ALKALOIDS

4.1.1 Definition

The term alkaloid was first of all introduced by W. Meissner in 1819. Originally the name alkaloid (which means alkali like, alk = alkoli, oids = like) was given to all organic bases isolated from plants. Meissner, first of all, reserved this term for the basic introgeneous compounds isolated from plants. Konigs (1880) defined alkaloids as naturally occurring organic bases which contain a pyridine ring. The definition is capable of embracing only a limited number of compounds, so the definition was again modified by Ladenburg who suggested that alkaloids should be defined as "naturally occurring compounds of plant origin having a basic character and containing at least one nitrogen atom in a heterocyclic ring system. The alkaloids are now generally defined as physiologically active, basic compound of plant kingdom, in which at least one nitrogen atom forms part of a cyclic system.

The example of the first type of compounds are ephedrine adrenalone, noradrenaline, etc which do not have nitrogen atom in a ring system, but in the side chain. Examples of the second type of compounds of purine group such as caffeine, thiobromine and xanthine which are physiologically active nitrogenous bases. But are not regarded as alkaloids.

4.1.2 Nomenclature

A large number of alkaloids derive their names from the plant from which they are isolated viz., paparverine from papaner somenijerus, hydrastine and barberine from berberis velgoris. A few alkaloids are named from their physiological action such as morphine (Germany morphine – God of dreams) only one group of alkaloids pelleterine has been named after the alkaloid chemist P.J. Pelletier. The minor alkaloids are named by adding one prefix or suffix to the name of the principal alkaloid.

4.1.3 Occurrence

As many as more than two thousand alkaloids have been isolated and are well known. But they are found only in 10 – 15% of all the vascular plants. Alkaloids occur almost exclusively in flowering or seed bearing dicotyledons. They are nearly found in lower plants like algae, fungi etc. (the ergot alkaloids which occur in one or two families of fungi are the exception). Alkaloid content of plants varies with the season, age and its locality closely related alkaloids are generally found in the same plant nearly twenty four alkaloids have been isolated from opium poppy.

Since the alkaloids are basic in nature, they are mostly prevent as salts of acids of plants usually of tannic, malic, oxalic, citric as nearly of acetic acid and lactic acid. The structurally related alkaloids are present as salt of the same organic acid e.g. all the opium alkaloids are present as salts of meconic acid.

4.1.4 Isolation

The isolation of alkaloids from their plant sources is usually not difficult first all the presence of an alkaloid is ascertained in the experimental plant for which the plant extract is treated with various alkaloidal reagents such as tannic acid, picric acid, picrolonic acid, potassium mermeric iodide, with which the alkaloids either give a precipitate (or) turbidity.

The dried and powdered plants material is first extracted with petroleum ethers and then filtered for the removal of soluble fats. The residue is then extracted with methyl alcohol to remove cellulosic and other insoluble material and the filtrate so obtained is evaporated. The evaporated mass is dissolved in water, acidified to pH 2 and finally stream distilled to remove methyl alcohol. The dark residual solution is either allowed t stand for several days in a refrigerator or heated with molten paraffin to remove suspended impurities. The filtrate is extracted with either or chloroform to remove water soluble non basic organic material and then stem distilled when the steam

volatile alkaloids are separated. The solution of the rest of the alkaloid salts is made alkaline and again extracted with either or chloroform and the ethereal layer obtained after this extraction is evaporated to give crude alkaloids.

The resulting crude alkaloid mixture is separated into individual alkaloids by means of fractional crystallization, fractional precipitation. C.C, portion C., G.O.

4.1.5 General methods for determining structure of alkaloids

The following methods are useful to elucidate the structure of alkaloids.

1. After a pure specimen has been obtained it is subjected to qualitative and quantitative analysis. From the above analysis the molecular weight and molecular formula of the alkaloids have been determined.
2. When alkaloid contains oxygen, the functional nature of this element is determined.

a. Hydroxyl group : The presence of this group may be ascertained by the action of the acetic anhydride, acetyl chloride (or) benzoyl chloride on the alkaloid.

b. Carbonyl group : The solubility of the alkaloid in aqueous Na_2CO_3 or NH_3 indicates the presence of carbonyl group.

c. Oxo group : The presence of oxo group is readily ascertained by the formation of oxime, semicarbozone and phenyl hydrazone

d. Hydrolysis of the alkaloid and an examination of the products led to information that the compound is an ester, lactone, amide, lectam or a betaine.

e. Methoxyl group : The alkaloid is heated with conc. HI at its boiling point (120°C), the methoxyl groups are converted into methyliodide, which is then absorbed by ethanolic $AgNO_3$ and the AgI is weighed.

f. Methylene dioxyl group (-OCH_2-O-) : The presence of this group is indicated by the formation of formaldehyde when the alkaloid is heated with HCl (or) H_2SO_4.

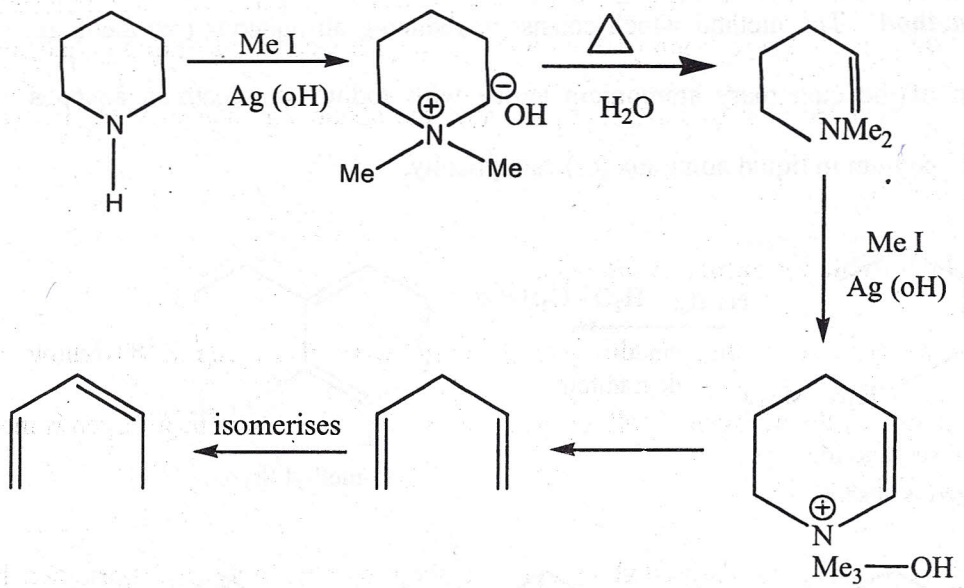
4.1.6 The Functional nature of nitrogen

a. The general reaction of the alkaloid with Ac_2O, CH_3I and HNO_2 show the nature of the nitrogen. If all the reactions are negative, then the nitrogen is most probably tertiary.

b. The presence of N-methyl groups and their number may be determined by means of the Herzig-Meyer method. When the alkaloid is heated with HI at 150 – 300°C under pressure, N-Methyl groups are converted into methyl iodide.

4.1.7 Hofmann's exhaustive Methyation method

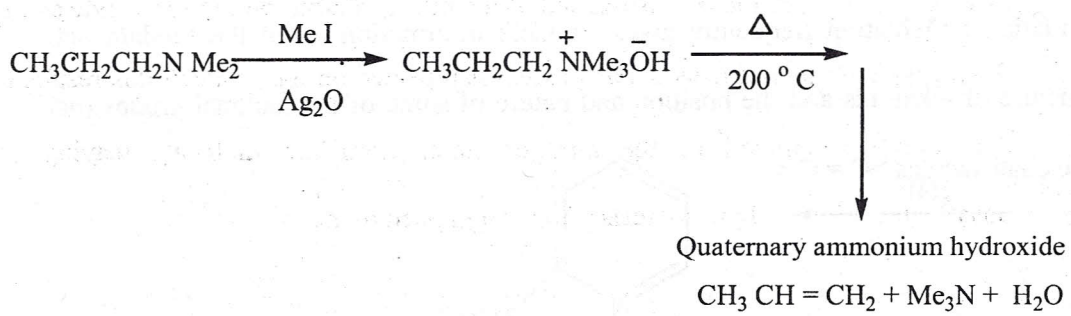
This is very important process is alkaloid chemistry. Since by its means heterocyclic rings are opened with the elimination of nitrogen, and the nature of the carbon skeleton is thereby obtained. The general procedure is to hydrogenate the heterocyclic ring, convert this compound to the quaternary methyl ammonium hydroxide which is then heated. In this stage a molecule of water is eliminated a hydrogen atom in the β position with respect to the nitrogen atom containing with hydroxyl group and the ring is opened at the nitrogen atom on the same side as the β-hydrogen atom eliminated. The process is repeated on the product, this results in the complete removal of the nitrogen atom from the molecule leaving on unsaturated hydrocarbon isomerises to a conjugated diene.



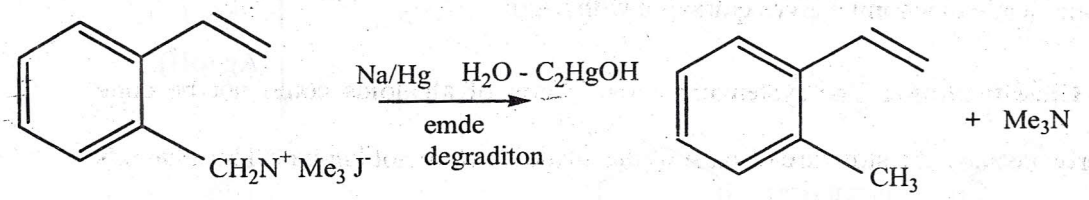
Degradation : This is the most important step in elucidating the structure of the degraded products it will be very easy to know the structure of the original molecule. The various degradative reactions used in elucidating the structure of alkaloids.

1 Hoffman exhaustive Methylation method

The method is based on the fact that when quaternary ammonium hydroxides are heated they decompose with the loss of water and clearage of a carbon-nitrogen linkage to give an olefin. The quaternary ammonium hydroxide is obtained by the complete methylation of the amine.

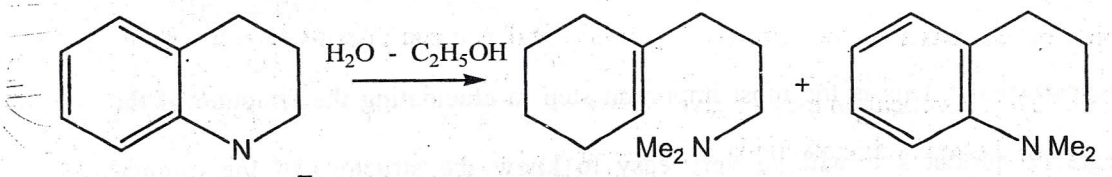


E_{mde} method : The method which consist in reducing an aqueous (or) alcoholic solution of the quaternary ammonium halide with sodium amalgam in aqueous ethanol, sodium in liquid ammonia (or) catalytically.



