure I.

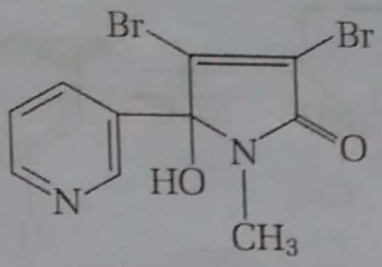


Nicotinic acid



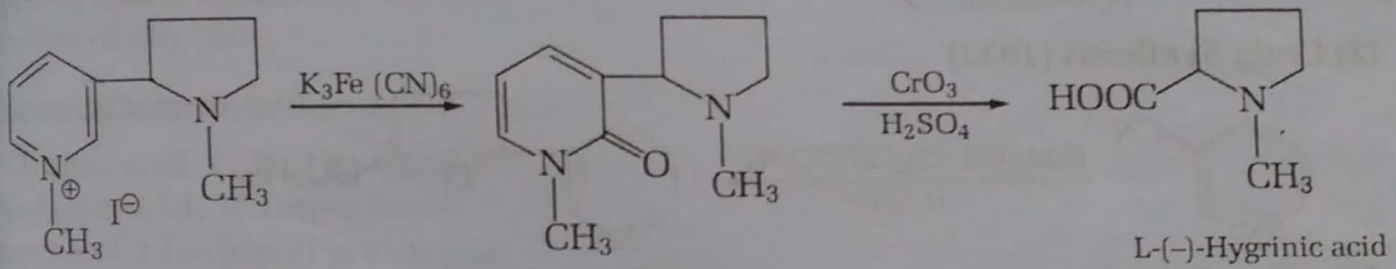
Malonic acid

The structure of dibromoticonine was established in 1973 by Quine *et. al.* as given on the next page.



Dibromoticonine

Direct evidence for the presence of pyrrolidine ring and its linkage to pyridine nucleus in nicotine was given by Karrev (1925). Oxidation of nicotine isomethiodide with potassium ferricyanide gave nicotone which on further oxidation with chromic acid produced L-(–)-hygrinic acid.



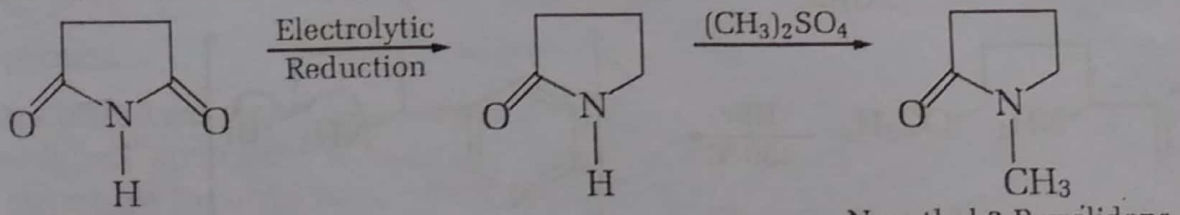
Nicotine isomethiodide

L-(–)-Hygrinic acid

Synthesis of Nicotine

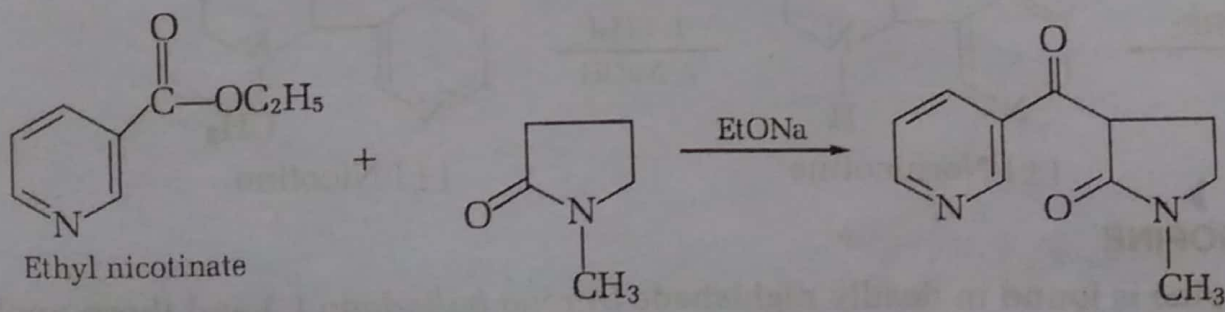
The structure of nicotine was finally confirmed by synthesis of (±)-nicotine which was resolved with (+)-tartaric acid and (–)-nicotine was found identical with natural nicotine.

(1) Spath and Bretschneider synthesis (1928).

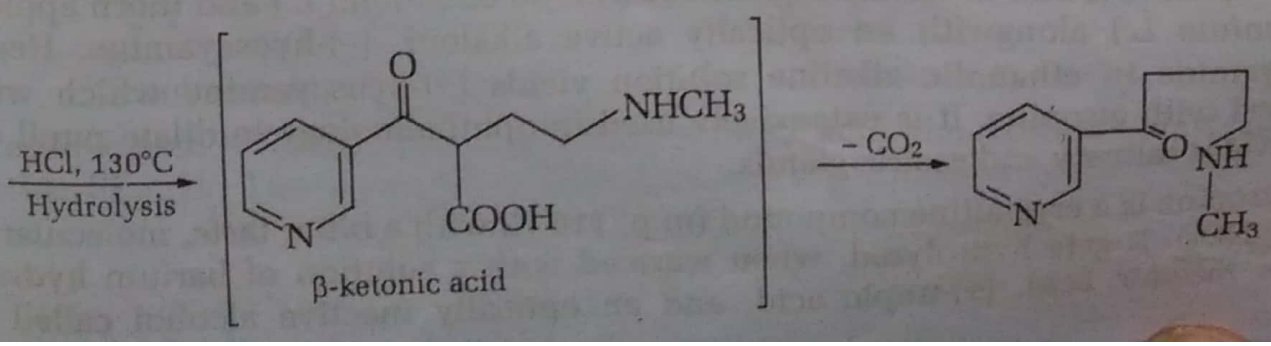


Ethyl nicotinate

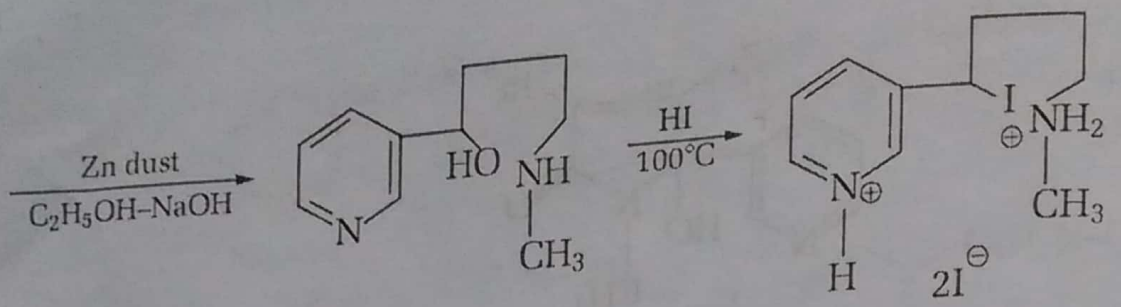
N-methyl 2-Pyrrolidone

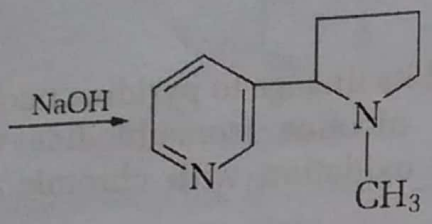


Ethyl nicotinate



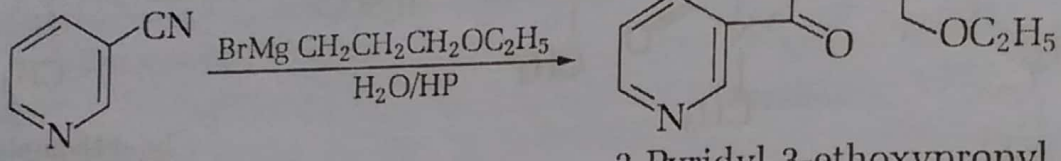
β-ketonic acid





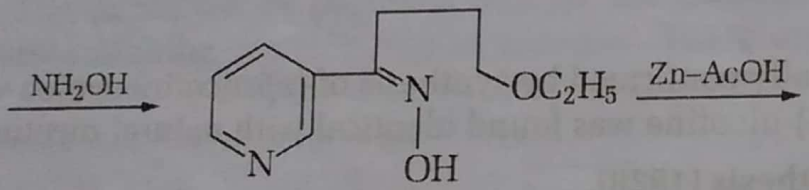
(±)-Nicotine

(2) Craig Synthesis (1933)

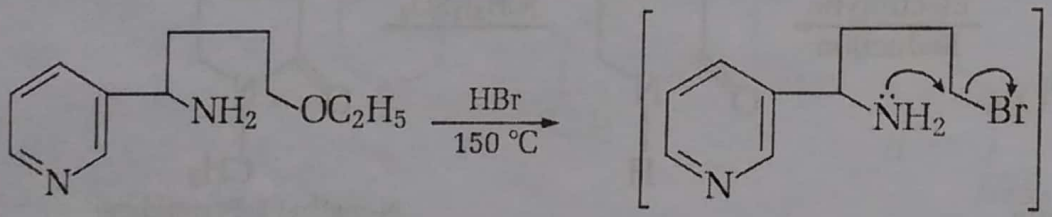


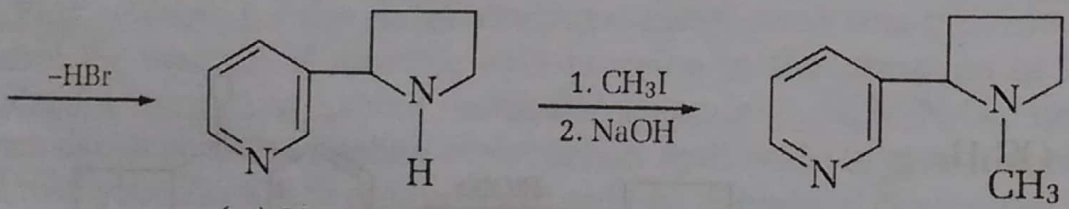
Nicotinonitrile

3-Pyridyl-3-ethoxypropyl ketone



Oxime





(±)-Nornicotine

(±)-Nicotine

4.7. ATROPINE

Atropine is found in deadly nightshade (*Atropa balladona* L.) and thorn apple (*Datura stramonium* L.) alongwith an optically active alkaloid, (–)-hyoscyamine. Heating (–)-hyoscyamine in ethanolic alkaline solution yields (±)-hyoscyamine which was found identical with atropine. It is extensively used in ophthalmology to dilate pupil of eye. It deactivates salivary and gastric glands.

Atropine is a crystalline compound (m.p. 118°C) with a bitter taste, molecular formula ($C_{17}H_{23}NO_3$). It gets hydrolysed, when warmed with a solution of barium hydroxide, to give a racemic acid, (±)-tropic acid, and an optically inactive alcohol called tropine.

Atropine is regenerated when a mixture of (±) tropic acid and tropine is heated in the presence of hydrochloric acid.

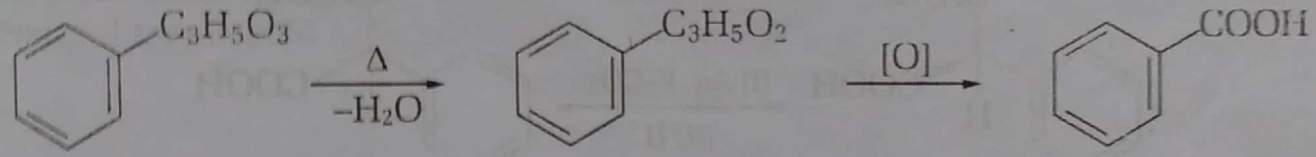
$$C_{17}H_{23}NO_3 \xrightarrow[H_2O]{Ba(OH)_2} C_9H_{10}O_3 + C_8H_{15}NO$$

$$\text{Atropine} \xleftarrow[\Delta]{HCl} (\pm)\text{-Tropic acid} + \text{Tropine}$$

These reactions showed that atropine may be either an ester or an amide. An amide produces a carboxylic acid and a primary or secondary amine on hydrolysis but N atom in tropine was a tertiary base confirming that atropine is a tropine ester of tropic acid, tropine tropate. Characterisation of hydrolysis product of atropine led to confirmation of structure of atropine.

