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Alkaloids

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- General methods of structural determination
- Structural elucidation of some alkaloids like-
  - Morphine, emetine, reserpine.

Introduction

- Alkaloids are a group of naturally occurring chemical compounds that mostly contain basic nitrogen atoms.
- The term alkaloid was coined by Meissner, a German pharmacist, in 1819.
- Alkaloids are cyclic organic compounds containing nitrogen in a negative state of oxidation with limited distribution among living organisms.

Properties

- Most alkaloids contain oxygen in their molecular structure; those compounds are usually colorless crystals at ambient conditions.
- Some alkaloids are colored, like berberine (yellow) and sanguinarine (orange).
- Most alkaloids are weak bases, but some, such as theobromine and theophylline, are amphoteric.
- Many alkaloids dissolve poorly in water but readily dissolve in organic solvents.
- Most alkaloids have a bitter taste or are poisonous when ingested.

Classification

- The alkaloids, as an important and enormously large conglomerate of naturally occurring nitrogen containing plant substances having very specific as well as most diversified pharmacological properties may be classified in a number of modes and means.
    i. Biosynthetic Classification
    ii. Chemical Classification
    iii. Pharmacological Classification
    iv. Taxonomic Classification

Classification

i. Biosynthetic Classification

In this particular instance the significance solely lies to the precursor from which the alkaloids in question are produced in the plant biosynthetically.

1) Indole alkaloids derived from tryptophan.
2) Piperidine alkaloids derived from lysine.
3) Pyrrolidine alkaloids derived from ornithine.
4) Phenylethylamine alkaloids derived from tyrosine.
5) Imidazole alkaloids derived from histidine.

Classification

ii. Chemical Classification

Here the alkaloids are classified based on the presence of the basic heterocyclic nucleus (*i.e.*, the chemical entity).

1) Pyrrolidine alkaloids *e.g.*, Hygrine
2) Piperidine alkaloids *e.g.*, Lobeline
3) Pyrrolizidine alkaloids *e.g.*, Senecionine
4) Tropane alkaloids *e.g.*, Atropine
5) Quinoline alkaloids *e.g.*, Quinine
6) Isoquinoline alkaloids *e.g.*, Morphine
7) Aporphine alkaloids *e.g.*, Boldine
8) Indole alkaloids *e.g.*, Ergometrine
9) Imidazole alkaloids *e.g.*, Pilocarpine
10) Diazocin alkaloids *e.g.*, Lupanine
11) Purine alkaloids *e.g.*, Caffeine
12) Steroidal alkaloids *e.g.*, Solanidine
13) Amino alkaloids *e.g.*, Ephedrine
14) Diterpene alkaloids *e.g.*, Aconitine

Classification

iii. Pharmacological Classification

Interestingly, the alkaloids exhibit a broad range of very specific pharmacological characteristics. Perhaps this might also be used as a strong basis for the general classification of the wide-spectrum of alkaloids derived from the plant kingdom.

1) Morphine as Narcotic analgesic
2) Quinine as Antimalarial
3) Strychnine as Reflex excitability
4) Lobeline as Respiratory stimulant
5) Boldine as Choleretics and laxatives
6) Aconitine as Neuralgia
7) Pilocarpine as Antiglaucoma agent and miotic
8) Ergonovine as Oxytocic
9) Ephedrine as Bronchodilator
10) Narceine as Analgesic (narcotic) and antitussive

Classification

iv. Taxonomic Classification

This particular classification essentially deals with the ‘Taxon’ *i.e.*, the taxonomic category.

1) Cannabinaceous Alkaloids
   Ex: Hemp, Marijuana
2) Rubiaceous Alkaloids
   Ex: Quinine, Katum, Kratum, Yohimbe
3) Solanaceous Alkaloids
   Ex: Belladona, Sweet Peppers, Corkwood Tree, Loveapple, Tree Tobacco, Ashwagandha.

Isolation

a) Soxhlet Extraction Process:

The soxhlet assembly is a continuous extractor which is generally suitable for the extraction of alkaloids from powdered plant materials with the help of organic solvents. In this instance, the powdered drug is usually moistened with dilute ammonia solution and then packed loosely in the thimble of the Soxhlet apparatus; and the organic solvent affords a deep penetration of the moist drug thereby allowing the greatest possible extraction of the alkaloids from the exposed surfaces of the cells and tissues of the crude drug. Once, the extraction is ascertained to have completed, the solvent is filtered and evaporated in a Rotary Thin-Film Evaporator and the residue is treated further for the isolation of individual alkaloids.