Tetrahydro isoquinoline
β - Hydrogen is absent

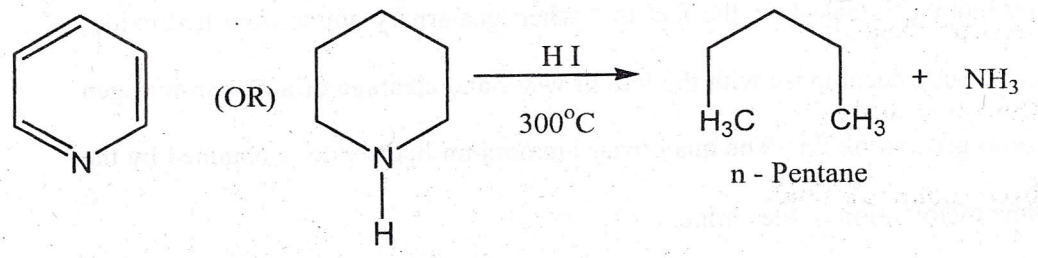
O-methyl Styrene



β - Hydrogen is Present

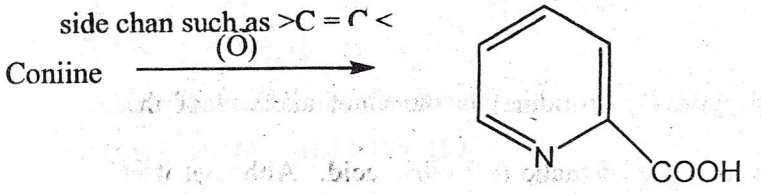
O - Propyl dimethyl aniline

Reductive degradation : The pyridine (or) piperidine nuclei in some cases may be eliminated as ammonia and n-pentane by heating with hydridic acid at 300°C



n - Pentane

Oxidation : Oxidation frequently gives valuable information about the fundamental structure of alkaloids and the position and nature of some of the factonal groups (or) side chan such as >C = C <



Picolinic Acid

Zinc dust (or) alkali distillation *Distillation of the alkaloid (or) its product over hot* zinc dust sometimes degrade it to a stable aromatic derivative. For example : Morphine gives phenanthrene on distillation with zinc dust combine gives 2-propyl pyridine, while cinchonine gives quinoline with alkali.

4.1.8 Classification : The systematic classification of alkaloids could not be done earlierly because the structure of most of the alkaloids were not known. The alkaloids were classified according to the plant genera in which they were found. E.g. Cinchona, ephdra, opium rouwoflia. It is probably most satisfactory to classify the alkaloids on the basis of the nature of main skeletal nucleus present in a group of alkaloids. The classification may be given below.

a. Phenyl ethyl amine alkaloids
b. Pyrrolidine alkaloids
c. Pyridine alkaloids
d. Pyridine pyrrolidine alkaloids
e. Tropane alkaloids
f. Quinoline alkaloids
g. Iso quinoline alkaloids
h. Phemanthrene alkaloids
i. Indole alkaloids
j. Tropolone alkaloids

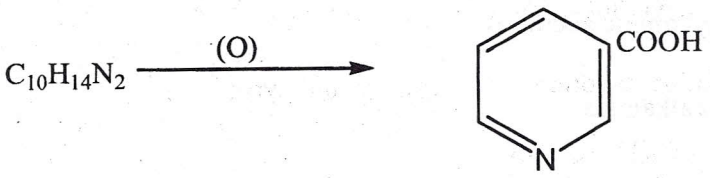
4.1.9 Nicotine : It (1-methyl-2-β-pyridyl pyrrolidine) is the chief alkaloid of the to acco plant. Where it is present as a salt of malic (or) citric acid. Although it is distributed throughout the plant, its highest concentration is found in the leaves. in

varying amounts 0.6% to 8.0%. Its name nicotine was given in the honour of Sir J. Nicot who introduced tobacco in France.

The formula was first of all, given by Pinner in 1892 but was confirmed by Pictet, its structure is based on the result of degradative methods like oxidation and on direct synthesis.

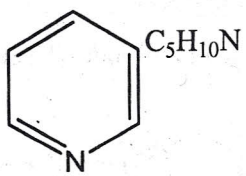
a) Molecular formula : Analysis and molecular weight determination shows its composition as $C_{10}H_{14}N_2$.

b) Oxidation : When oxidized with dichromate sulphuric acid (or) (permanganate (or) nitric acid) nicotine forms nicotinic acid



Nicotine Acid

This shows that the nicotine molecule contains a pyridine necleui substituted in the β-position.



Di-tertiary base : Nicotine forms diacid salts, such as the dihydrochloride, $C_{10}H_{14}N_2$: 2HCl and it forms two isomeric monomethiodides and a dimethiodide indicating the presence of two nitrogen atoms. Hence the side chain can not be a piperidine nucleus.

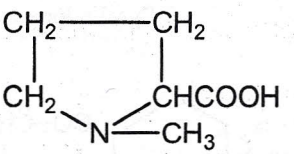
Nature of the side chain : Since the side chain, $C_5H_{10}N$ has the same composition as the piperidyl group and for sometime it was assumed that nicotine was piperidyl pyridine.

Herzig and Meyer's method shows the presence of one $N.CH_3$ group and this must be present in side chain. Again, when a nicotine zinc chloride is distilled with lime, the products pyridine methylamine and pyrrole are obtained.

The side chain is $C_4H_7.N.CH_3$. Hence the side chain is very likely a pyrolidine system. The presence of N-Methyl pyrrolidine nucleus is nicotine is very clearly indicated by the conversion of nicotine into hygrinic acid

$$C_{10}H_{14}N_2 \xrightarrow{CH_3\,I} C_{10}H_{14}N_2\ CH_3\,I \xrightarrow[NaOH]{K_4[Fe(CN)_6]} C_{10}H_{23}NO_2CH_3$$

$$\xrightarrow{CrO_3}$$



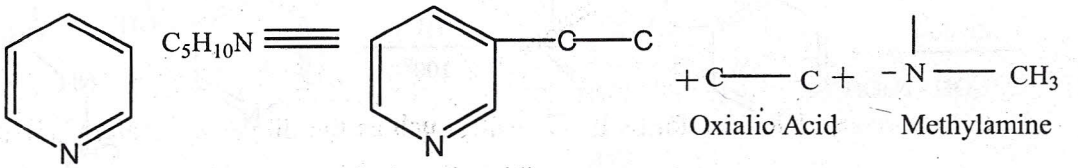
1 - Hygrinic acid

Also, on mild oxidation, nicotine is changed into nicotyrine

$$C_{10}H_{14}N_2 \longrightarrow C_{10}H_{10}N_2 + 4H$$

Nicotyrine

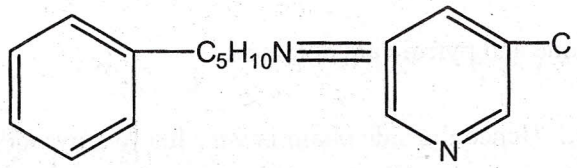
Treatment of nicotine with bromine in presence of acid gives dibromo cotinine, $C_{10}H_{10}NO_2\ Br_2$. This on heating with a mixture of sulphous acid and sulphuric acid forms 3-acetyl pyridine, oxalic acid and methylamine.



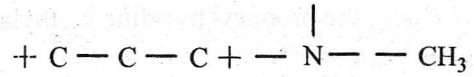
3- Acetyl pyridine

Oxialic Acid Methylamine

Now bromine in the presence of hydrobromic acid, reacts with nicotine to give dibromoticonine, $C_{10}H_{10}NO_2\ Br_2$ which, on heating with barium hydroxide solution at 100°C, forms nicrotonic acid, malonic acid and methylamine. Hence the structure of nicotine must also account for the following skeleton structures.

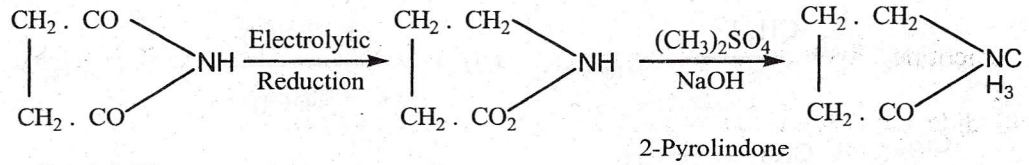


Nicotinic acid

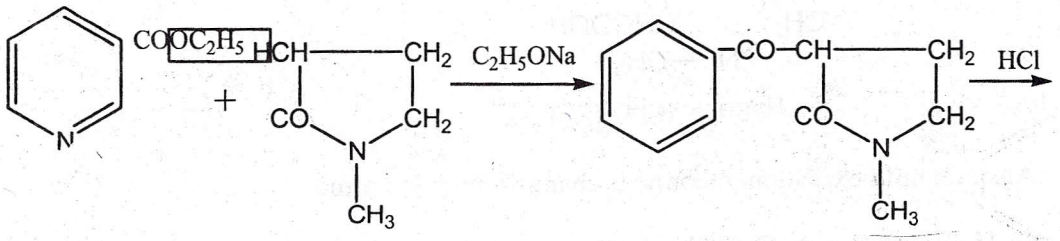


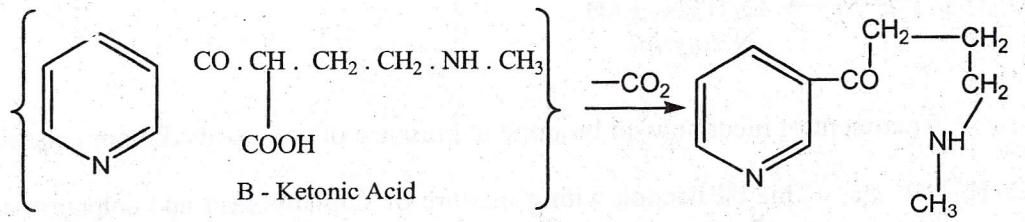
Malonic acid Methylamine

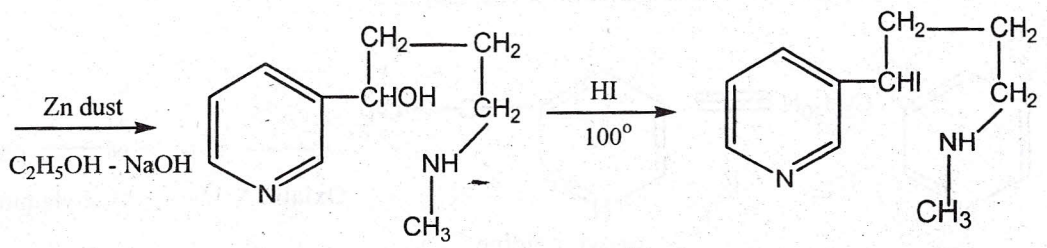
Synthesis : Spath and Bretschneider's synthesis (1928)