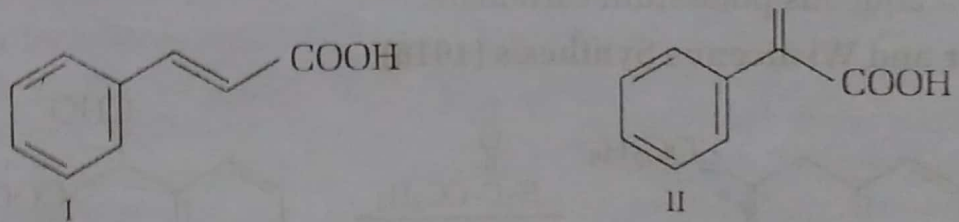
Structure Determination of (±)-Tropic Acid

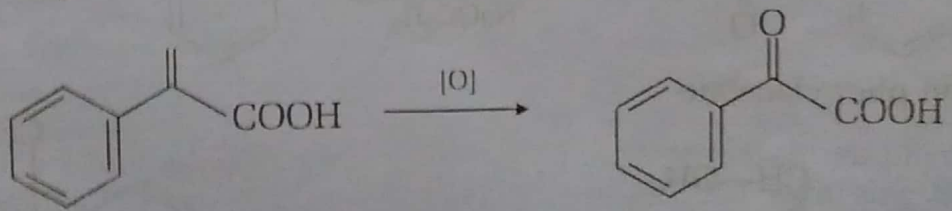
Tropic acid, $C_9H_{10}O_3$, consumes one equivalent of alkali to form salt showing it to be monobasic acid. It forms monoacetate when treated with acetyl chloride confirming the presence of a hydroxyl group also. It undergoes dehydration when heated strongly to give an optically inactive, unsaturated carboxylic acid named atropic acid which forms benzoic acid on oxidation. The formation of benzoic acid suggests that atropic and tropic acids also have benzene nucleus.



Tropic Acid — Atropic Acid — Benzoic Acid

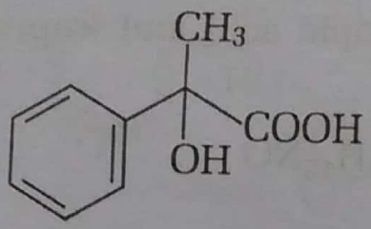
There are only two structures (I and II) that can be considered for atropic acid. Atropic acid was assigned structure II because oxidation of atropic acid yields phenylglyoxylic acid while structure I would have given benzoldehyde.



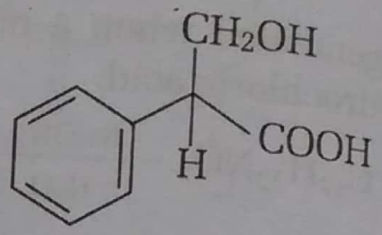


Atropic Acid — Phenylglyoxylic acid

Since atropic acid is formed by dehydration of tropic acid, the structure of tropic acid must be either III or IV. The structure of tropic acid was confirmed by synthesis to be IV.

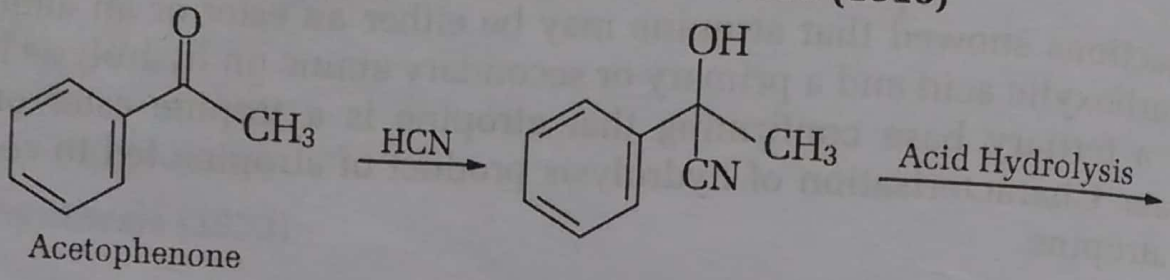


III

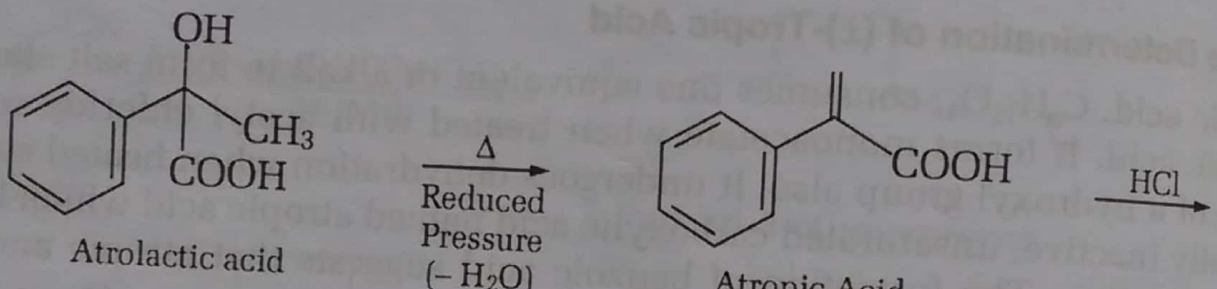


IV

(1) Synthesis of Tropic acid by Mackenzie and Wood (1919)

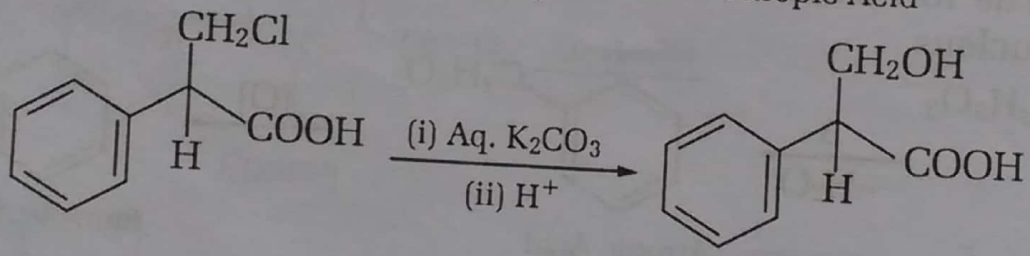


Acetophenone



Atrolactic acid

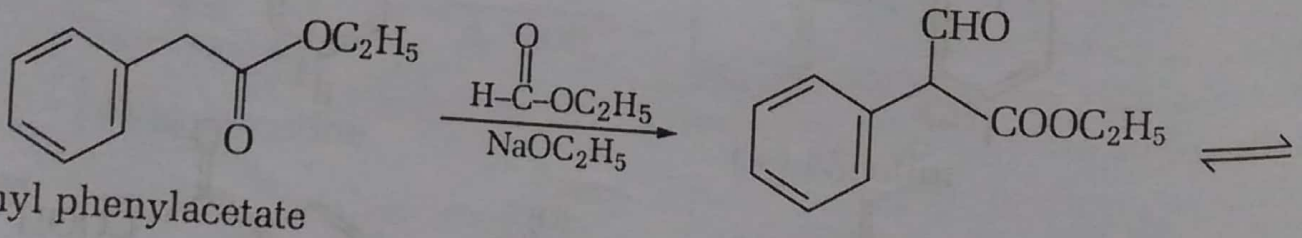
Atropic Acid



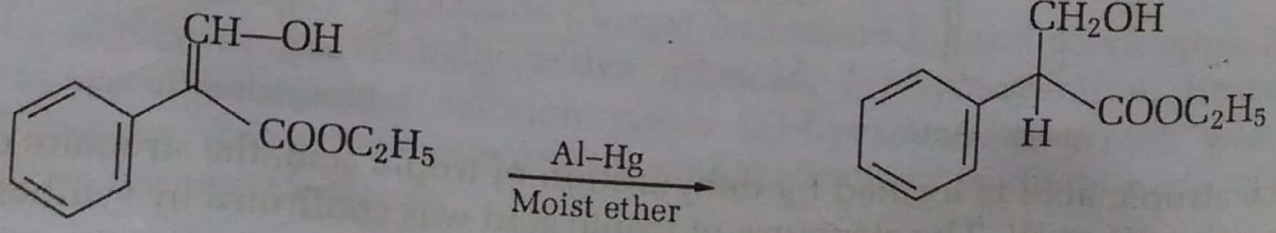
(±)-Tropic Acid

It must be noted that addition of hydrochloric acid to atropic acid gave anti-Markownikoff's product. Markownikoff product would have reproduced atrolactic acid on treatment with aqueous potassium carbonate.

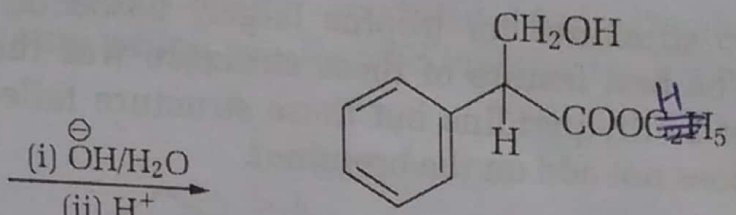
(2) Muller and Wislicenus Synthesis (1918)



Ethyl phenylacetate

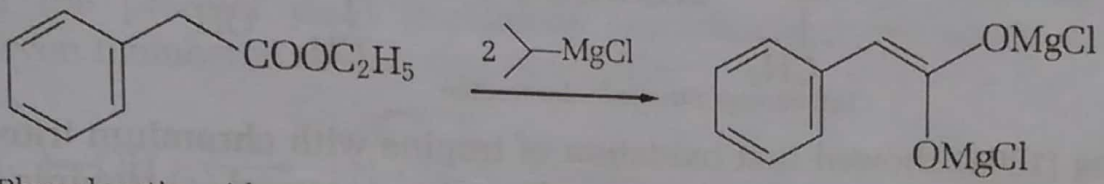


Enol form



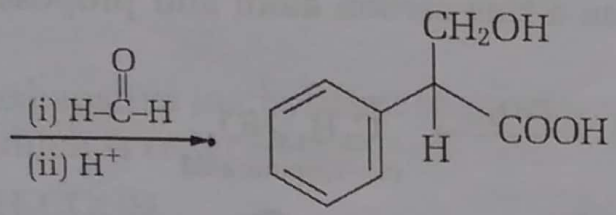
(±)-Tropic acid

(3) Blicke *et.al.* Synthesis (1952)



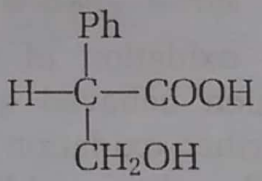
Phenylacetic acid

Fenolate



(±)-Tropic Acid

Fodder *et.al.* established the configuration of (–)-tropic acid by its correlation with (–)-alanine. Natural tropic acid may be represented as (*S*)-(–)-tropic acid.

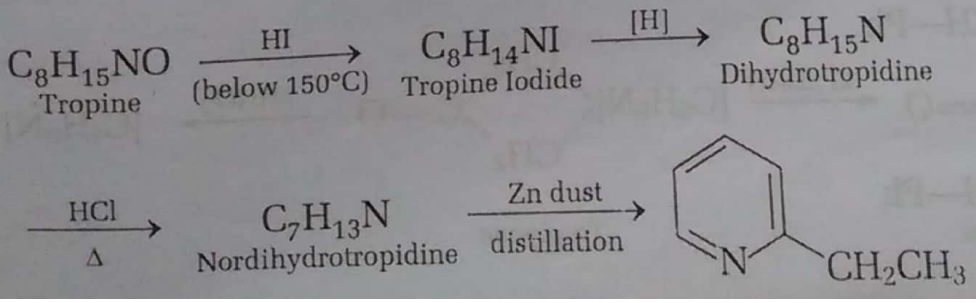


(S)-(–)-Tropic acid

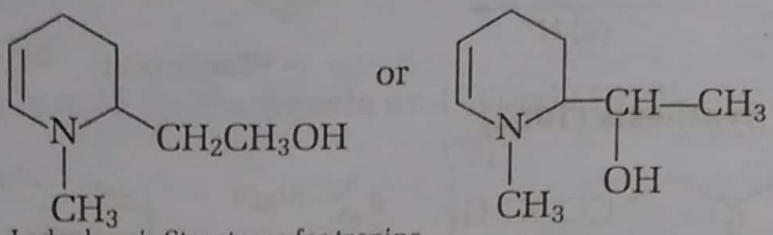
Structure Determination of Tropine

Tropine has molecular formula $C_8H_{15}NO$ which corresponds to 2 DBEs. It forms a crystalline addition product, $[C_8H_{15}NO.CH_3]^{\oplus}I^{\ominus}$, with one molar equivalent of methyl iodide and liberates one molecule of methyl iodide when heated with hydroiodic acid at 150°C showing that a tertiary nitrogen having a methyl group attached is present. The oxygen atom was present as hydroxyl group because tropine formed monoesters.

Ladenburg (1883, 1887) studied the reactions of tropine and confirmed the presence of a six-membered *N*-containing heterocyclic ring. Heating tropine with hydroiodic acid below 150°C gave tropine iodide by replacement of –OH with iodine atom which on reduction formed dihydrotropidine which when distilled with hydrochloric acid produced nordihydrotropidine by removal of $N–CH_3$ group. Finally, nordihydrotropidine was distilled with zine dust to yield 2-ethylpyridine.