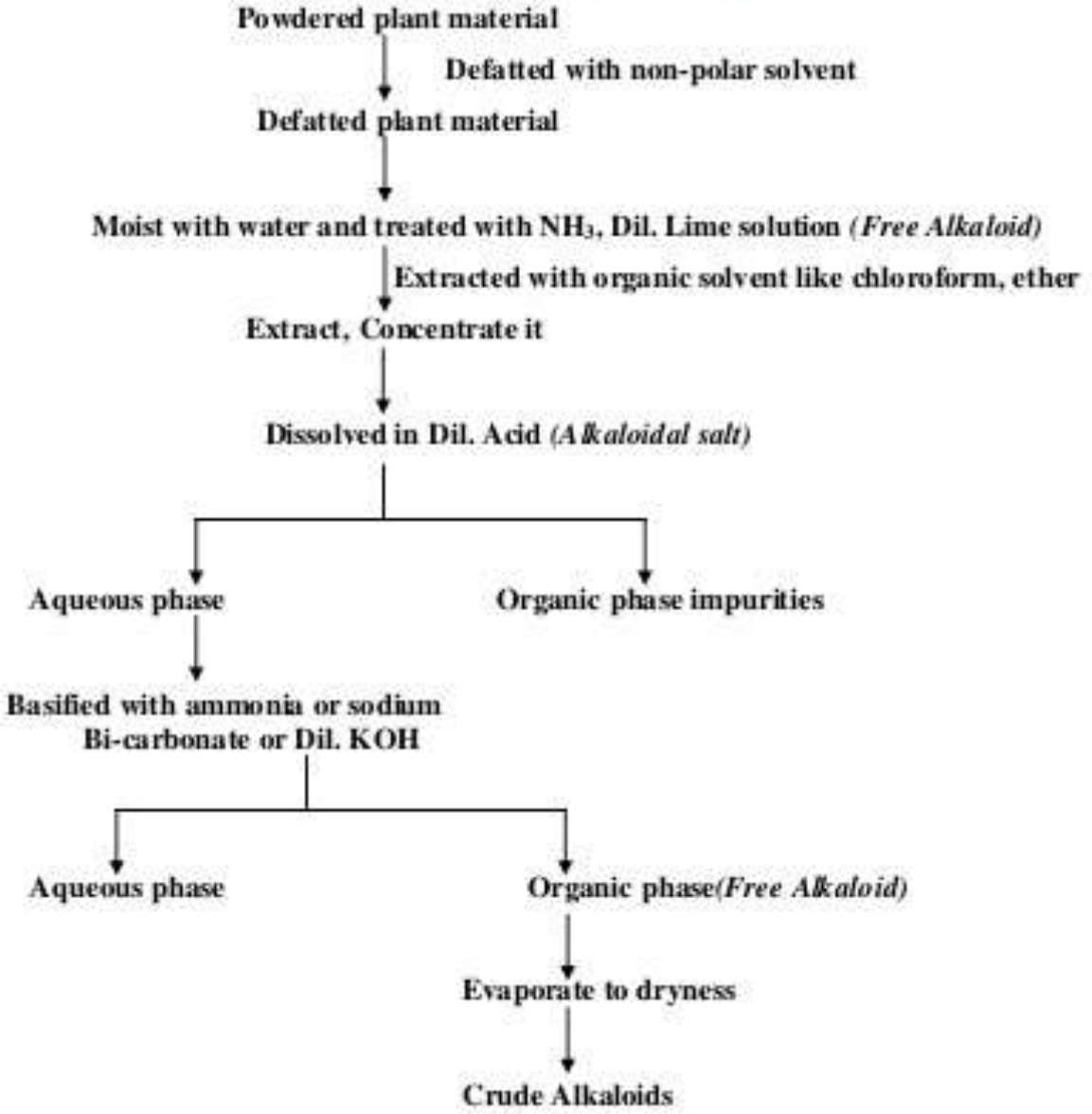
Isolation

b) Stas-Otto Process:

The Stas-Otto process essentially consists of treating the powdered and sieved drug substance with 90–95% (v/v) ethanol, previously acidified with tartaric acid. The proportion of crude drug to solvent should be maintained as 1 Kg to 1 L. The alcohol is distilled off under vacuum and the resulting aqueous residue is treated with petroleum-ether (60-80°C) to remove the fatty components completely. If any alkaloid is removed by the petroleum ether, it must be recovered by treating it with dilute mineral acid. Thus, the resulting aqueous extract is mixed with the main bulk of aqueous extract. The combined aqueous extract is filtered and evaporated to dryness preferably in a Rotary Thin-Film Evaporator under vacuum. The residue is extracted with absolute ethanol thereby dissolving the total alkaloids.

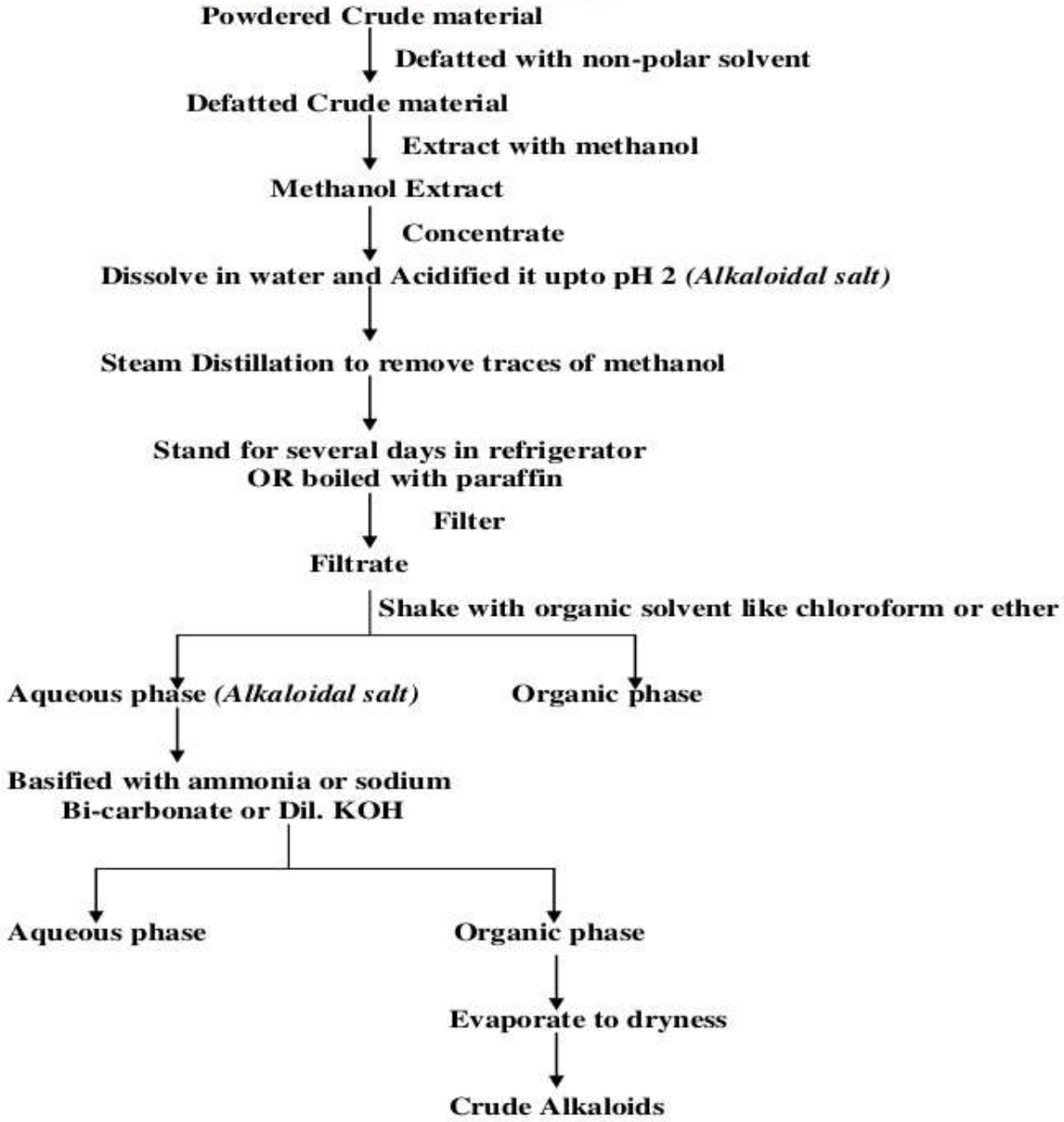
Extraction of alkaloids

1. Stass otto method



Extraction of alkaloids

2. Manske's method



Purification

1. Direct crystallisation from solvent
2. Repeated acid base treatment
3. Chromatographic techniques
   Ex: Partition, ion-exchange and column chromatography
4. Precipitation method
   Ex: $AuCl_3$, $PtCl_4$, Mayer's Reagent,

Chemical tests

- Dragendorff's test: To 2–3 mL of the alkaloid solution add few drops of Dragendorff's reagent (potassium bismuth iodide solution). An **orange brown** precipitate is formed.
- Mayer's test: To 2–3 mL of the alkaloid solution add few drops of Mayer's reagent (potassium mercuric iodide solution). **White brown** precipitate is formed.
- Wagner's test: To 2–3 mL of the alkaloid solution add few drops of Wagner's reagent (iodine-potassium iodide solution). **Reddish brown** precipitate is formed.

Biological activity

- In Plants
  - They may act as protective against insects and herbivores due to their bitterness and toxicity.