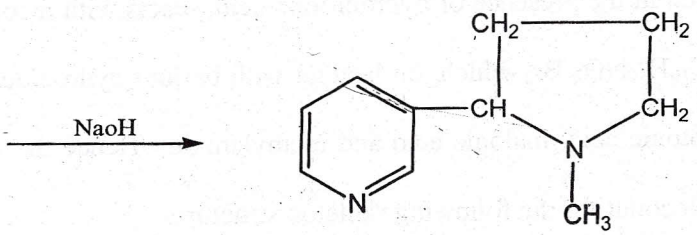


Succinimide 2-Pyrolindone







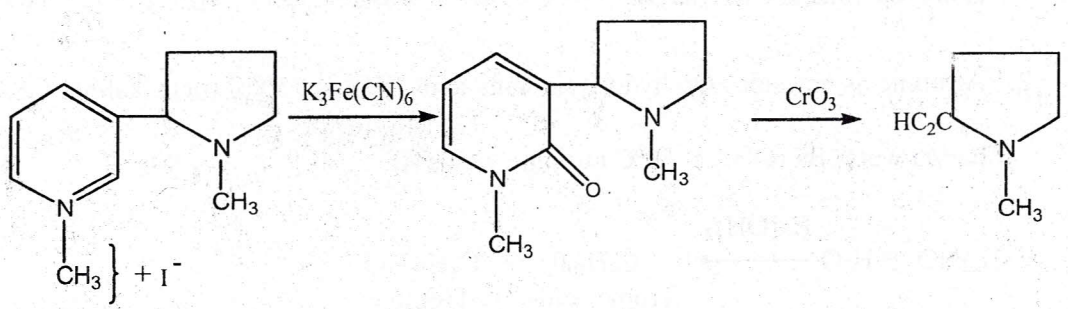


(±) Nicotine

The dl-nicotine is resolved by means (+)-tartaric acid, the synthetic (-)-nicotine is identical with the natural compound.

4.1.10 Stereochemistry : Nicotine contain pyridine ring and pyrrolidine ring. The pyrrolidine ring has L- configuration and rotating in the plain polarized line towards left side. It is Leo form. It is confirmed by Karrer by the following reaction.

Nicotine hydrodide forms nicotine isomethiodide when warmed with methyliodide and this, oxidation with potassium ferricyanide, is converted into nicotine with, an oxidation with chromium trioxide, gives L (-) hygrinic acid.



Nicotine isomethiodide Nicotone L(-)-hygrinic acid

4.2.1 Atropine ($G_7H_{23}NO_3$) m.p = 118°C

It occurs in deadly night shade (Atropa delladome) together with Hyoscyamine. Hyoscyamine is optically active (α) D-22°, but readily racemises to atropine is (+) hysocyamine.

When warmed with barium hydroxide solution, atropine is hydrolyzed to (±) tropic acid and trapine (an alcohol), thus is the tropine ester of tropic acid. When (-)-hysocyamine is hydrolysed with cold water, tropine and (-)-tropic acid are obtained.

1. Molecular formula : The molecular formula of atropine as deduced from the analytical data is $C_{17}H_{22}NO_3$.

2. Atropine as an ester : On hydrolysis with acids, HCl at 130°C (or) alkalines i.e, baryta water Ba $(OH)_2$ at 60°C atropine yields (I).

$$C_7H_{22}NO_3 + H_2O \xrightarrow{Ba(OH)_2} \underset{\text{Tropic acid}}{C_9H_{10}0_3} + \underset{\text{Tropine}}{C_8H_{15}NO}$$

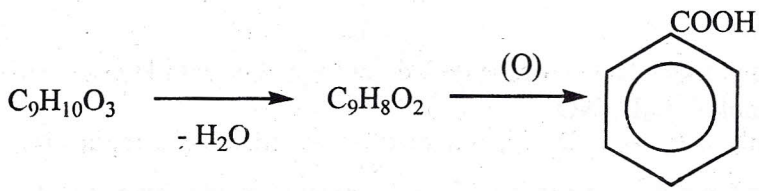
He evaporated a mixture of tropine and tropic acid in presence of hydrochloric acid and obtained atropine. Atropine can not be an amide because tropine, the product of hydrolysis is a tertiary base.

4.2.2 Structure of topic acid :

a. Its molecular formula is $C_9H_{10}O_3$.

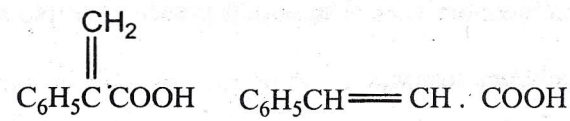
b. It contains the carboxyl group as well as alcoholic group as determined by usual tests.

c. Tropic acid, on heating with baryta water, gives atropic acid which on vigorous oxidation with chromic acid yields benzoic acid.

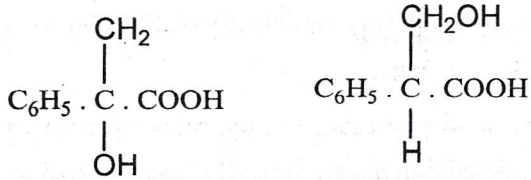


Tropic acid Atropic acid Benzoic acid

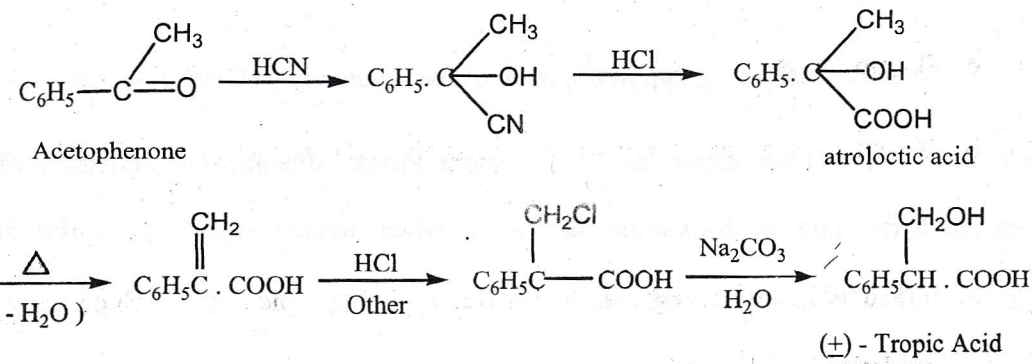
Again atropic acid, isomeric with cinnamic acid, may be represented as



But since II is a well known compound, the cinnamic acid, I must be atropic acid. Lastly since atropic acid is formed by the dehydration of tropic acid, addition of a molecule of water to the former would therefore give tropic acid. Hence tropic acid must be either II (or) III



Mackenzie and wood (1919) :



4.2.3 Structure of tropine

a. Its molecular formula is $C_8H_{15}NO$

b. When treated with methyl iodide, tropine forms a crystalline additive product

$$C_8H_{15}NO + CH_3I \longrightarrow C_8H_{15}NO.CH_3I$$

The nitrogen atom is, therefore, tertiary. The actual presence of N-methyl group is indicated by the results of alkaline fusion.

c. Tropine presence of dehydrating agents like sulphuric acid is glacial acetic acid, is changed into tropidine.

$$\underset{\text{Tropine}}{C_8H_{15}ON} \longrightarrow \underset{\text{Tropidine}}{C_8H_{13}N} + H_2O$$

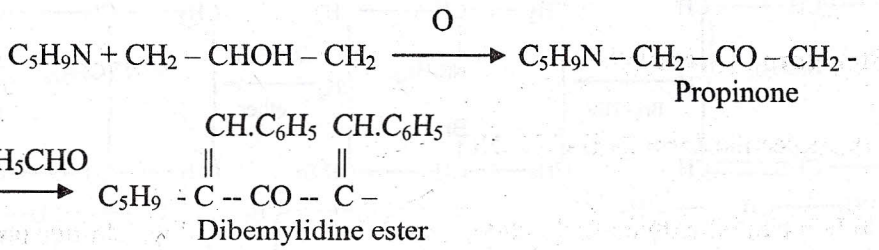
It indicates that tropine contains a secondary (or) tertiary alcoholic hydroxyl group.

d. Tropine on gentle oxidation with cromic acid gives an optically inactive ketone, tripinone.

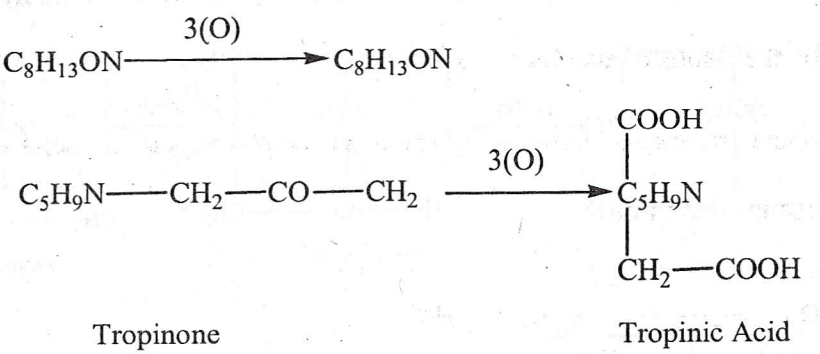
$$C_8H_{15}ON \xrightarrow{CrO_3} C_8H_{13}ON$$

Thus the alcoholic group in tropine must be secondary (> CHOH) group

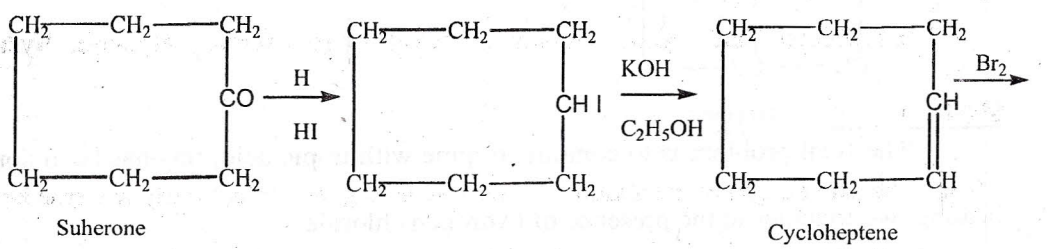
e.Wilsttater (1897) has shown th[illegible]inone forms a dibenzyldine derivative with benzaldehyde, and a di-oximino derivative when treated with aryl nitrite and hydrochloric acid