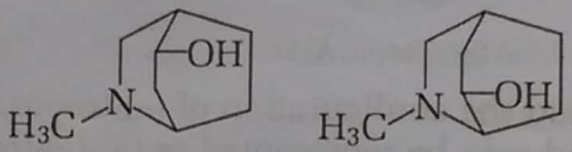
He suggested two structures for tropine largely based on his study and functional group information. The best feature of these structure was their carbon skeleton which was similar to that of 2-ethylpyridine but these structure failed to explain the saturated nature of tropine (it does not add on the bromine).



Ladenburg's Structures for tropine

Merling (1891) showed that oxidation of tropine with chromium trioxide produced a dicarboxylic acid with same number of carbon atoms, named (±)-tropinic acid. He argued that hydroxyl group must be present on a ring carbon atom and proposed two saturated structures for tropine.

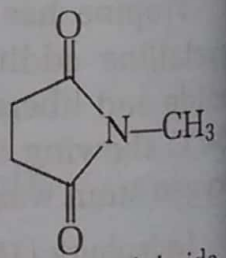
$$\underset{\text{Tropine}}{C_8H_{15}NO} \xrightarrow{CrO_3} \underset{\text{(±)–Tropinic acid}}{C_8H_{13}NO_4}$$



Merling's structures for tropine

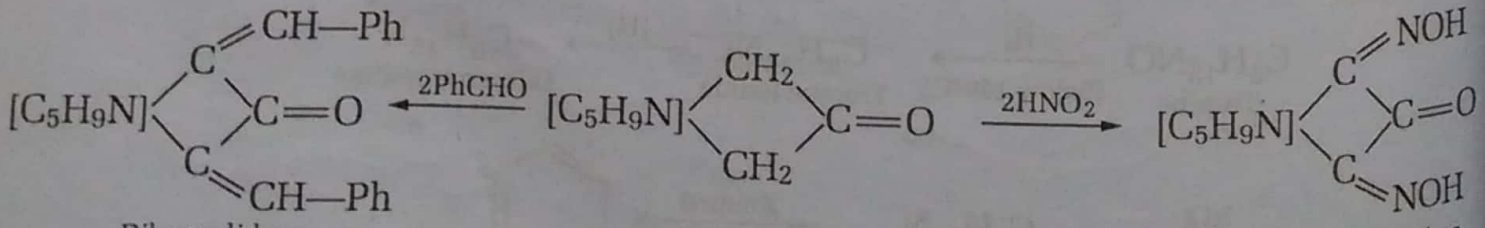
Willstatter reinvestigated the oxidation of tropine with chromium trioxide and isolated tropinone ($C_8H_{13}NO$) which behaved as a ketone confirming the nature of hydroxyl group as secondary. Further oxidation of tropinone with chromium trioxide produced (±)-tropinic acid which when oxidized with chromic acid yielded N-methylsuccinimide confirming the presence of a five membered N-containing heterocyclic ring in tropine. Nitrogen atom must be common to both piperidine as well as pyrrolidine ring since there is only one N atom in tropine.

$$\underset{\text{Tropine}}{C_8H_{15}NO} \xrightarrow{CrO_3} \underset{\text{Tropinone}}{C_8H_{13}NO} \xrightarrow{CrO_3} \underset{\text{(±)–Tropinic acid}}{C_8H_{13}NO_4} \xrightarrow[H_2SO_4]{CrO_3}$$



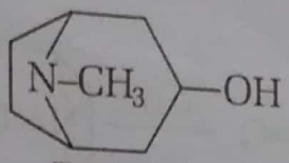
N-Methylsuccinimide

He then studied the reactions of tropinone and prepared several derivatives. Tropinone when treated with nitrous acid gave a dioxime. Similarly, reaction of tropinone with benzaldehyde yielded a dibenzylidene derivative. These products confirmed the presence of —CH_2—CO—CH_2—moiety in tropinone.



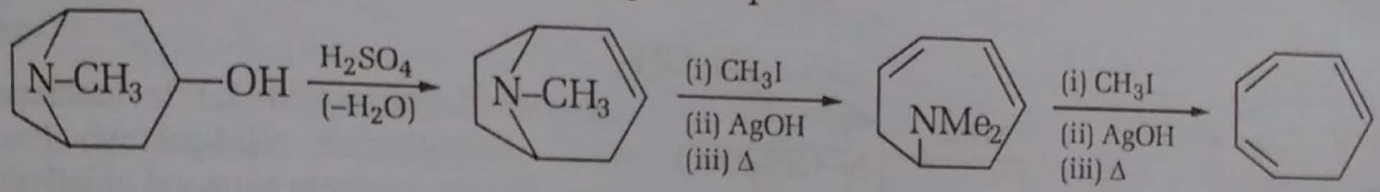
Dibenzylidene Tropinone Dioxime

Based on these findings, Willstatter modified Merling's structure and proposed following structure for tropine which was found correct by further degradation studies.



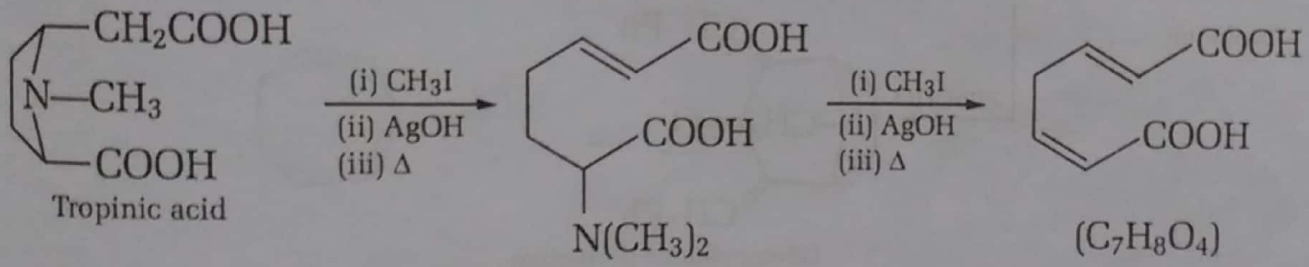
Tropine

Dehydration of tropine with sulphuric acid followed by Hofmann exhaustive methylation of the product yield tropilidene (cycloheptatriene) which confirms the presence of a seven membered carbon ring in tropine.



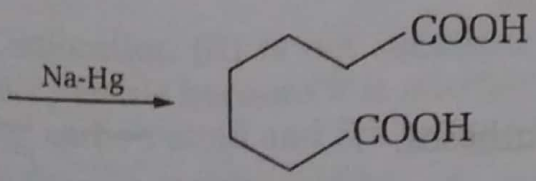
Tropilidine

Hofmann exhaustive methylation of tropinic acid yielded an unsaturated dicarboxylic acid, $C_7H_8O_4$, which is reduced to pimelic acid.



Tropinic acid

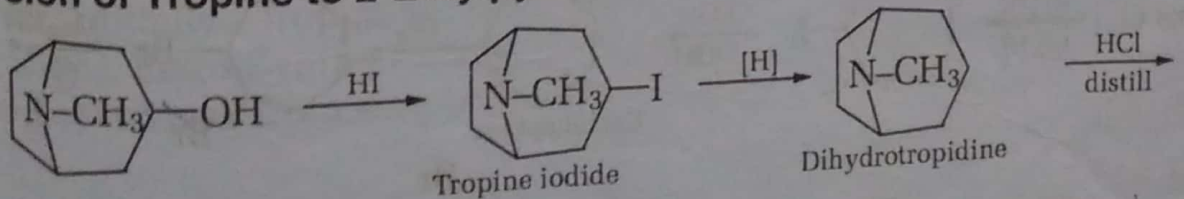
$(C_7H_8O_4)$



Pimelic acid

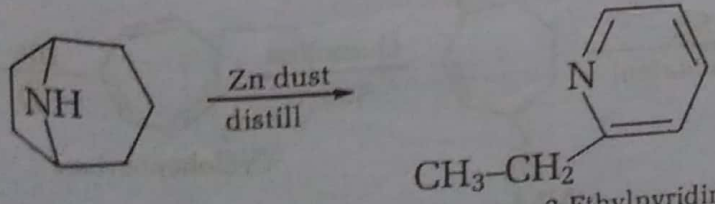
All the foregoing reactions of tropine can be explained by Willstatter formula as given below :

Conversion of Tropine to 2-Ethylpyridine



Tropine iodide

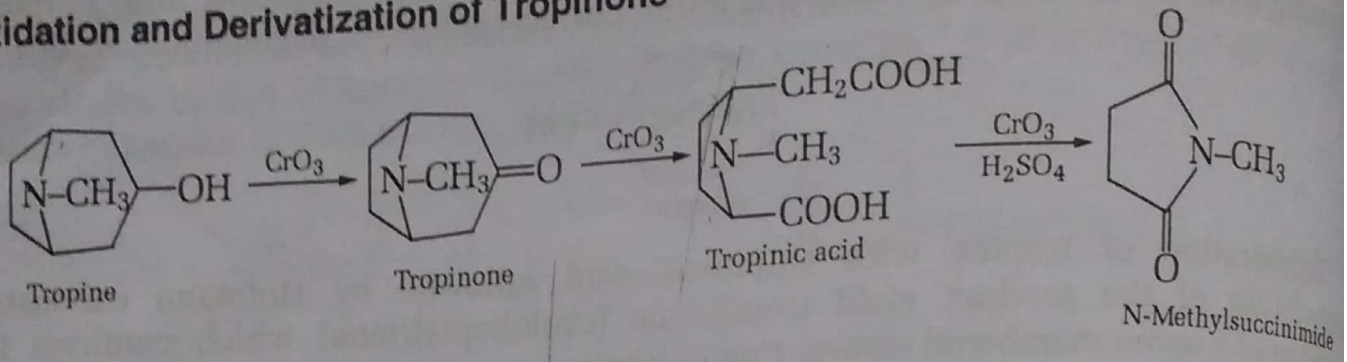
Dihydrotropidine



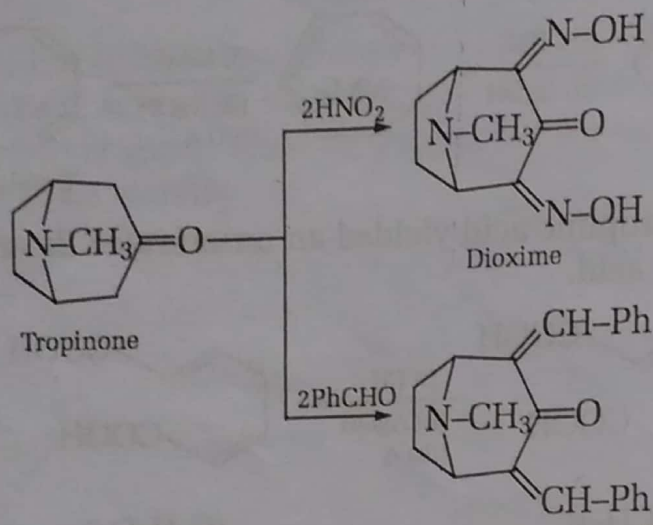
Nordihydrotropidine

2-Ethylpyridine

Oxidation and Derivatization of Tropinone



Tropine — Tropinone — Tropinic acid — N-Methylsuccinimide



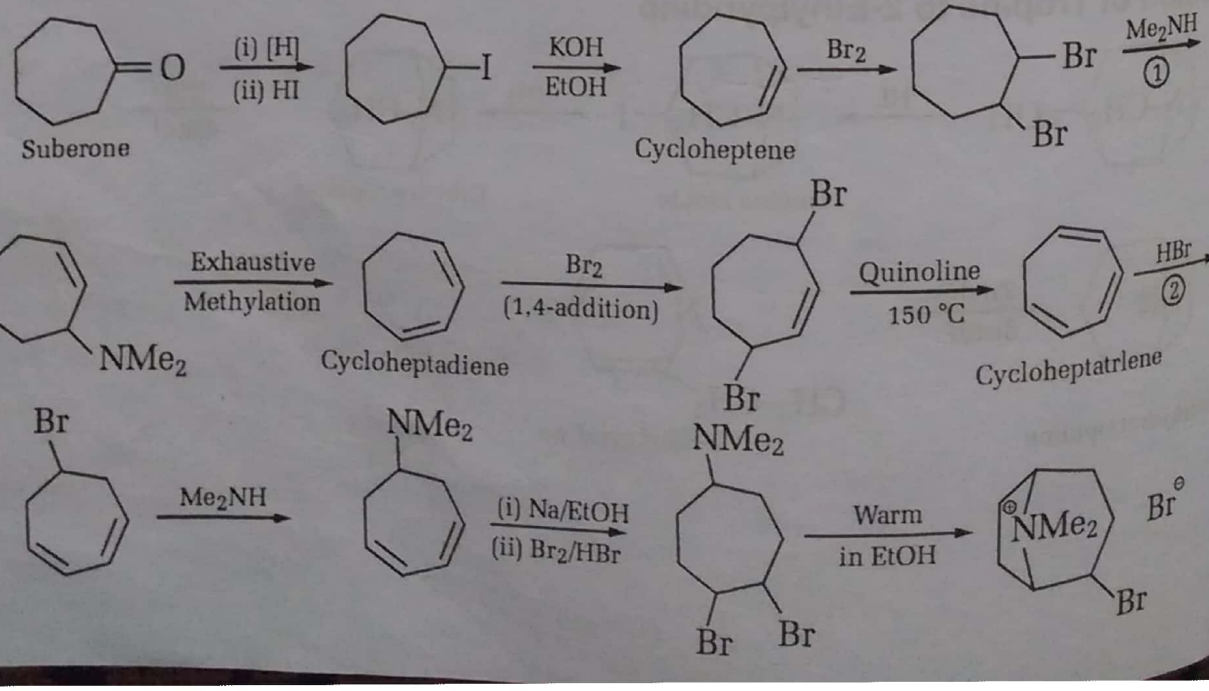
Tropinone — Dioxime — Dibenzylidene derivative