  - They are, in certain cases, the final products of detoxification (waste products).
  - Source of nitrogen in case of nitrogen deficiency.
  - They sometimes act as growth regulators in certain metabolic systems.
  - They may be utilized as a source of energy in case of deficiency in carbon dioxide assimilation.

Biological activity

- In Humans
  - High biological activity.
  - Produce vary degrees of physiological and psychological responses – largely by interfering with neurotransmitter.
  - In large doses – highly toxic – fatal.
  - In small doses – many have therapeutic value.
  - Muscle relaxant, pain killers, tranquilizers, mind altering drugs, chemotherapy.

General methods of structural determination of alkaloids

- **Molecular Formula :** The first step in structural elucidation is the determination of molecular formula and optical rotatory power. Elemental composition and hence the empirical formula is found by combustion analysis.
- **Determination of Unsaturation:** The unsaturation can be determined by adding bromine, halogen acids or by hydroxylation with $KMnO_4$ or by reduction (using either $LiAlH_4$ or $NaBH_4$). Number of Double bond: - Number of Rings present in an alkaloids can be determine by following formula- $C_a H_b N_c O_d$

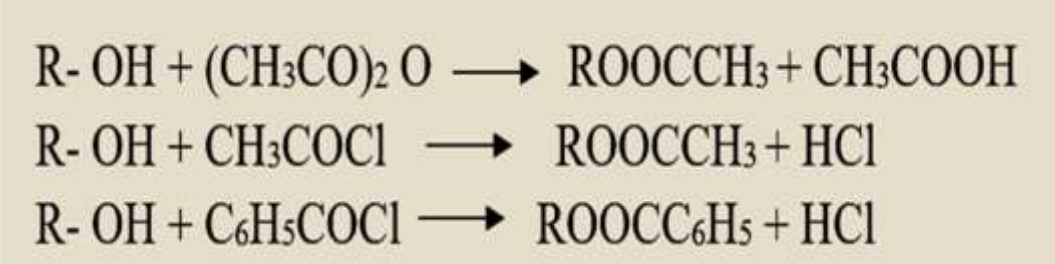
$$\text{Number of double bond present} = \frac{\text{No. of hydrogen in alkane} - \text{No.of hydrogen in formula}}{2}$$

General methods of structural determination of alkaloids

- **Functional Group Determination**

  By using the usual **standard chemical tests** or by **infrared (IR) spectroscopy**

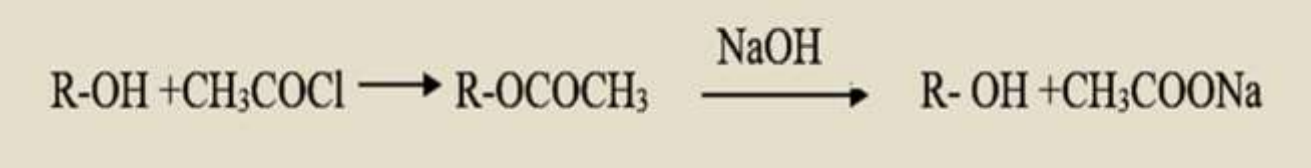
  - **Hydroxyl group: -** Formation of Acetate on treatment with Acetic anhydride /Acetyl chloride or benzoate on treatment with Benzyl chloride.