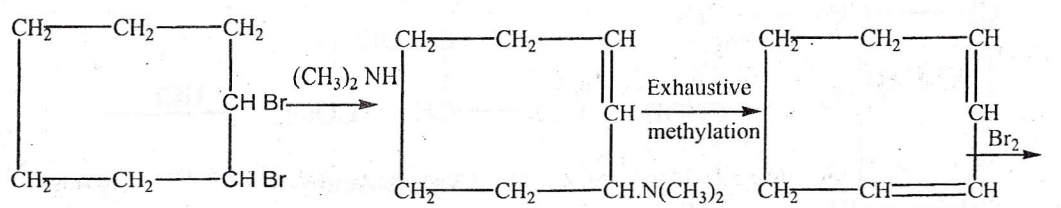


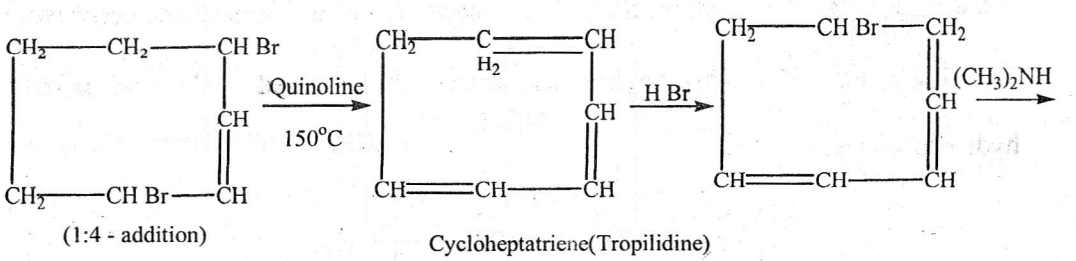
f.Tropinone on further oxidation gives a dicarboxylic acid, tropinic acid with the same number of carbon atoms

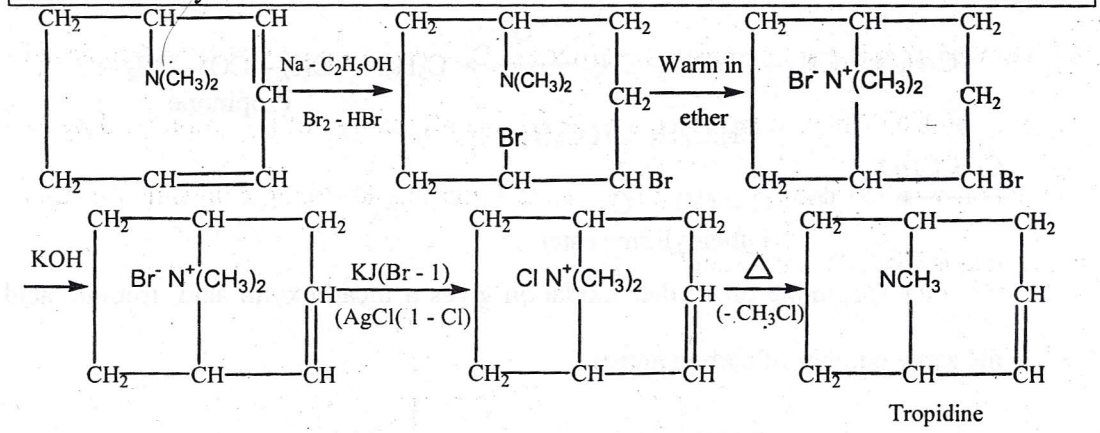


4.2.4 Synthesis : 1 Will Statter synthesis (1900-1903)

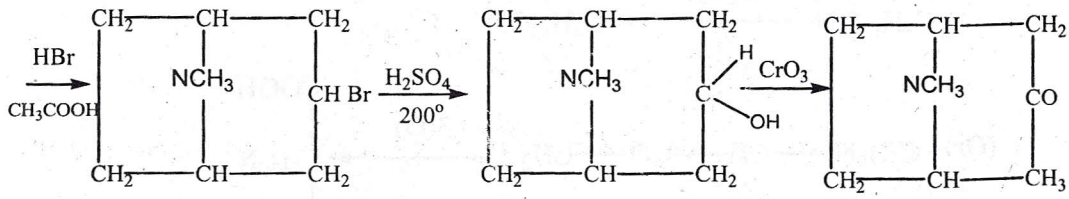






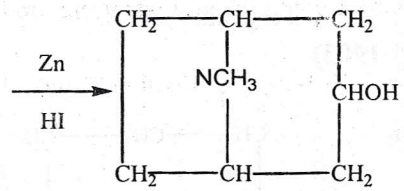


Tropidine



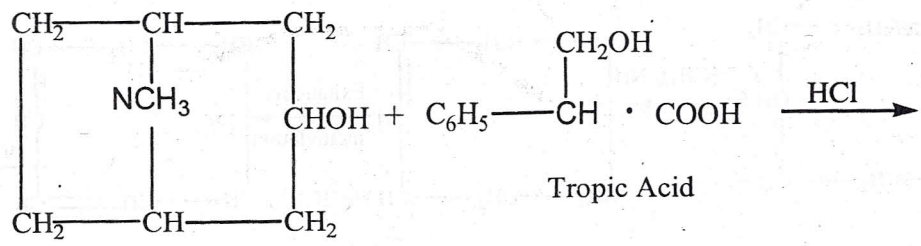
P - Tropine

Tropinone



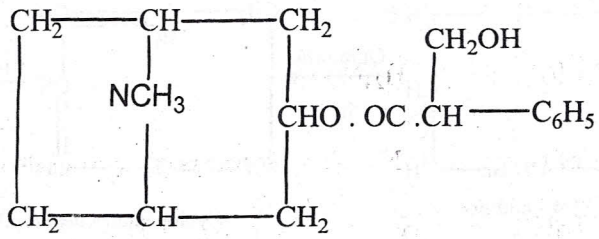
Tropine

The final problem is to combine tropine with tropic acid; this has been done by heating two together in the presence of hydrogen chloride.



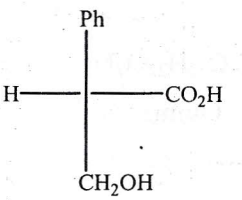
Tropic Acid

Tropine

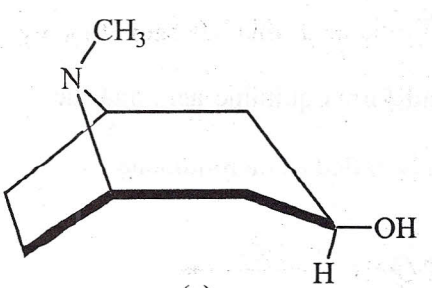


Atropine

4.2.5 Stereo chemistry : Atropine, $C_{17}H_{23}NO_3$, consists of tropine molity and tropic aid molity. FODOR have established the absolute configuration of (-)- tropic acid by its correlation wit (-)- alanine. According to the Cann-Ingold-Prelog convention natural tropic acid is (S)- (-) – tropic acid

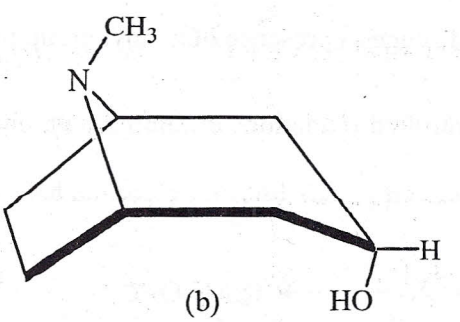


Tripinone can be reduced to a mixture of two alcohols and tropine and Ψ-tropine (psedotropine). Fodor proposed the boat confirmation in both isomers, the axial orientation of methyl group in both isomers,but axial hydroxyl in Ψ-tropine and equatorial hydroxyl in tropine. The evidence was based on rearrangements similar to those used for ephedrine and Ψ- ephedrine



(a)

Ψ - Tropine



(b)

Tropine

4.2.6 Quinine

1. Molecular formula : $C_{20}H_{24}N_2O_2$

2. Presence of two tertiary N atoms : It forms dimethoidide on treatment with CH_3I.

$$C_{20}H_{24}N_2O_2 + 2CH_3I \rightarrow C_{20}H_{24}N_2O_2.2CH_3.I$$

Crystalline dimethiodide

3. Presence of secondary alcoholic group : Since quinine forms a mono acelate and mono benzoate, one – OH group must be present and this is secondary alcoholic in nature.

$$\underset{\text{Quinine}}{C_{20}H_{20}N_2} \xrightarrow{CrO_3} \underset{\text{Quininone}}{C_{20}H_{22}O_2N_2}$$

4. Presence of a methyl group : The second oxygen atom is quinine is present as – OCH_3 group

$$-O-CH_3 \xrightarrow[HCl]{\Delta} CH_3Cl + -OH$$

Methylchloride

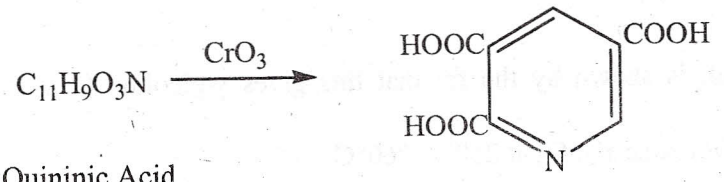
5. Presence of vinyl group (-CH =CH_2) : On controlled oxidations with $KMnO_4$ quinine gives a mono carboxylic acid and formic acid. The formation of formic acid suggests presence of a vinyl group in quinine.

6. Controlled oxidation of quinine with chronic acid forms quininic acid and the other component known as 'second half' commonly called as meroquinene

$$\underset{\text{Controlled oxidation}}{C_{20}H_{24}O_2N_2} \xrightarrow{CrO_3} \underset{\text{Quininic acid}}{C_{11}H_9O_3N} + \underset{\text{Meroquinene}}{C_9H_{15}NO_2}$$

7. Structure of quininic acid

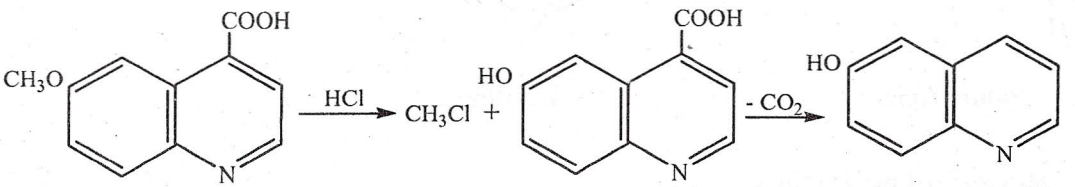
Quininic acid on oxidation with chronic acid forms pyridine – 2 : 3 : 4 tri-carboxylic acid.