Synthesis of Tropine

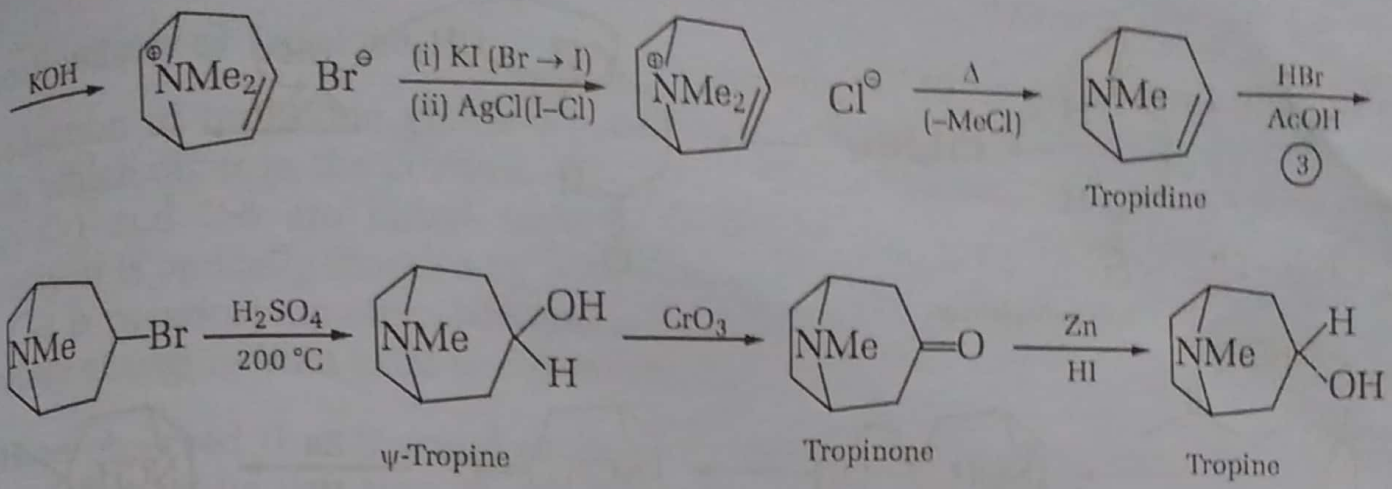
Structure of tropine was confirmed by several syntheses.

(1) Willstatter Synthesis (1903)

First synthesis of tropine was reported by Willstatter starting from suberone (cycloheptanone). Suberone was converted to cycloheptatriene in seven steps. Tropine was obtained in 10 steps from cycloheptatriene.



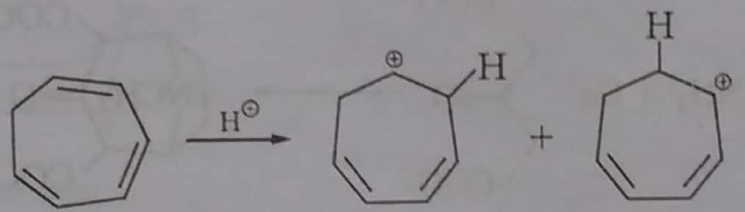
Suberone — Cycloheptene — Cycloheptadiene — Cycloheptatrlene



Remarks

(1) Treatment of 1,2-dibromocychloheptane with dimethylamine results in dehydrobrominaion and nucleophilic substitution. Double dehydrobromination product was not formed probably because stereochemical requirements were not met.

(2) Addition of HBr to cycloheptatriene yielded symmetrical bromo derivative through more stable carbocation (I).

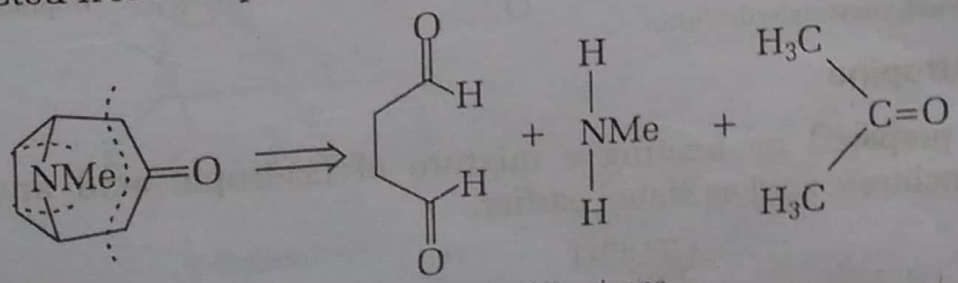


Carbocation (II) is not stabilized by resonance because it is not planar. Carbocation (I) is more stable because it is attached to two Sp^3 carbon atoms while (II) is attached to a sp^3 and Sp^2 carbon atom and Sp^2 carbon atom is more electronegative.

(3) Addition of HBr in the presence of acetic acid to tropidine gave symmetrical bromo derivative through more stable carbocation.

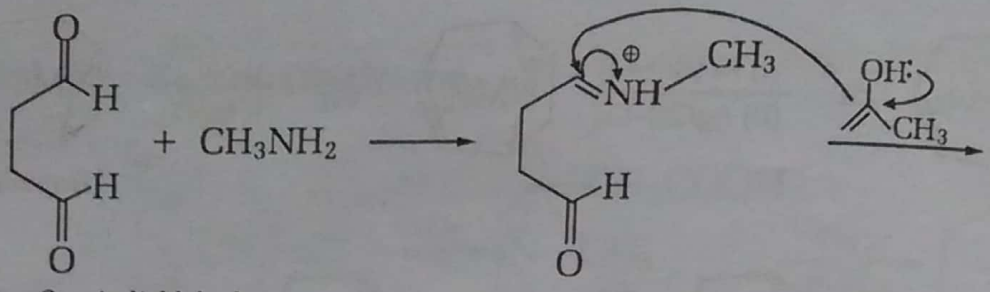
(2) Robinson's Synthesis (1917)

Robinson designed a beautiful synthesis of tropine in a single step. Though the yield was poor initially, tropinone was obtained in 81% yield in one step after few modifications. Retro-Synthetic-Analysis of tropine led him to believe that tropine skeleton could be constructed from simple compounds in a single step.

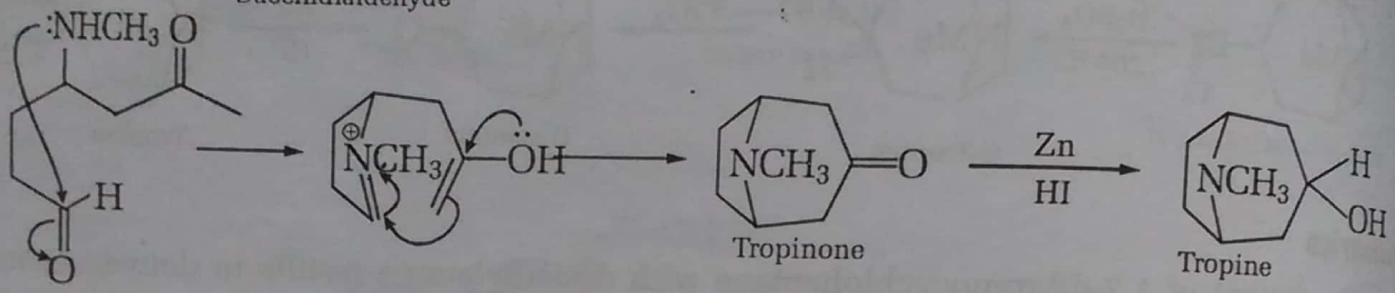


Retro-Synthetic-Analysis of Tropinone

When a mixture of succindialdehyde, methylamine and acetone was allowed to stand in water for 30 min, tropinone was obtained.

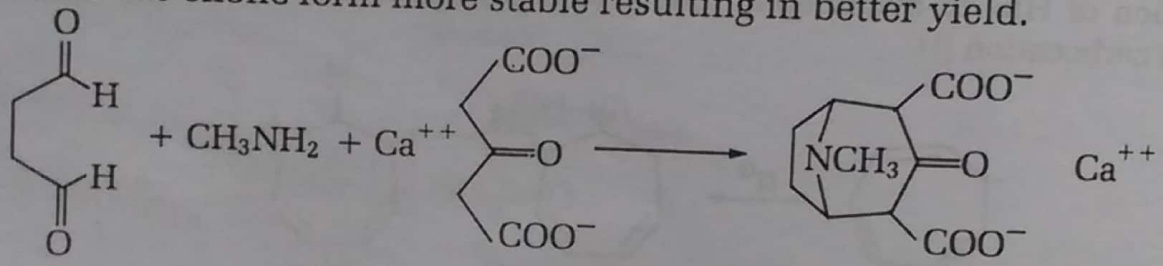


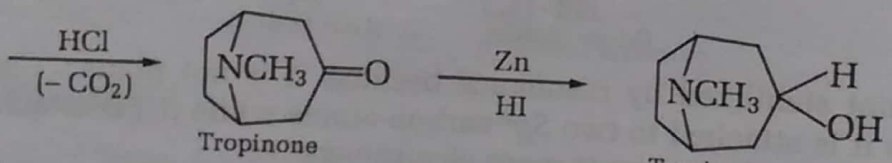
Succindialdehyde



Tropinone Tropine

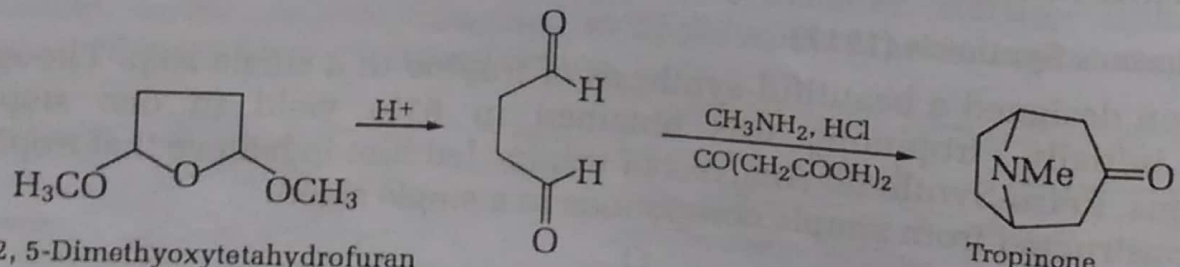
The yield was improved to 40% by replacing acetone with calcium acetonedicarboxylate or ethylacetone dicarboxylate. The presence of carboxylic groups at α-carbon atoms make enolic form more stable resulting in better yield.





Tropinone Tropine

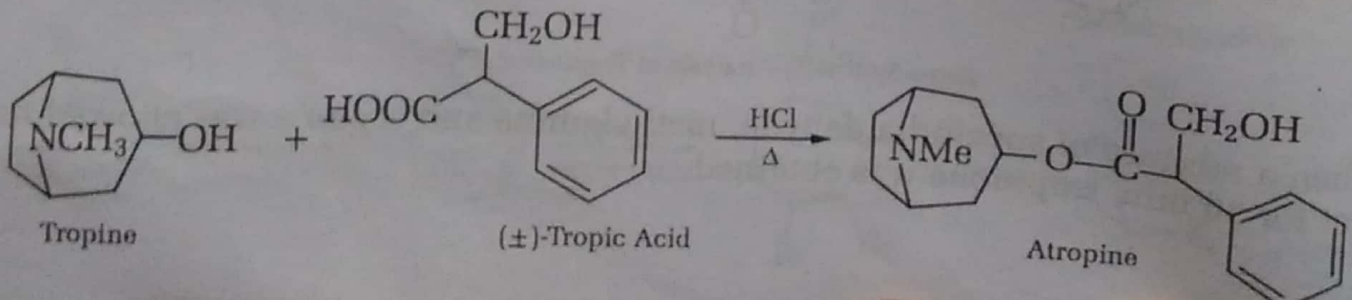
The yield was further improved (81%) by generating succindialdehyde *in-situ* from 2, 5-dimethoxytetrahydrofuran under acidic condition and using acetonedicarboxylic acid.