  - By determining the amount of Acetic anhydride /Acetyl chloride or benzoate that reacted with alcohol to form an ester, the number of hydroxyl groups can be determined.

General methods of structural determination of alkaloids

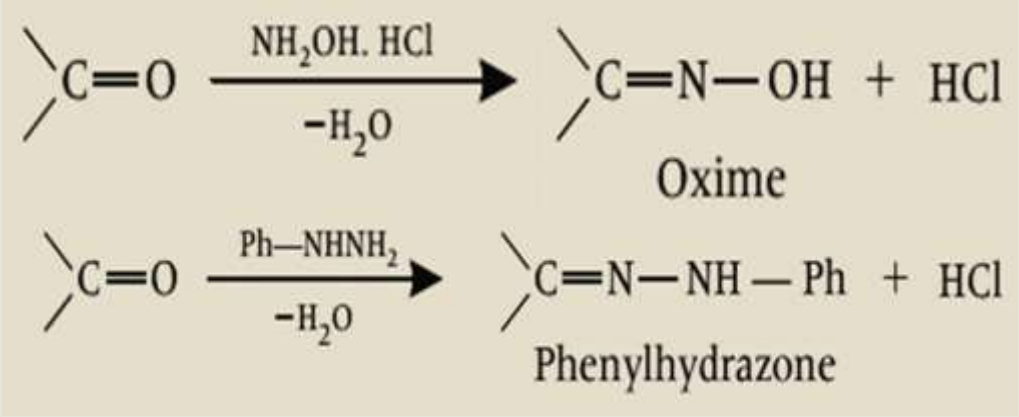
- Then check (alcoholic-OH or phenolic –OH) + $FeCl_3$ = color phenolic –OH Or if Soluble in NaOH = phenolic – If not Phenolic –OH:
- Alkaloid +H2SO4 -> unsaturated + $KMNO_4$ -> aldehyde or ketone or acid
- If Primary amines are present in an alkaloids also give this test. Then Hydroxyl group is can be determined.



- Excess of Alkali is estimated by titration with standard HCl. Number of -OH group can be calculated from the volume of Alkali used for Hydrolysis.

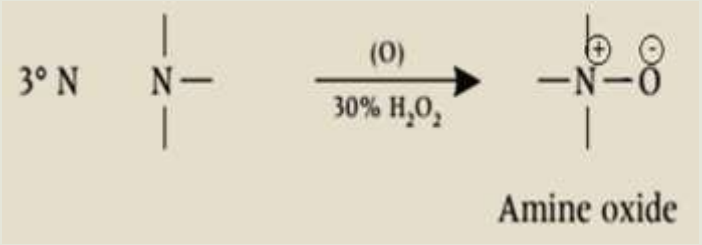
General methods of structural determination of alkaloids

- **Carboxylic group:** - soluble in aqueous solution sodium carbonate Na_2CO_3 or ammonia NH_3 , on treat with alcohol form ester.
- **Specific IR and NMR signals**. - Number of -COOH group can be determined by volumetrically by titration against a standard $Ba(OH)_2$ or NaOH solution using phenolphthalein as an indicator.
- **Carbonyl group:** The presence of aldehydes and ketones can be detected by their reaction with hydroxylamine to form the corresponding oxime.