Quininic Acid

Pyridine 2 : 3 : 4 - Tricarboxylic Acid

Position of – OCH_3 group : Quininic acid on heating with hydrochloric acid is demthylated and then decarboxylation of the demethylated product gives 6-hydroxy quinoline



1, Quinic Acid

6-Hydroxy Quinoline

Structure of meroquinene :

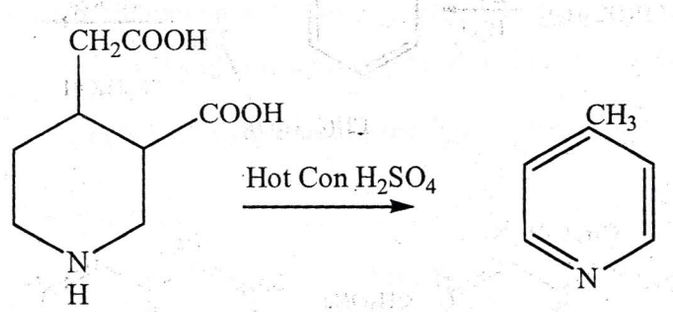
1. The molecular composition of meraquinene is $C_6H_{15}O_2N$
2. Presence of ethylenic linkage : On reduction, neroquinene takes up one molecule (H_2) of hydrogen which suggests that ethylenic double bond is present in it.

$$C_9H_{15}O_2N \xrightarrow[H_2]{\text{Cat. reduction}} C_9H_{15}O_2N$$

3. On oxidation with acidic $KMnO_4$, meroquinine yields a dicarboxylic acid, cincholoiponic acid and formic acid. Cincholoiponic acid on further oxidation gives loiponic acid.

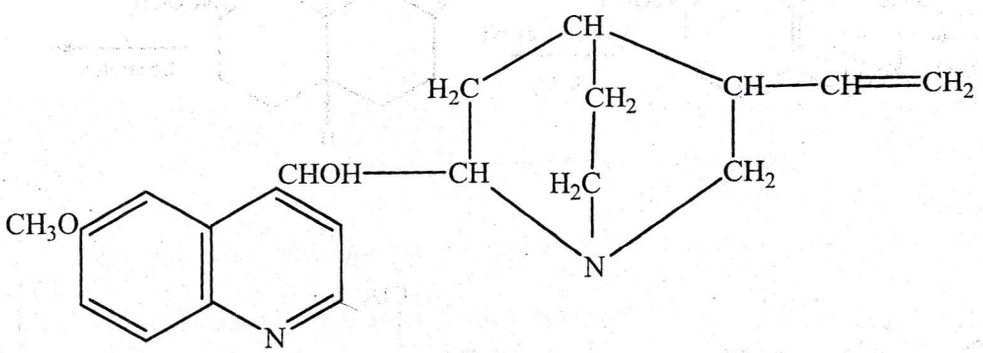
$$C_9H_5O_2N \xrightarrow[KMnO_4]{\text{Acidic}} HOOOH + \underset{\text{Cincholoiponic Acid}}{C_8H_2NO_4} \xrightarrow{O} \underset{\text{Loiponic acid}}{C_7H_{11}NO_4}$$

Cincholoponic acid, is shown by the fat that this gives γ-picoline (4-methyl pyridine) by the action of hot conc.H_2SO_4 at 250° – 260°C

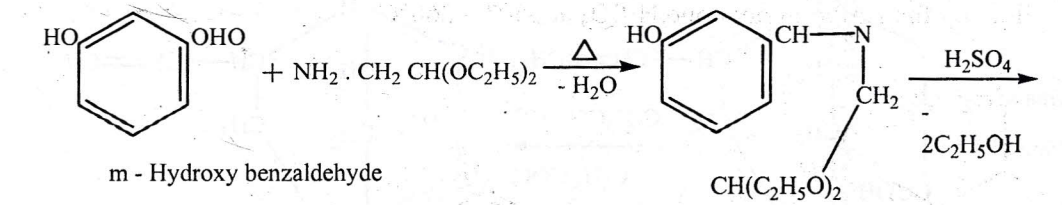


Cincholoiponic Acid γ - Picoline

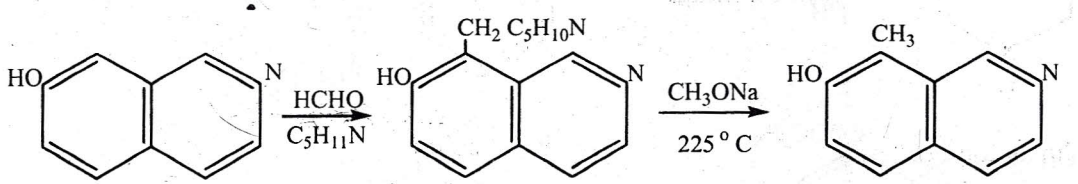
4. Structure of the Quinine

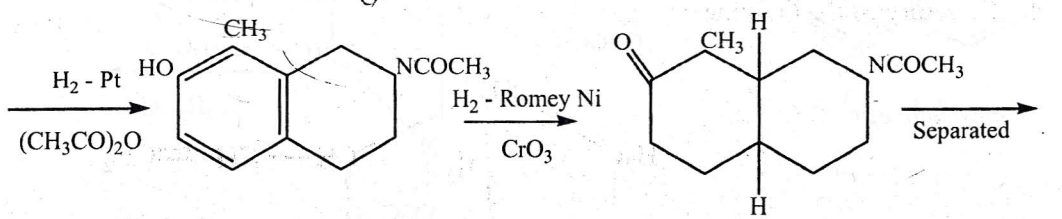


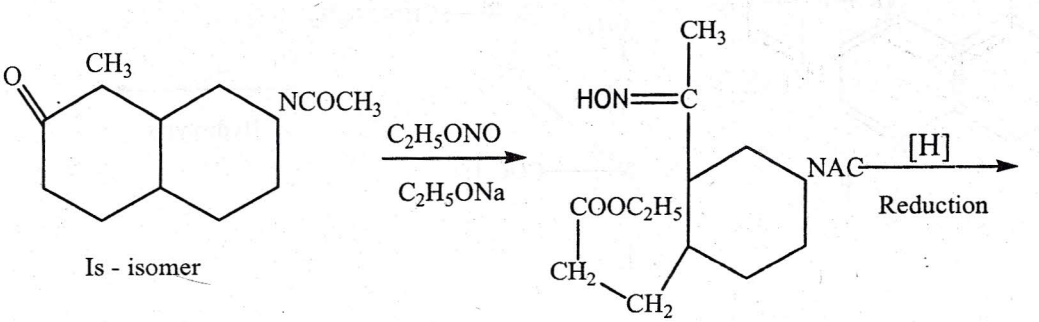
4.2.7 Synthesis (R.B.Woodword, W.E. Doering, 1944)