2, 5-Dimethyoxytetahydrofuran Tropinone

Preparation of Atropine

Atropine is prepared by heating a mixture of (±)-tropic acid and tropine in the presence of hydrochloric acid as stated earlier.

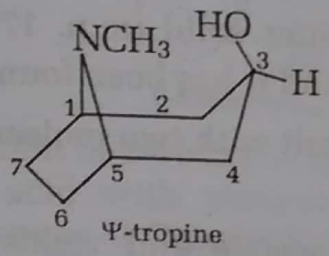


Tropine (±)-Tropic Acid Atropine

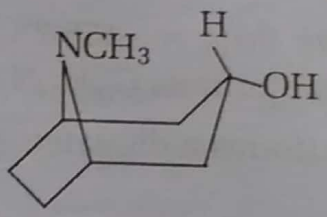
Stereochemistry of Tropines

Reduction of tropinone yields a mixture of two epimeric alcohols, tropine and ψ-tropine, which differ in the position of H at C-3. Both these alcohols are optically inactive though C-1 and C-5 are chiral carbons which means that molecule has a plane of symmetry. It is optically inactive by internal compensation, and so each isomer is a meso-form, C-3 is pseudosymmetric. Nirogen will be in a state of oscillation and N–CH_3 will be constantly changing from axial to equatorial and *vice versa*.

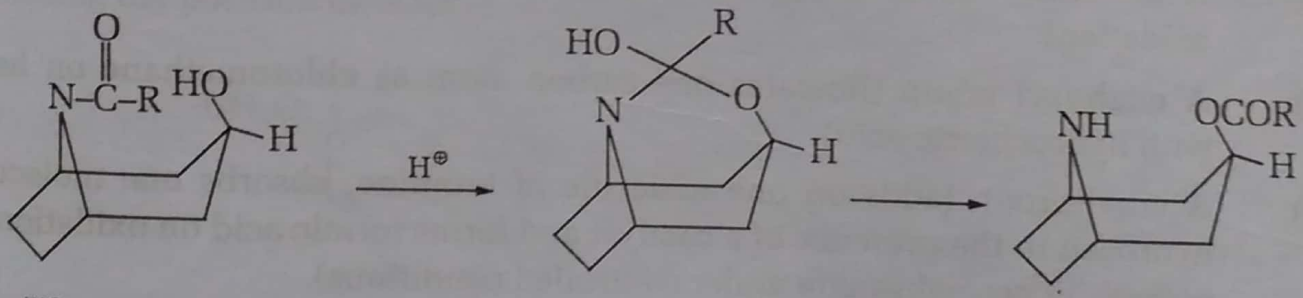
It was observed that N-acetyl or N-benzoyl-nor-ψ-tropine readily undergoes N → O acyl migration while this type of migration does not take place in tropine. These results suggest that –OH and N-bridge are in *cis* position (*Syn* compound) in ψ-tropine while tropine must be anti-compound. Fodor (1953) proposed boat conformation for piperidine ring of both the isomers, while axial hydroxyl in ψ-tropine and equatorial of hydroxyl in tropine.



Ψ-tropine

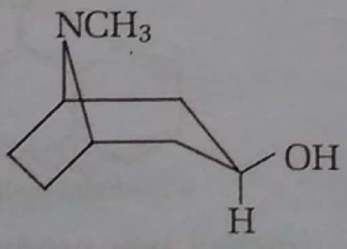


Tropine

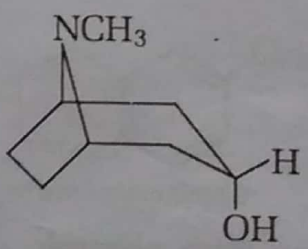


Ψ-Tropine Derivative

Bose (1953) argued that chair form for piperidine ring must be more stable, by analogy with conformations of cyclohexame, and proposed following stereochemistry to two epimers.

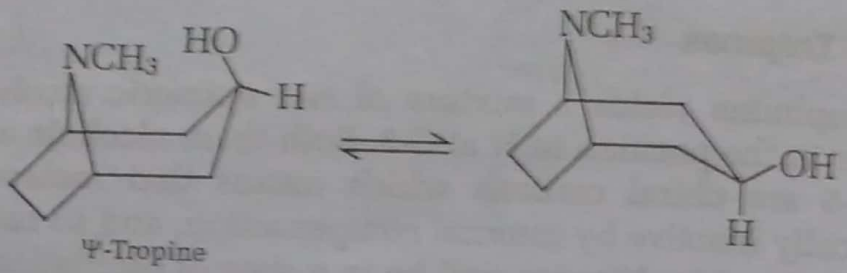


Ψ-Tropine



Tropine

His proposal is based on the observation that heating tropine with amyl alcohol containing sodium amyloxide results in the isomerization to ψ-tropine confirming that ψ-tropine is thermodynamically more stable. Fodor's results can be explained by an equilibrium between chair and boat form.



Ψ-Tropine

Several evidences in support of Bose's stereochemistry have since been provided. It is now believed that in tropine, the predominant conformation of piperidine ring is deformed chair form together with a minor amount of boat form.

4.8 QUININE

Quinine is one of about thirty alkaloids found in cinchona bark of which several have been found to be antimalarial. Quinine is commonly used for the treatment of malaria and as a febrifuge. It is extracted from cinchona bark for commercial use.

Quinine is an optically active ($[\alpha]_D = -158.2°C$), bitter solid (m.p. 177°C) which is insoluble in water. It has molecular formula $C_{20}H_{24}N_2O_2$ and it has been found to have :

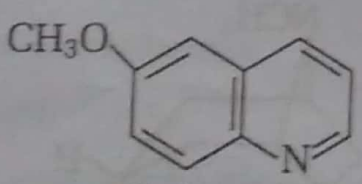
(a) Two tertiary N atoms (forms a diquaternary salt with two molecules of methyl iodide).

(b) A secondary hydroxyl group (forms monoacetate and yields a ketone on oxidation).

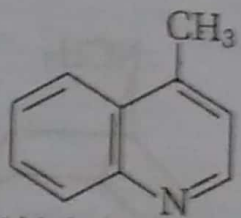
(c) A methoxyl group (liberates one carbon atom as chloromethane on heating with hydrochloric acid)

(d) A vinyl group (adds on one molecule of bromine, absorbs one molecule of hydrogen in the presence of a catalyst and forms formic acid on oxidation with potassium permanganate under controlled conditions).

The presence of a quinoline nucleus in quinine was indicated by fusion with potassium hydroxide which yielded 6-methoxyquinoline and 4-methylquinoline (Lepidine).



6-Methoxyquinoline



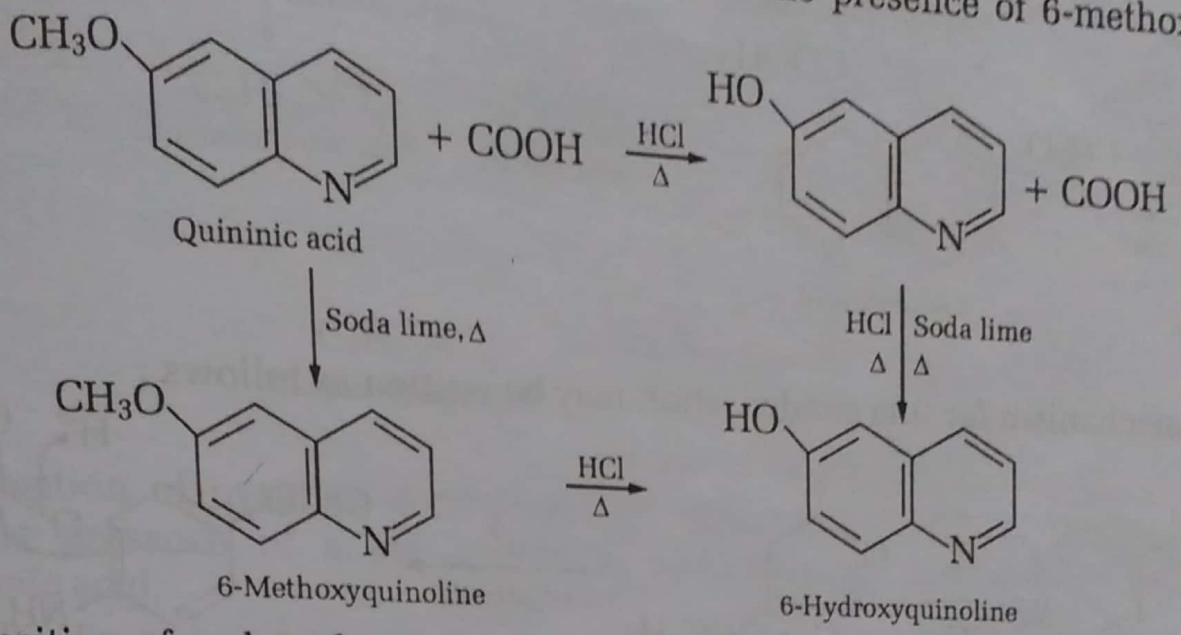
4-Methylquinoline

Oxidation of quinine with chromic acid furnished two products, quininic acid and meroquinene. Characterization of these oxidation products led to the structure elucidation of quinine.

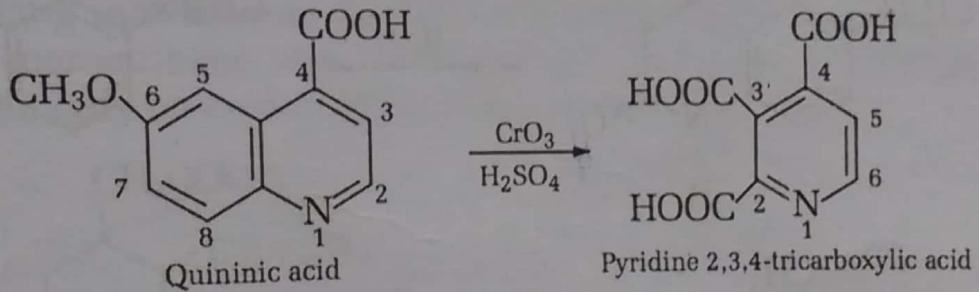
$$\underset{\text{Quinine}}{C_{20}H_{24}N_2O_2} \xrightarrow[\text{Controlled}]{CO_3} \underset{\text{Quininic acid}}{C_{11}H_9NO_3} + \underset{\text{Meroquinene}}{C_9H_{15}NO_2}$$

Characterization of Quininic Acid

Heating quininic acid with hydrochloric acid gives another carboxylic acid which when heated with soda lime yields 6-hydroxyquinoline (Known at that time). Similarly, heating quininic acid with soda lime yielded 6-methoxyquinoline, which formed 6-hydroxyquinoline. These two sequences confirmed the presence of 6-methoxyquinoline moiety in quininic acid