General methods of structural determination of alkaloids

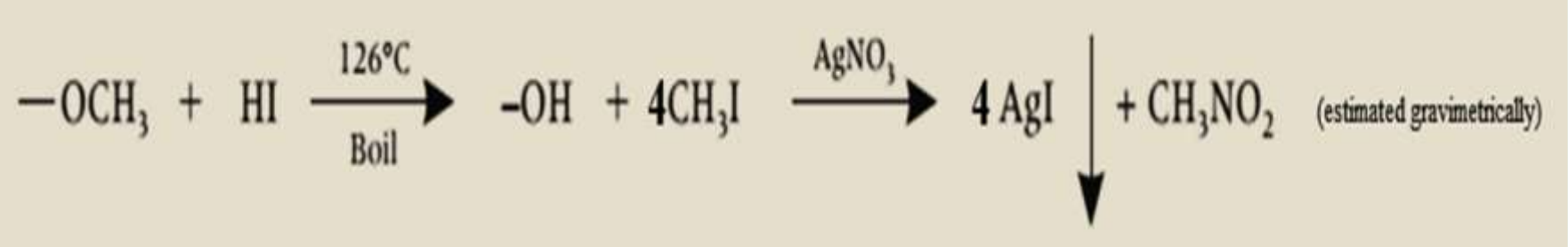
- **Nature of Nitrogen:** General reactions of alkaloids with acetic acid, methyl iodide and nitrous acid indicates the nature of nitrogen. If all reactions are negative – N2 probably tertiary
- Majority of nitrogen presence in alkaloids are secondary and tertiary: If tertiary when treated with H_2O_2 (30%) form amine oxide.



- Nature and No. alkyl group attached to Nitrogen: Distillation with Aq. KOH, formation of methylamine, dimethylamine and trimethylamine (Vol. products)
- Herzig- Mayer method: presence and number of N- methyl group.

General methods of structural determination of alkaloids

- The **aldehydes** and **ketones** are distinguished by their oxidation or reduction products.
- The carbonyl groups of aldehyde, ketone and carboxyl groups are further confirmed by their spectral data such as IR, UV and NMR.
- **Methoxyle group:** determination by *Zeisel* method: When methoxy group present in a alkaloids treated with HI at 126^0C perform methyl iodide which can treated further with silver nitrite to perform silver iodide precipitate. Which estimated gravimetrically : e.g.. **Papavarine.**



Degradation of alkaloids

- Study of degradation of alkaloids gives rise to some identifiable products of known structure.
- Knowing structure of the degraded products and the changes occurred during the degradation, it is convenient to know the structure of the original molecule. Different degradation reactions
  - Hoffman exhaustive methylation method
  - Emde’s method
  - Von Braun’s (VB) method for 3° cyclic amines
  - Reductive degradation
  - Oxidation
  - Zinc distillation
  - Alkali fusion
  - Dehydrogenation

1. Hoffman exhaustive methylation method

- The method was applied by Willstater in 1870 and was further developed by Hoffmann.
- Heterocyclic rings are opened with elimination of nitrogen and the nature of the carbon skeleton can be obtained.
  - Hydrogenation of heterocyclic ring (if it is unsaturated)
  - Convert the saturated compound to the quaternary methylammonium hydroxide which is then heated.
  - In this stage, a molecule of water is eliminated, a hydrogen atom in the β position with respect the N atom combining with –OH group.
  - The ring is opened at the N atom on the same side as the β-H atom eliminated.
  - This process is repeated on the same product . This resulted in the complete removal of N atom from the molecule, leaving an unsaturated hydrocarbon, which is isomerizes to a conjugated diene.

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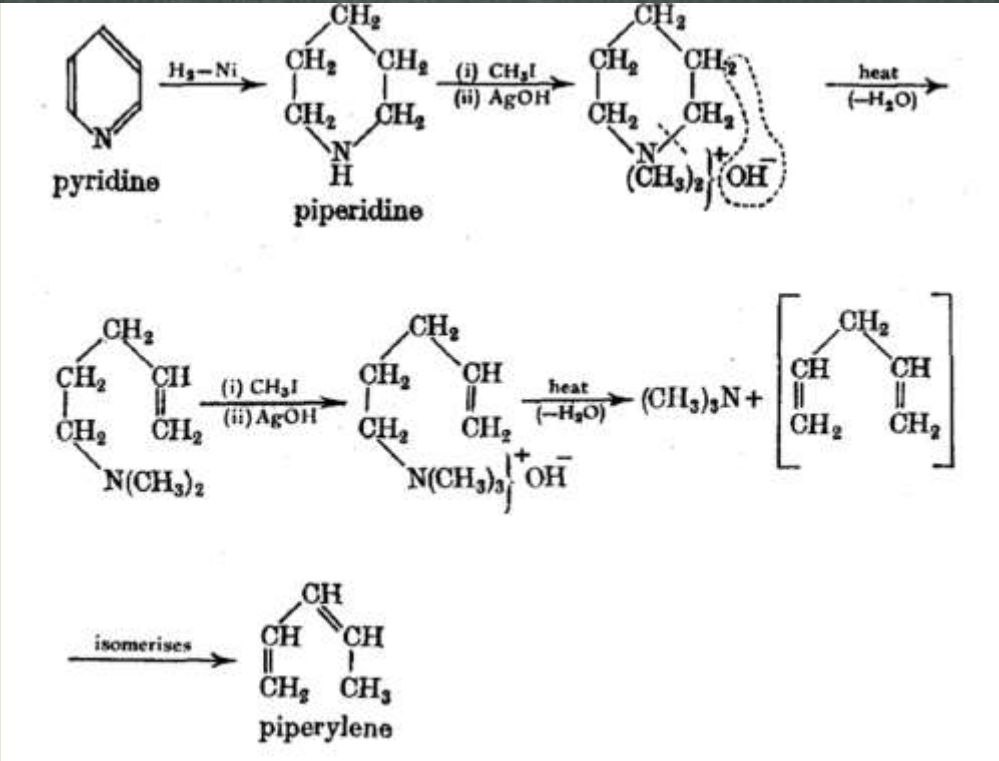