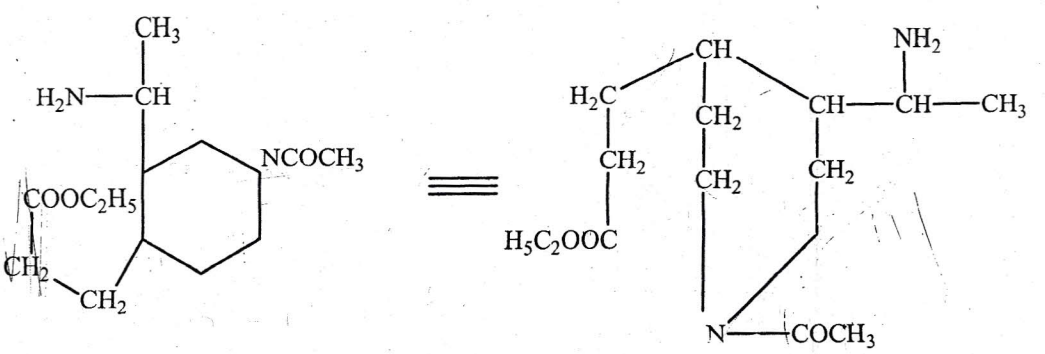
m - Hydroxy benzaldehyde

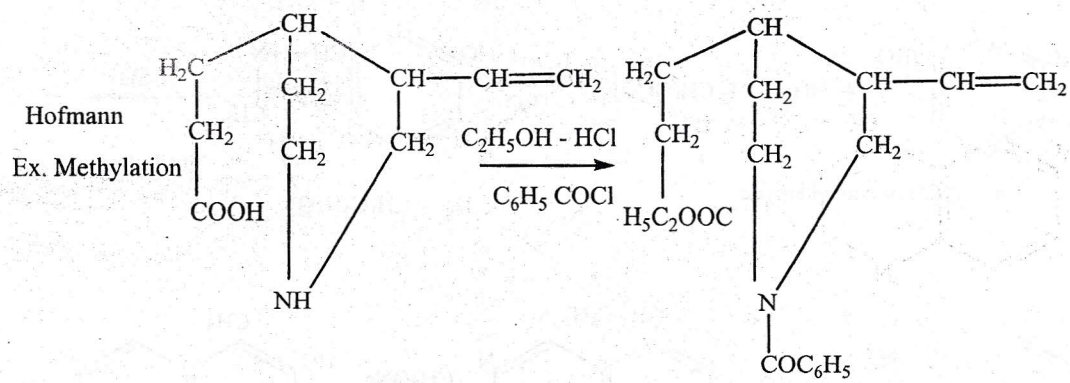


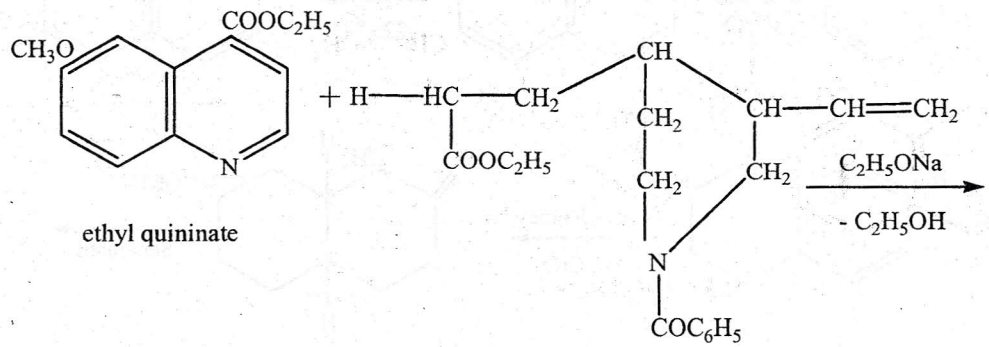


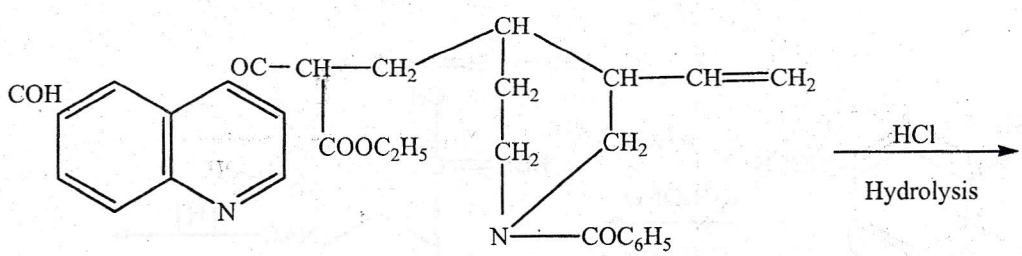


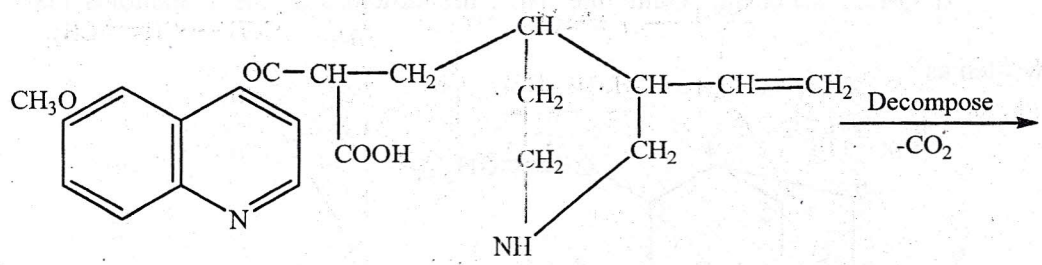
Is - isomer

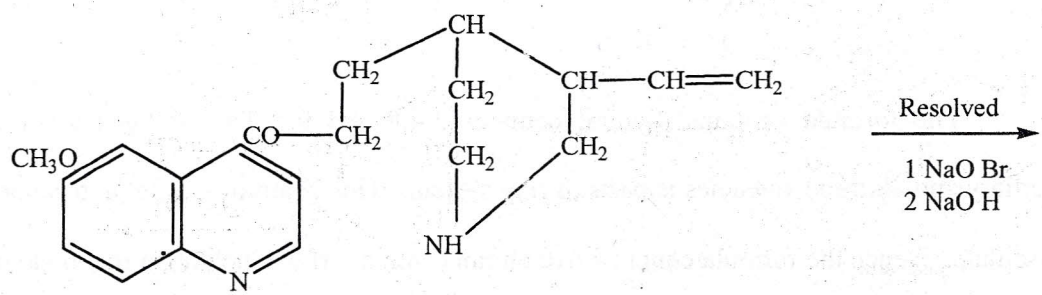



Hofmann
Ex. Methylation
C_2H_5OH - HCl
C_6H_5 COCl

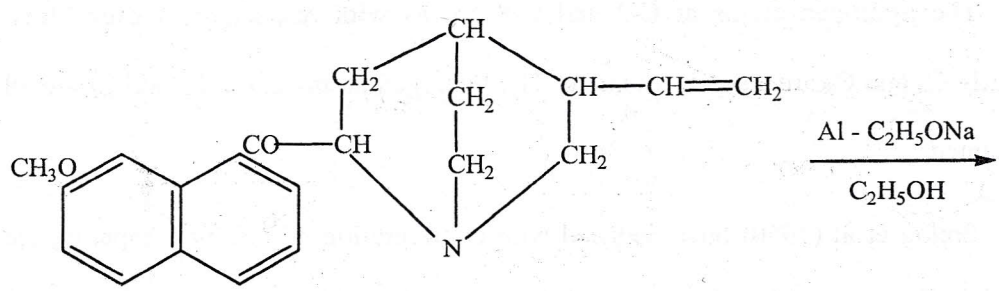

ethyl quininate
C_2H_5ONa
- C_2H_5OH


HCl
Hydrolysis

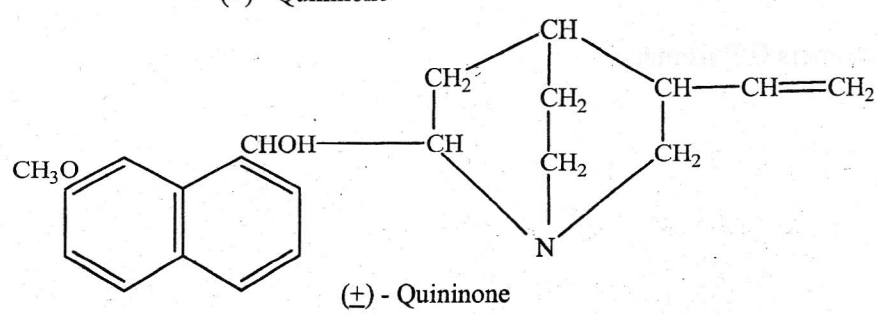




(±) - Quinotoxine



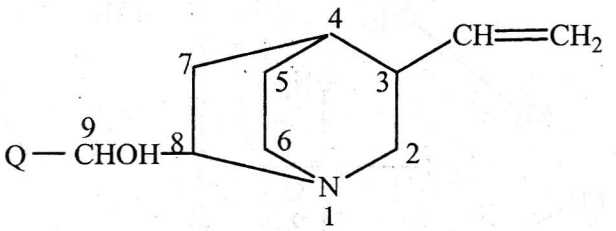
(+) - Quininone



(±) - Quininone

4.2.8 Stereochemistry

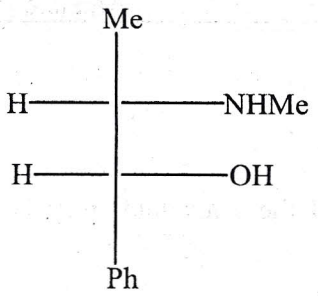
If Q-represents the 'Quinoline half', the structure of these alkaloids may be written as



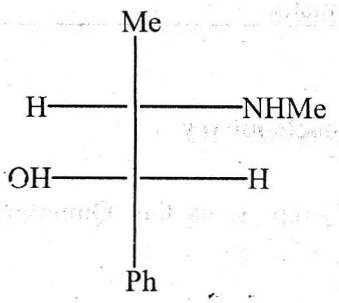
The formula contains 4-chiral contains 3,4,8 and 9. The nitrogen atom is tertiary and all three valencies is parts of ring system. This N atom is chiral and cannot oscillate. Hence the formula contains five chiran centres.. If we include nitrogen atom, however, the bridge must be a cis fusion atoms 1 and 4 behaves as one 'chiral unit'

The hydrogen atoms at C-3 and C-8 are as with respective to each other. Similarly C_4 and C_8 are also cis oriented. The hydrogen atoms at C_3, C_4 and C_8 are all cis oriented.

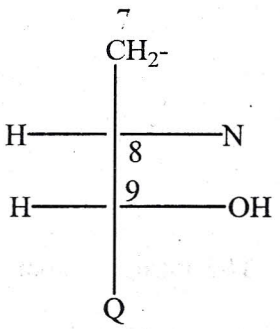
Prelog et al (1950) have deduced with configuration at C-9 by comparing the basicities of (-)- ephedrine and (+)-4 ephidrine with (2)-quinine and (+) ephedrine and all isomers C-9 isomers.



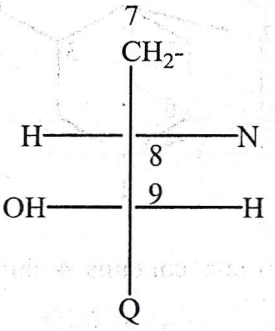
(-) - ephedrine



(+) - Ψ - ephedrine

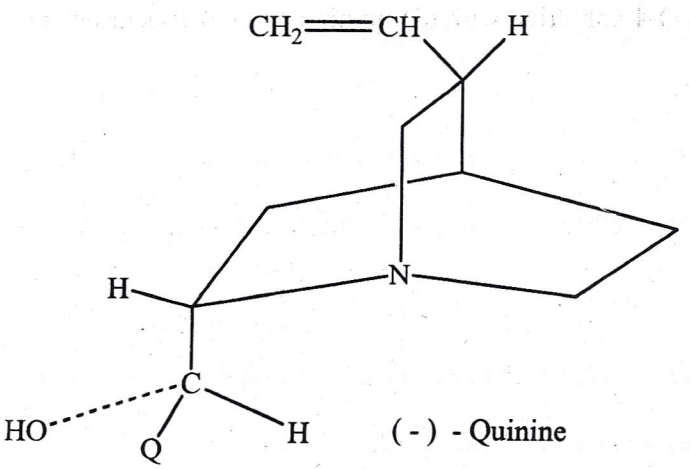


(-) - quinine



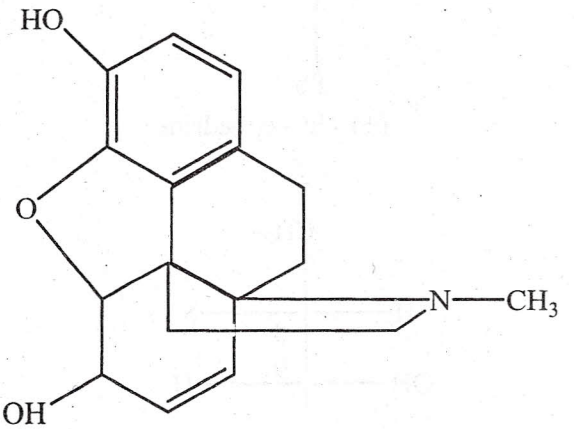
(+) - ephedrine

Inspection of the pKa values shows that Ψ-ephedrine is a stronger base the ephedrine. Similarly ephequinine is a stronger base than quinine basing on the results the authors purposed similar configuration for (+)-ephaquinine and (+)Ψ-ephedrine both of them of having three configuration on other hand erythreo configuration is purposed for (-)-quinine and (-)-ephedrine. It is therefore no possible to write absolute configuration(-)-quinine.



(-) - Quinine

4.3.1 Morphine



Molecular formula $C_{17}H_{19}O_3N$

Nature of N-atom : One molecule of methylicdide is added to morphine is from quatarnary salt. This sources that contains tertiary nitrogen atom. It is conformed by Haffmann's degradation.

Nature of oxygen : Morphine when acetylated (or) benzlated it gives diacetyl (or) dibenzyl derivation. This indicates morphine contains two – OH groups

$C_{17}H_{17}ON(OH)2$ → ($C_{13}COCl$) $C_{17}H_{17}ON(OCOCH_3)_2$

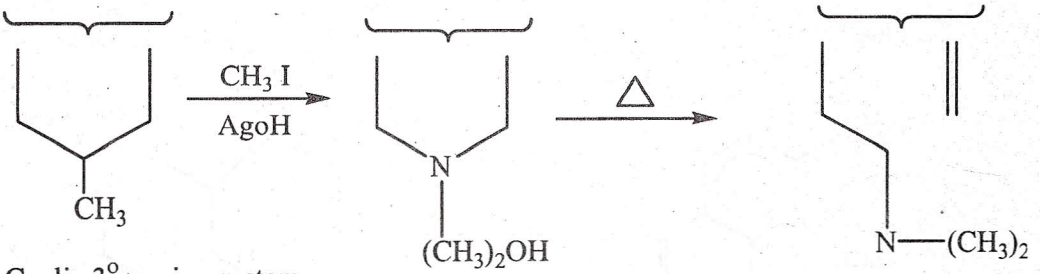
$C_{17}H_{17}ON(OH)2$ → (C_6H_5COCl) $C_{17}H_{17}ON(OCOC_6H_5)$

With $FeCl_3$ morphine gives characteristic colour, it is also solubility NaOH solution to form mono sodium salt. Which is reconverted into morphine but possessing CO_2 gas through it.

Presence of athylenic bond : When codeine reduced catalytically $C_{18}H_{23}O_3N$ suggesting the presence of an isolated ethylenic bond.