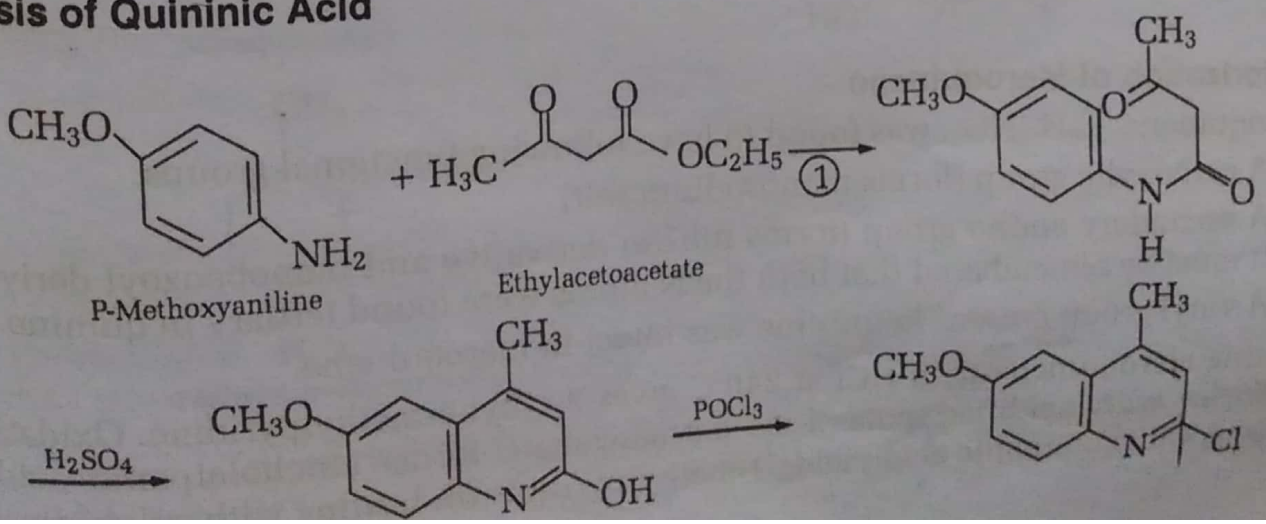


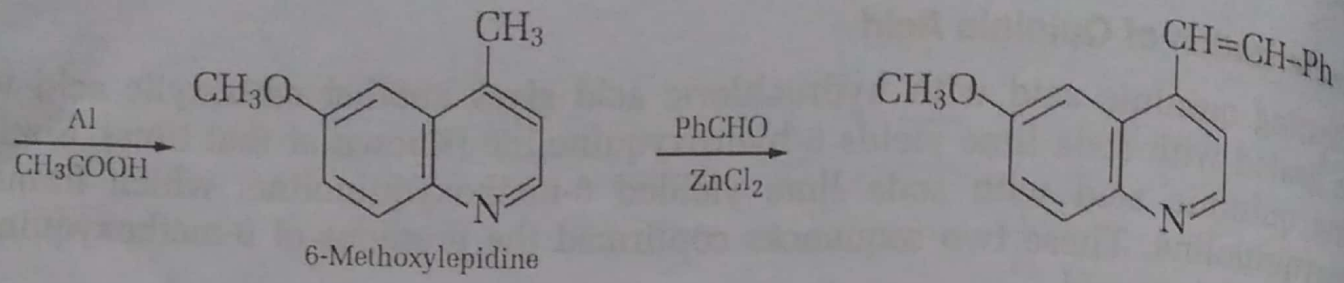
The position of carboxylic group in quininic acid was confirmed by further oxidation of quininic acid with chromic acid which yielded pyridine-2,3,4-tricarboxylic acid. Carboxylic groups at C-2 and C-3 would have been produced by oxidation of benzene ring confirming the position of –COOH group in quininic acid at C-4.



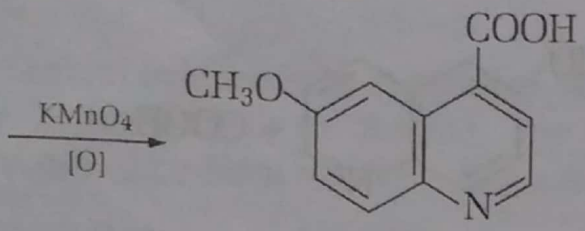
The structure of quininic acid was finally confirmed by synthesis starting from p-methoxyaniline by Rabe *et. al.* (1931).

Synthesis of Quininic Acid





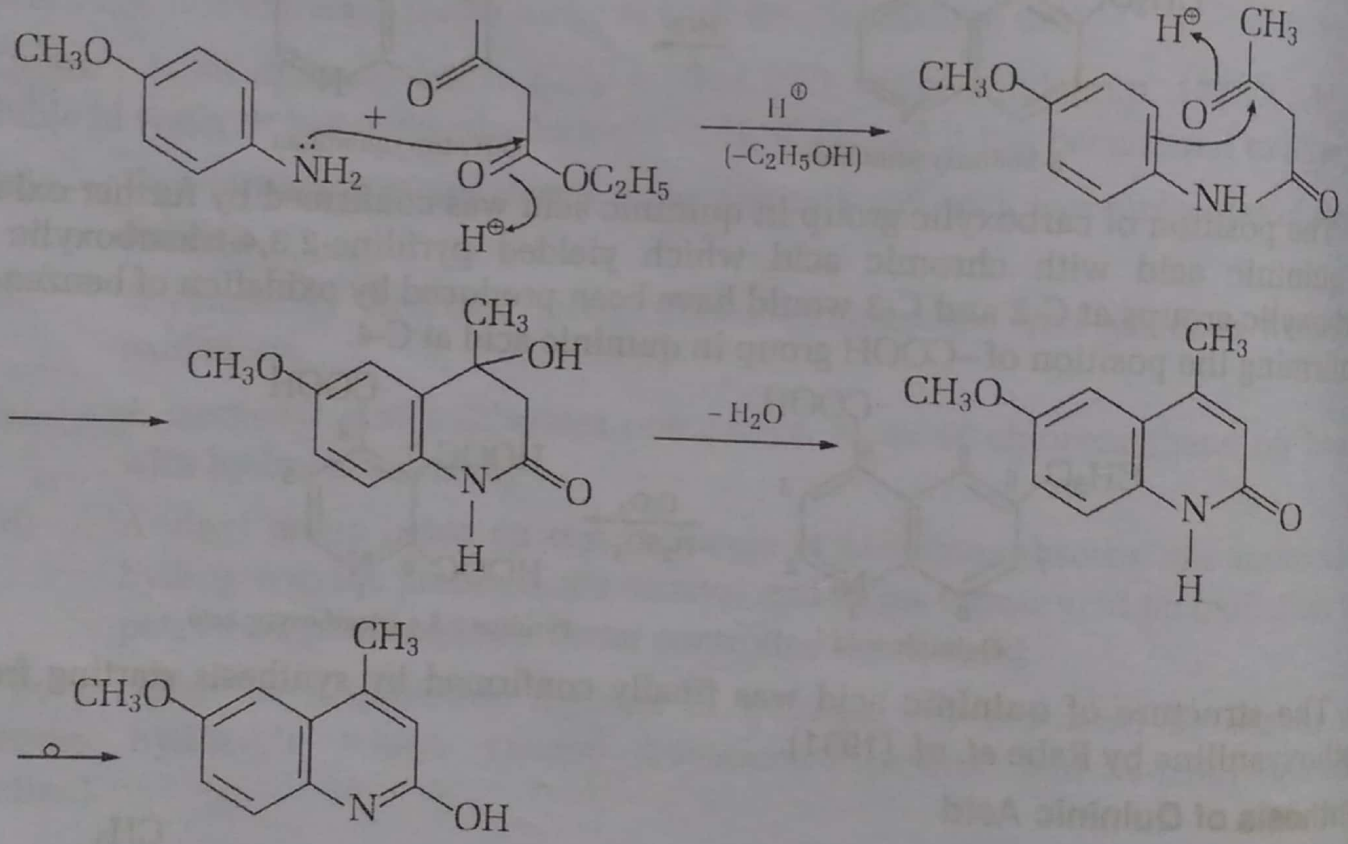
6-Methoxylepidine



Quininic acid

Remark

(1) The mechanism for this condensation may be written as follows :



Characterization of Meroquinene

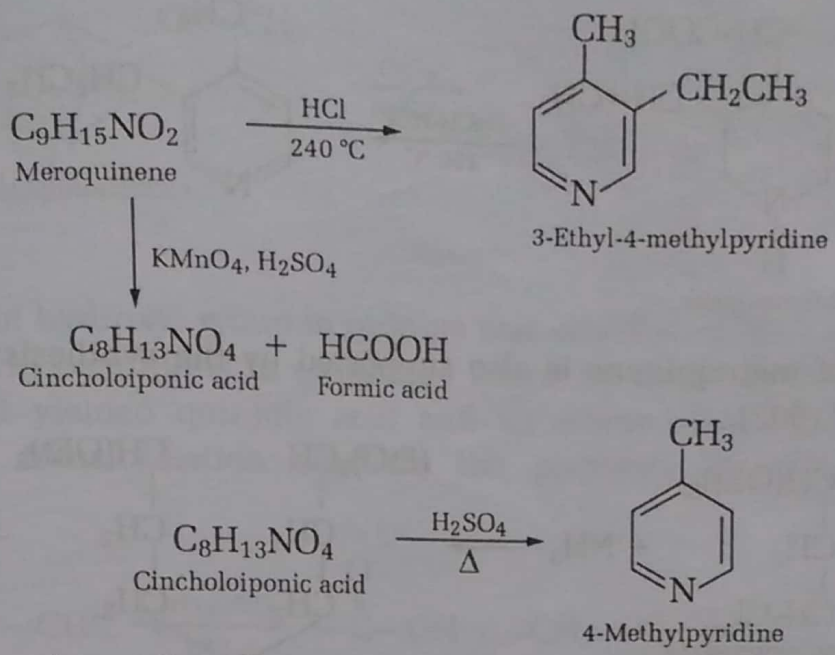
Meroquinene, $C_9H_{15}NO_2$, was found to have following functional groups.

(a) A carboxylic group (forms monosodium salt)

(b) A secondary amino group (forms nitroso derivative and monobenzoyl derivative). It must be remembered that both the N atoms were found tertiary in quinine.

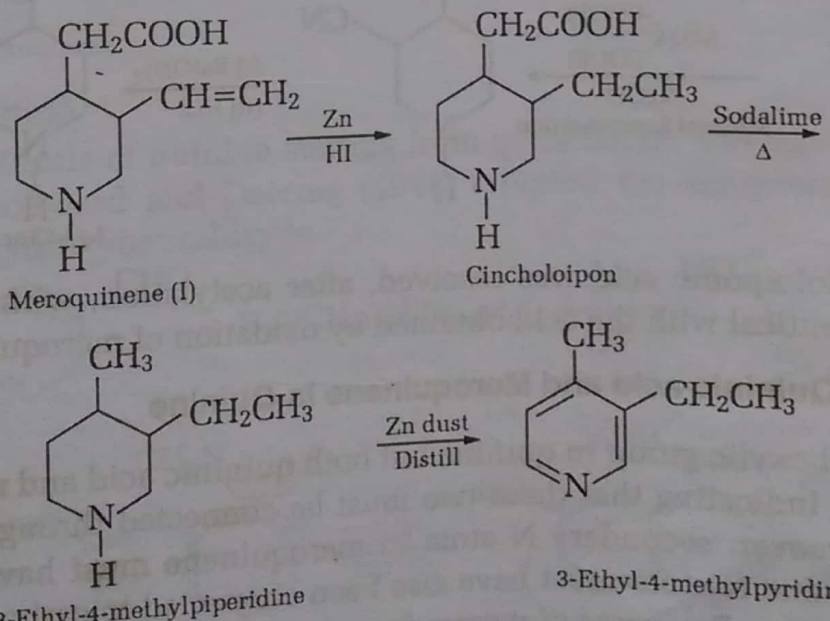
(c) A vinyl group present in quinine was intact in meroquinene.

Heating meroquinene with HCl at 240°C gives 3-ethyl-4-methylpyridine. Oxidation of meroquinene with acidified potassium permanganate forms cincholoiponic acid and formic acid. Cincholoiponic acid yields 4-methylpyridine on heating with sulphuric acid.

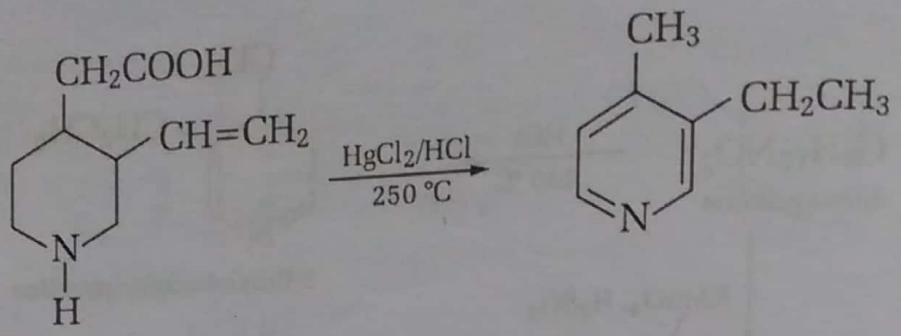


The formation of pyridine derivative from meroquinene and its oxidation product confirms the presence of a six membered N-containing ring in meroquinene and cincholoiponic acid.

Molecular formula of meroquinene corresponds to 3 DBEs. One vinyl and one carboxylic group accounts for 2 DBEs meaning the heterocyclic ring must account for one DBE. Meroquinene is thus a piperidine derivative with substituents at C-3 and C-4 and these substitutes could be either (a) – CH_2COOH and $-CH=CH_2$ or (b) –COOH and $-CH_2CH=CH_2$, taking into account its molecular formula and functional group analysis. The structure of meroquinene was confirmed as I by following sequence of reactions. These reactions can only be explained by assigned structure.

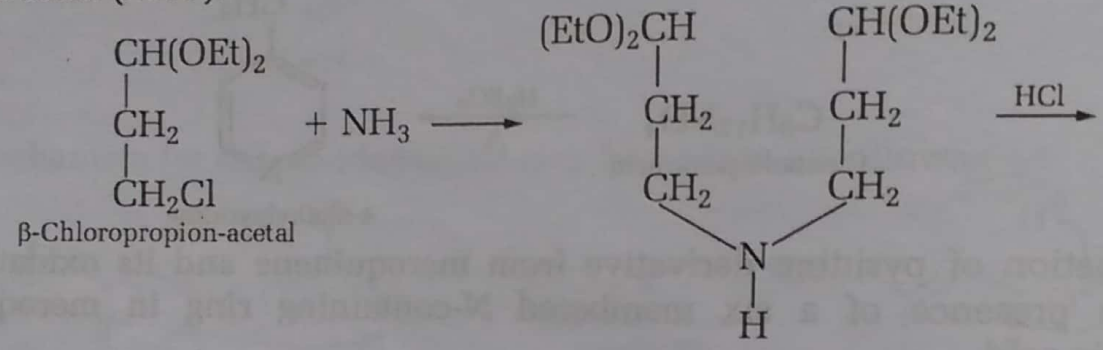


The structure is supported by the fact that heating meroquinene with a solution of mercuric chloride in HCl also yields 3-ethyl-4-methylpyridine.

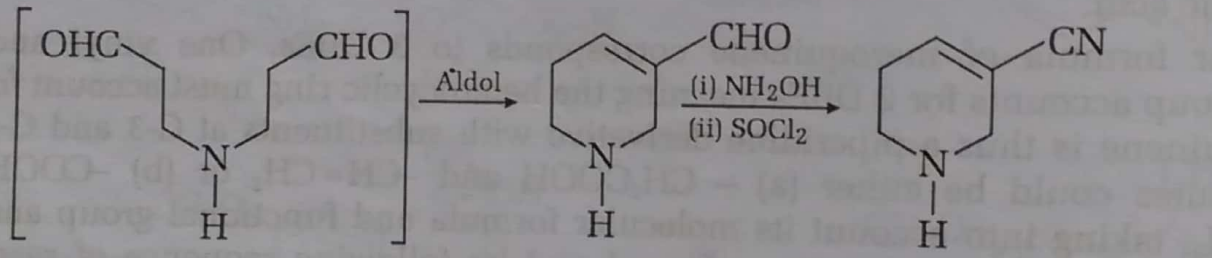


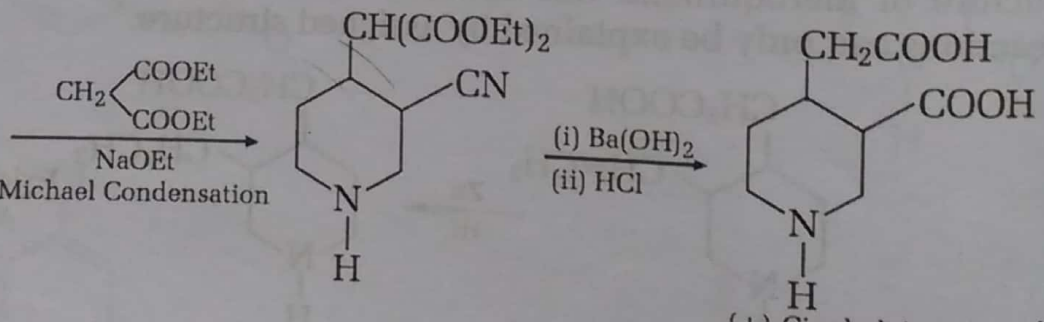
Meroquinene

The structure of meroquinene is also supported by the synthesis of cincholoiponic acid by Wohl *et.al.* (1907).



β-Chloropropion-acetal



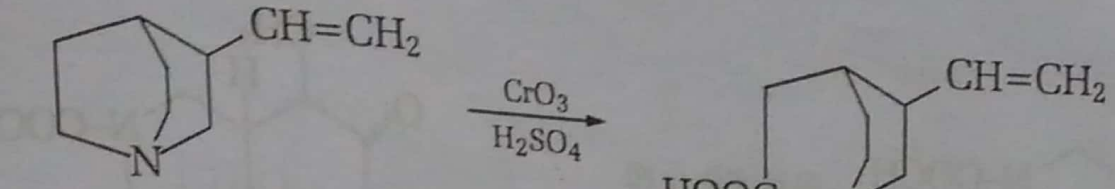


(±)-Cincholoiponic acid

Racemic cincholoiponic acid was resolved, after acetylation, with brucine and (+)-form was found identical with the acid obtained by oxidation of meroquinene.

Linkage between Quininic acid and Meroquinene in Quinine

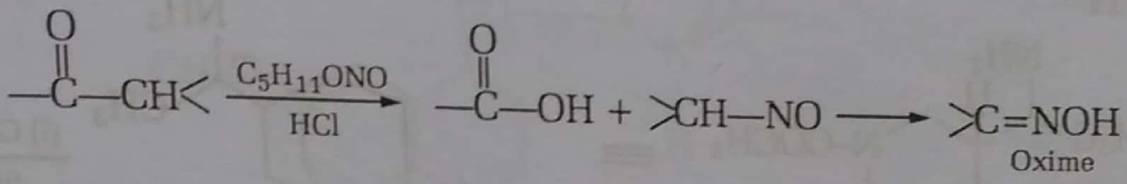
There is no carboxylic group in quinine but both quininic acid and meroquinene have a carboxylic group indicating that these two must be connected through their carboxylic carbon atoms. Moreover, secondary N atom in meroquinene must have been tertiary in quinine suggesting that N-atom must have also been connected to carboxylic carbon atom present in meroquinene. Precursor of meroquinene may, therefore, be 3-vinylquinuclidine which was found true. Oxidation of 3-vinyl quinuclidine with chromic acid gave meroquinene.



3-Vinylquinuclidine

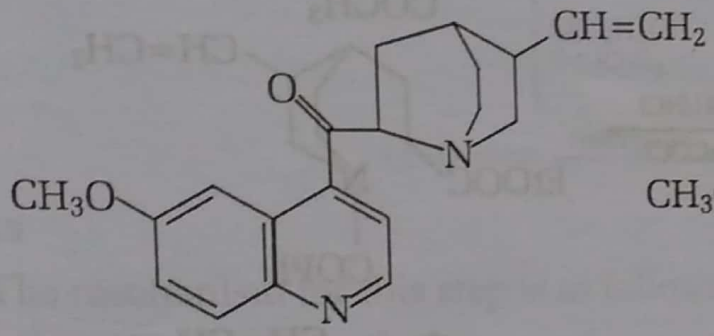
Meroquinene

The position of hydroxyl group in quinine was established by Rabe *et.al.* He oxidized quinine under mild conditions to quininone which on treatment with amyl nitrite and hydrochloric acid yielded quininic acid and an oxime which gave meroquinene on hydrolysis. This transformation confirms the presence of —CO—CH< moiety in quininone.

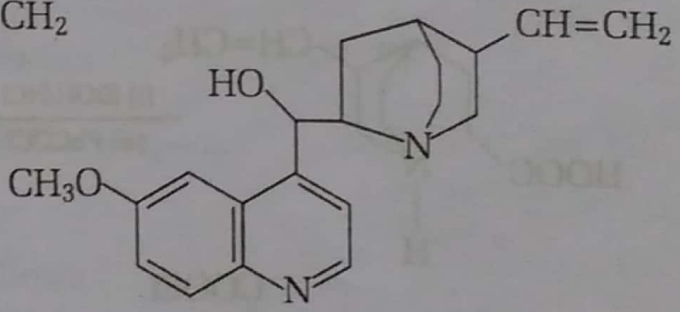


Oxime

On the basis of these observations, the structures of quininone and quinine were proposed as below.



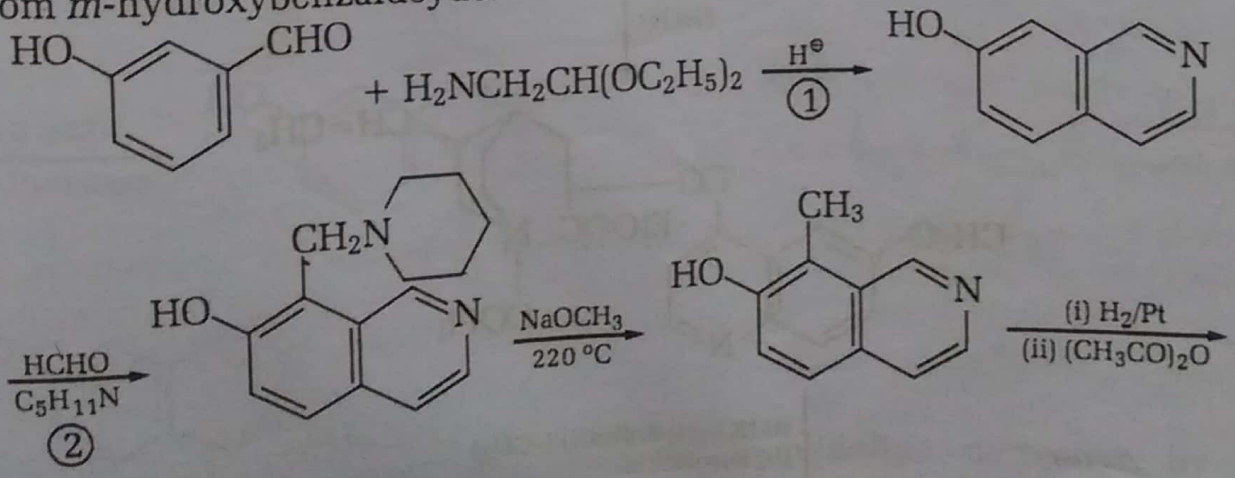
Quininone

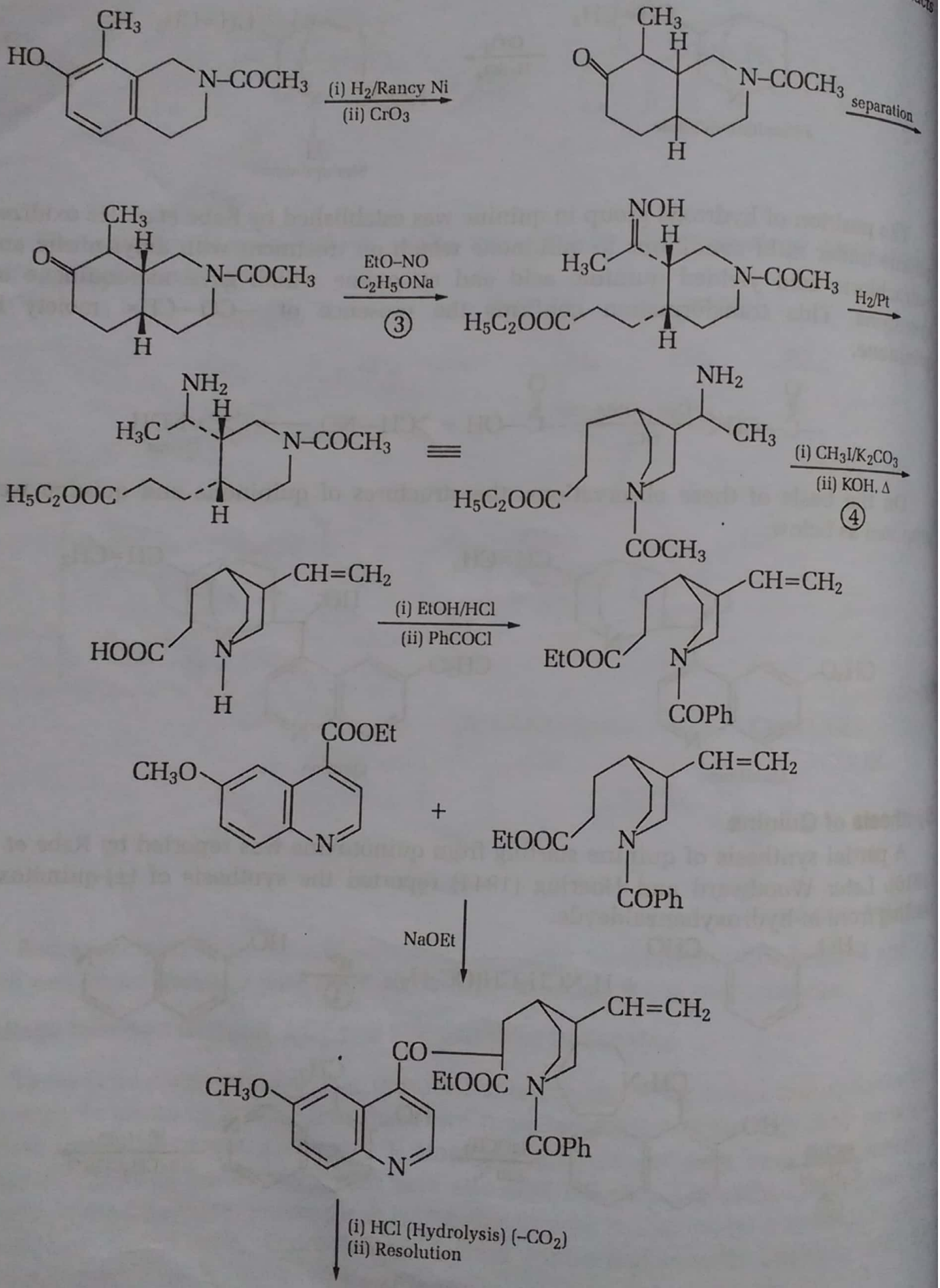


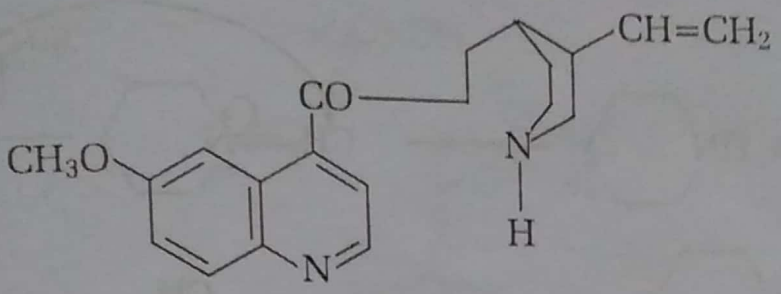
Quinine

Synthesis of Quinine

A partial synthesis of quinine starting from quinotoxine was reported by Rabe *et. al.* (1918). Later Woodward and Doering (1944) reported the synthesis of (±)-quinotoxine starting from *m*-hydroxybenzaldeyde.