Presence of benzene nucleus : Morphine when brominated gives a mono bromo derivative along with evolution of HBr. This indicates that morphine contains benzene nucleus

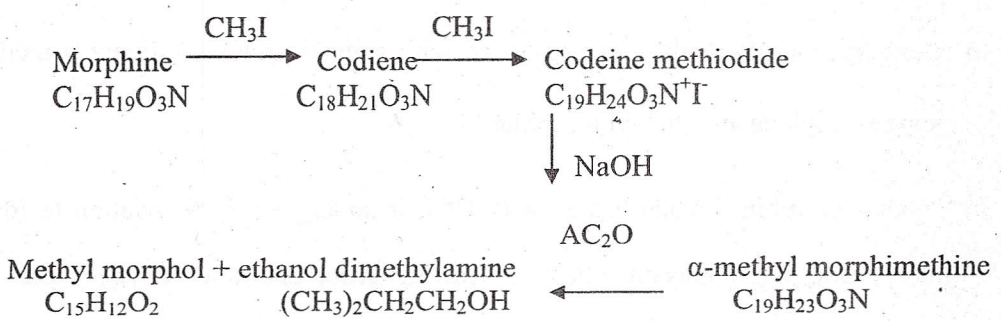
If codiene contains a cyclic tertiary amine system, the product obtain would passes less number of carbon atoms and there is also loss of nitrogen. The experimental results indicates that codiene contains cyclic 3° amine system.



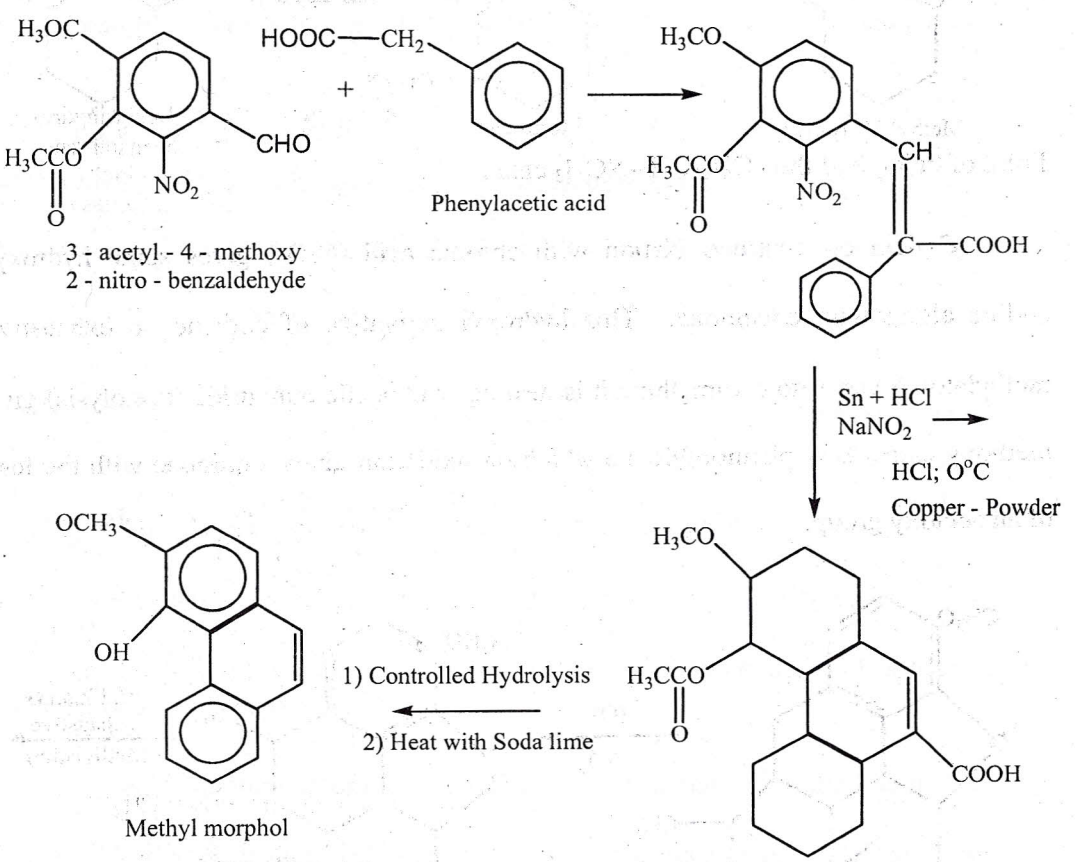
Cyclic 3° amine system

3° amine system in α – codeinmethene

When codeine is treated with CH_3I, it gives codeine methiodide this when boiled with NaOH solution it gives α-methyl morphine this on heating with AC_2O gives a mixture of methyl morphol and ethanol dimethyl amine



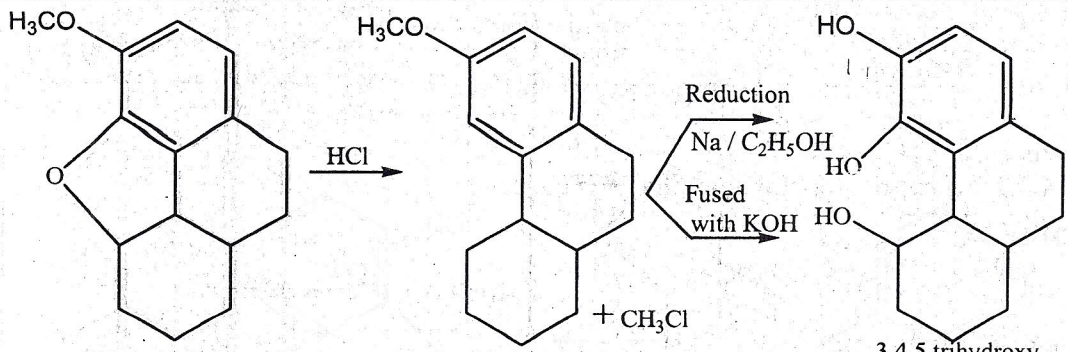
4.3.2 Structure of methyl morphol :Synthesis



4.3.3 Structure of morphenol :

a) β-methyl morphomethine when heated with water it gives a mixture trimethyl amine, ethylene and methyl morphinol

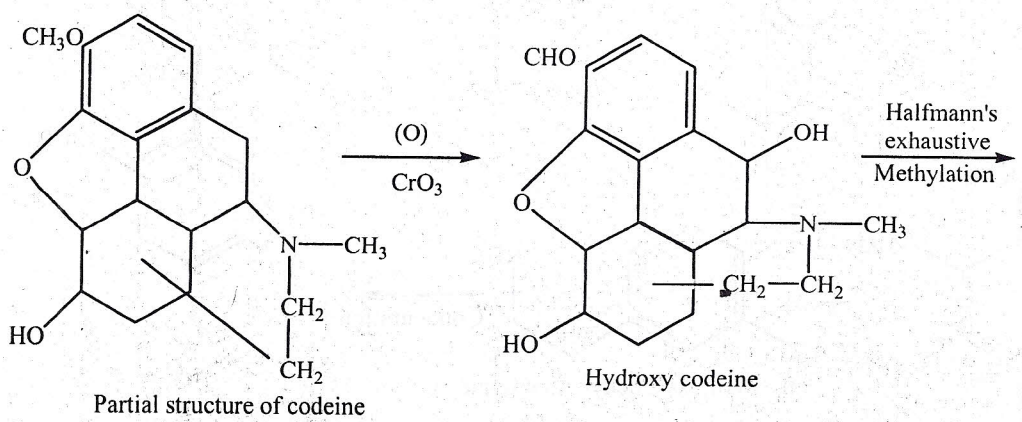
b) Methyl morphinol when heated with HCl, it undergoes d-methylation to form morphinol. It contains one phenolic hydroxyl group and inhert oxygen atom



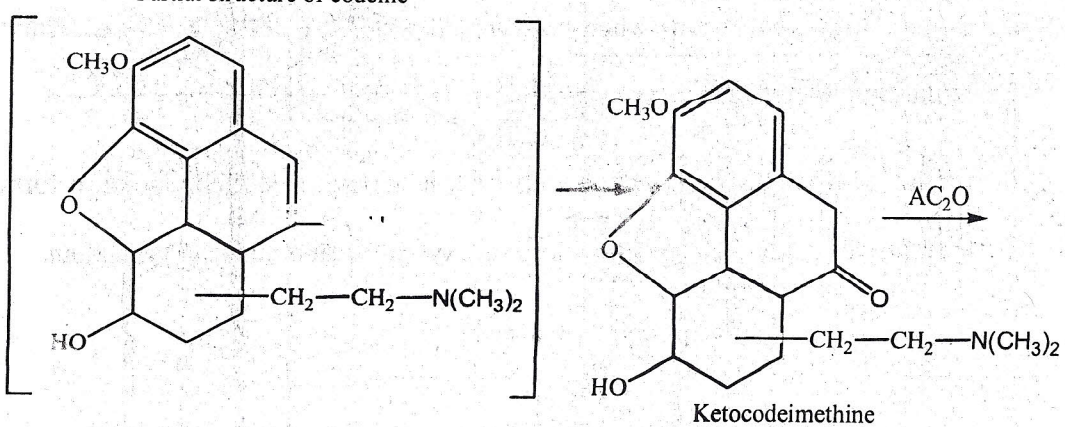
Methyl Morphenol Morphenol 3,4,5 trihydroxy phenanthrene

Point of linkage of the $-CH_2-CH_2-NCH_3$ chain

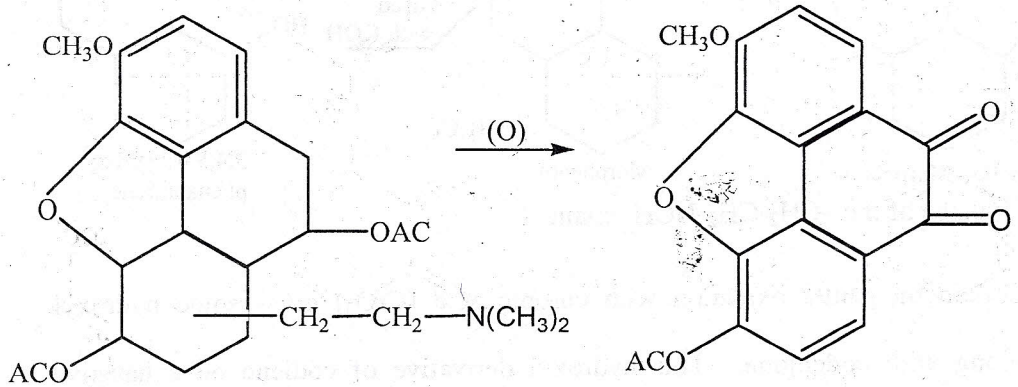
Codein on gentle oxidation with chronic acid (CrO_3) gives some hydroxyl codine along with codeinone. This hydroxyl derivative of codiene on exhaustive methylaton given keto codimethine it is heating with acetic onhydride (acetolysis) give methoxy diaacetoxy phemonthreone which on oxidation gives a quinone with the loss of an acetoxy group.