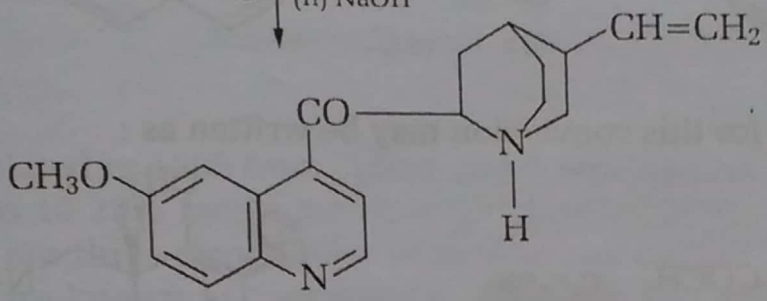






(+)-Isomer

⑤ (i) NaOBr
(ii) NaOH



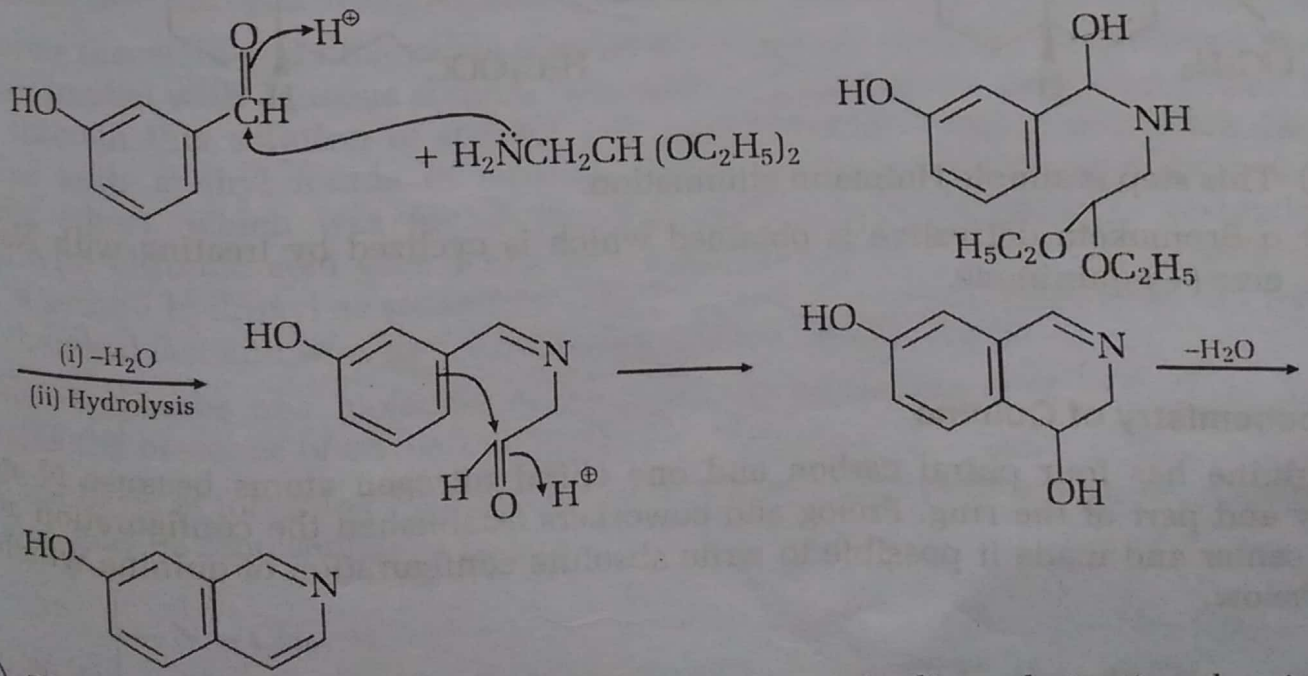
(+)-Quininone

Al/C_2H_5OH
$NaOC_2H_5$

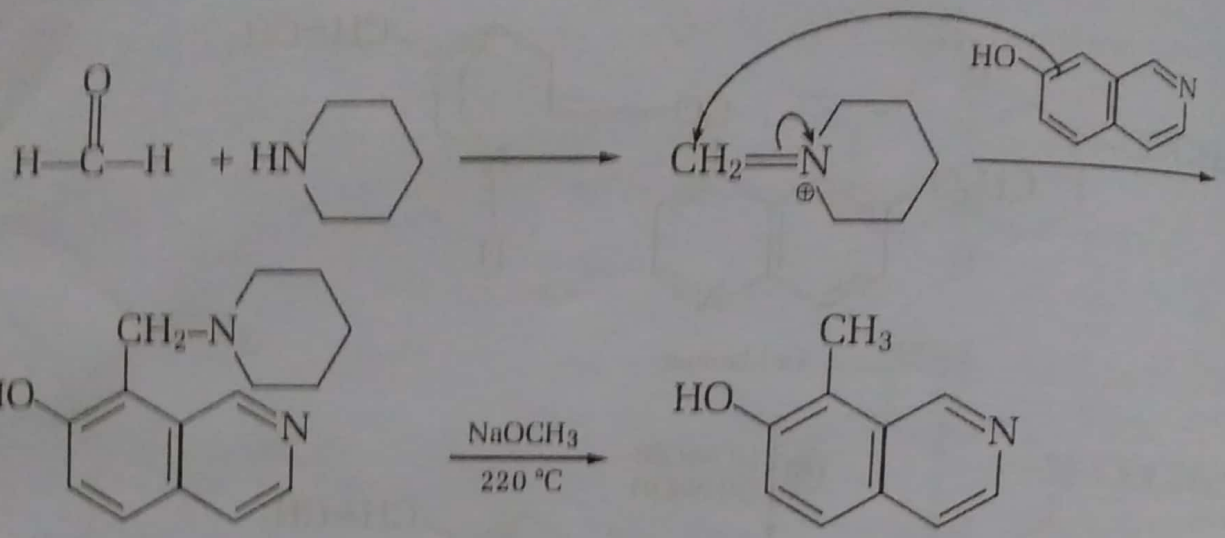
(±)-Quinine $\xrightarrow{\text{resolution}}$ (–)-Quinine

Remarks

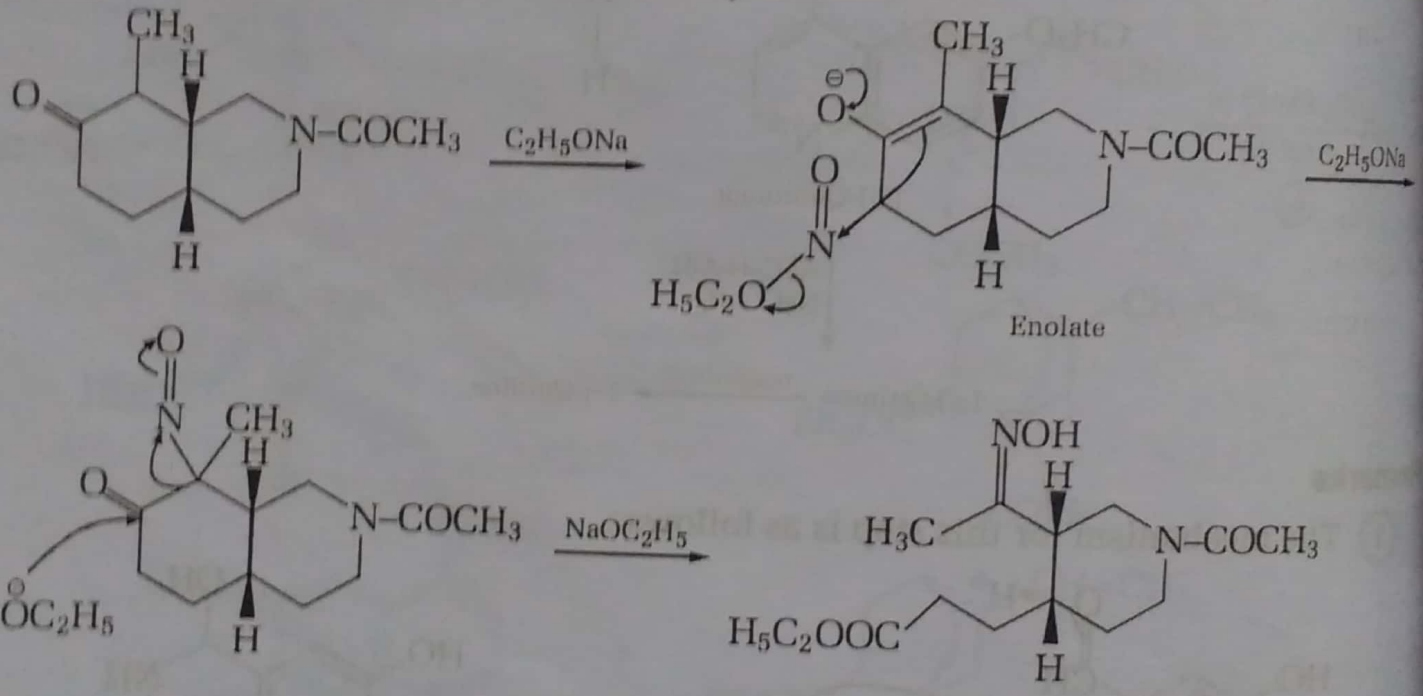
① The mechanism for this step is as follows :



② The methyl group was introduced in isoquinoline derivative by treating hydroxyisoquinoline with formaldehyde in the presence of piperidine followed by decomposition of the product with sodium methoxide.



(3) The mechanism for this conversion may be written as :

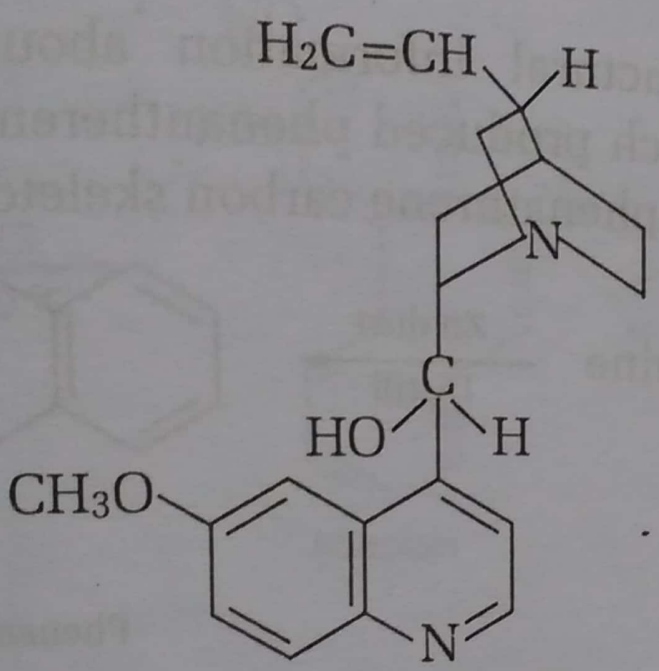


(4) This step is simple Hofmann elimination.

(5) α-Bromoketo derivative is obtained which is cyclized by treating with NaOH to give (+)-quininone.

Stereochemistry of Quinine

Quinine has four chiral carbon and one chiral nitrogen atoms because N atom is tertiary and part of the ring. Prelog and coworkers established the configuration at each chiral center and made it possible to write absolute configuration of quinine which is as given below.



Absolute configuration of quinine