Partial structure of codeine Hydroxy codeine



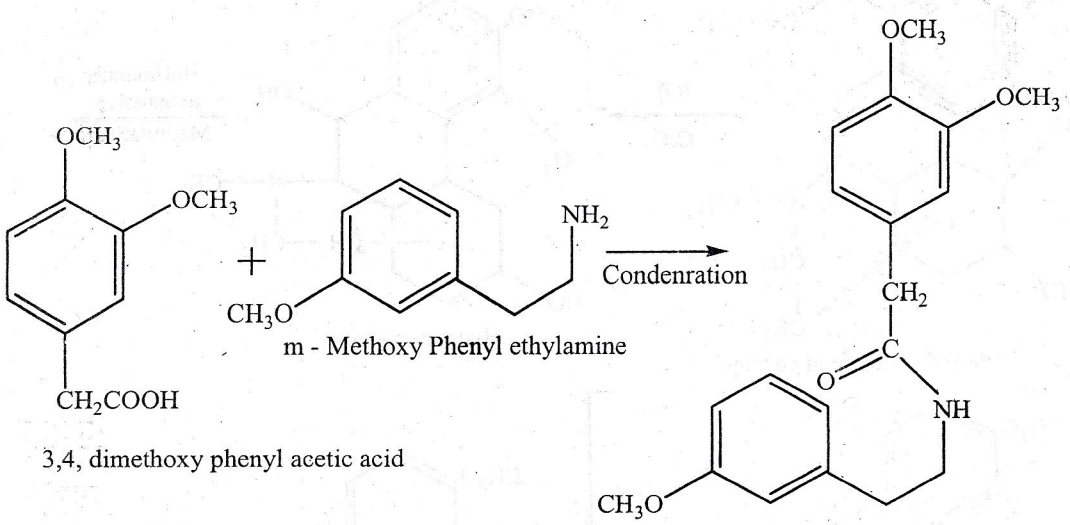
Ketocodeimethine



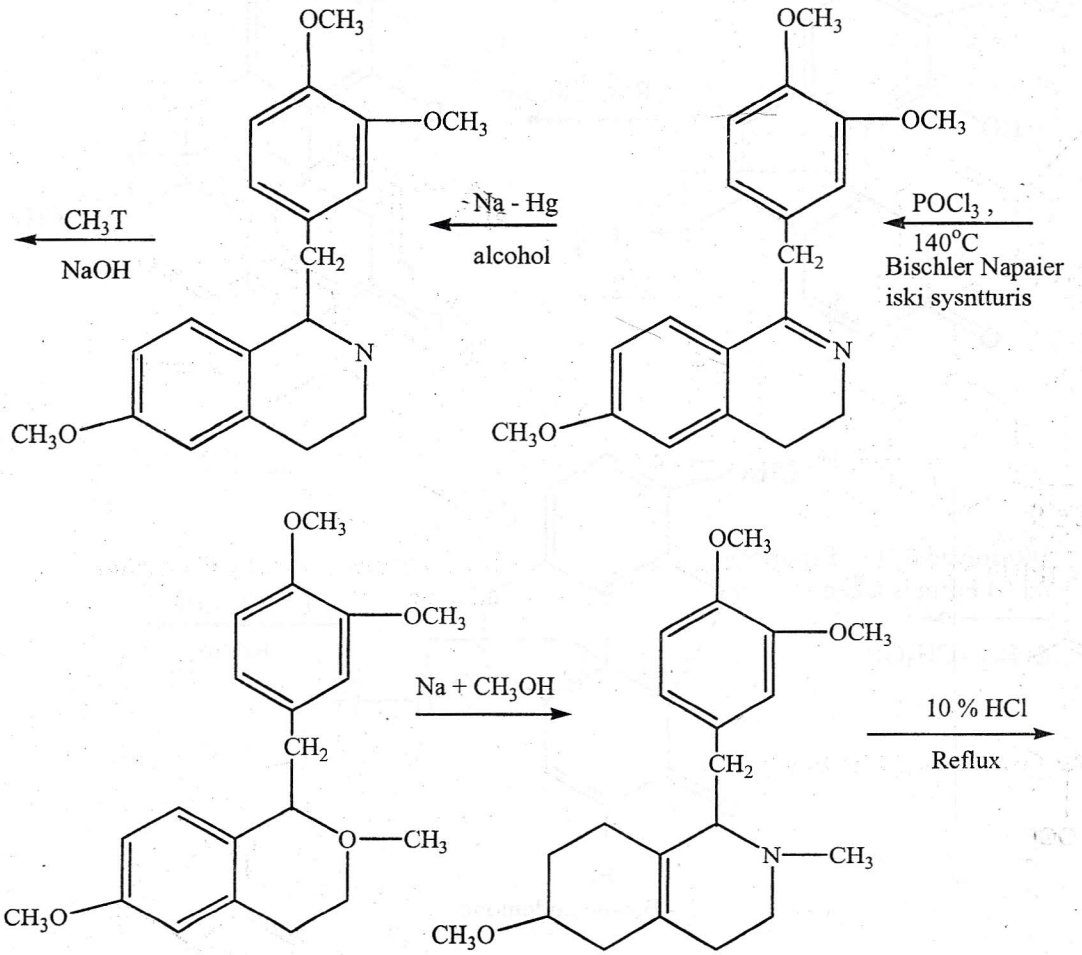
Methoxy diacetoxy Phenathrene

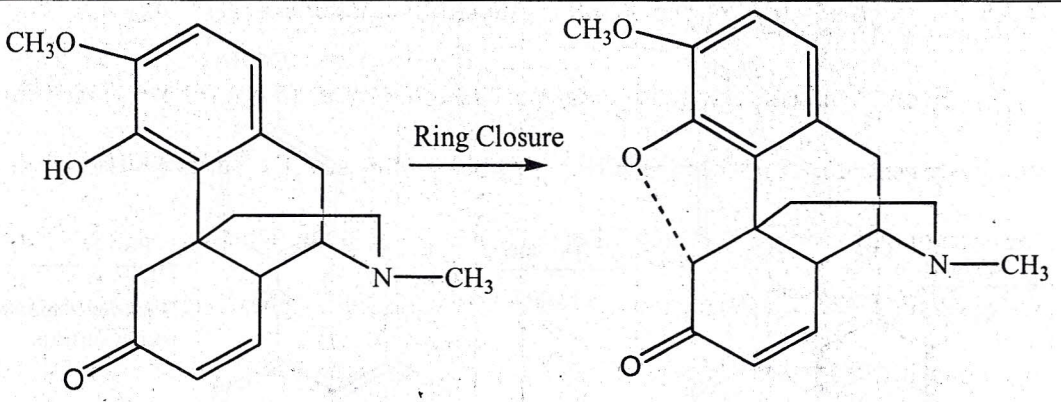
Methoxy mono acetoxy Phenanthra - quinone

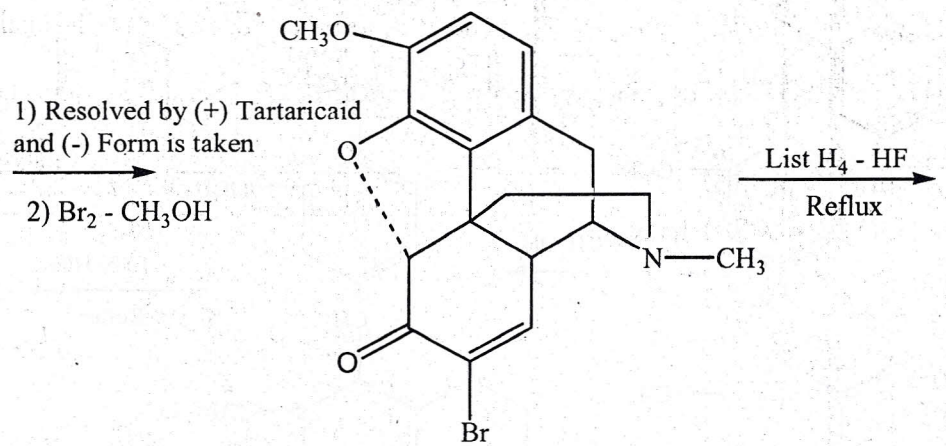
4.3.4 Synthesis of Morphine :



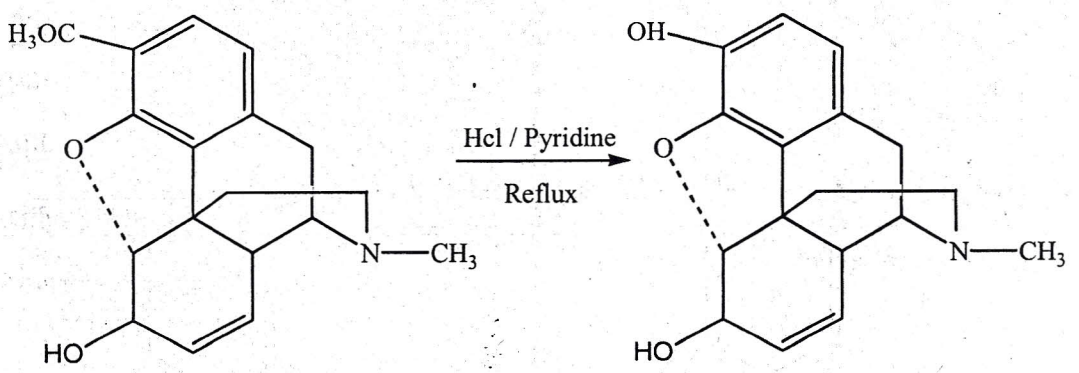
3,4, dimethoxy phenyl acetic acid


OCH3
OCH3
CH2
N
CH3O
CH3T
NaOH
Na - Hg
alcohol
POCl3 ,
140°C
Bischler Napaier
iski sysntturis
Na + CH3OH
10 % HCl
Reflux
O—CH3
N—CH3





1 - Bromo codeinone



Codeine

Morphine

4.3.5 Stereochemistry: Stereochemistry morphin and codeine

Each of these compounds contains five chiral centres (5,6,9, 13 & 14) the bridge end system is present across the positions 9, 13 and it is in the cis form. So, each of these compounds exsist in 8 pairs of enensiomers. The hydrogen atom at C-5, C-6 and C-14 are all cis and the bridge at C-9 and C-13 is also cis. These stereochemistry has been confirmed by x-ray analysis. The absolute stereochemistry at C-13 andC-14has been established from the dicarboxylic acid (A) obtained from degradation of thebaine. The configurational formula of morphine and codeine may be written as (B). The chair form has been used for the cyclohexanening and rings I, II and the oxide bridge lie approximately in the plane of the paper and ring III and IV are approximately perpendicular to the plane of the paper.