- HEM fails if there is no β-H atom available for elimination as water. In such cases the Emde modification may be used

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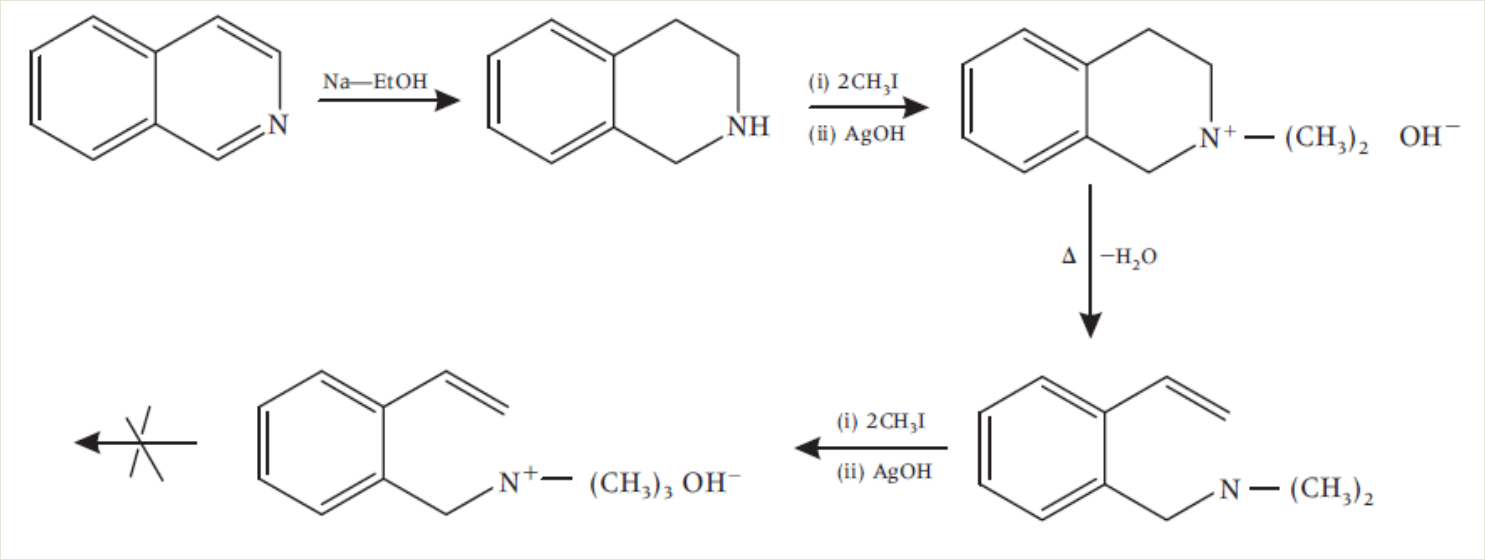
- As β-H atom is needed to cleave C–N bond and eliminate water molecule, the HEM fails on the ring system that does not have β-H atom.
- For example, in the degradation of isoquinoline, the cleavage of N atom does not occur at the final step as there is no β-hydrogen with respect to ‘N’.



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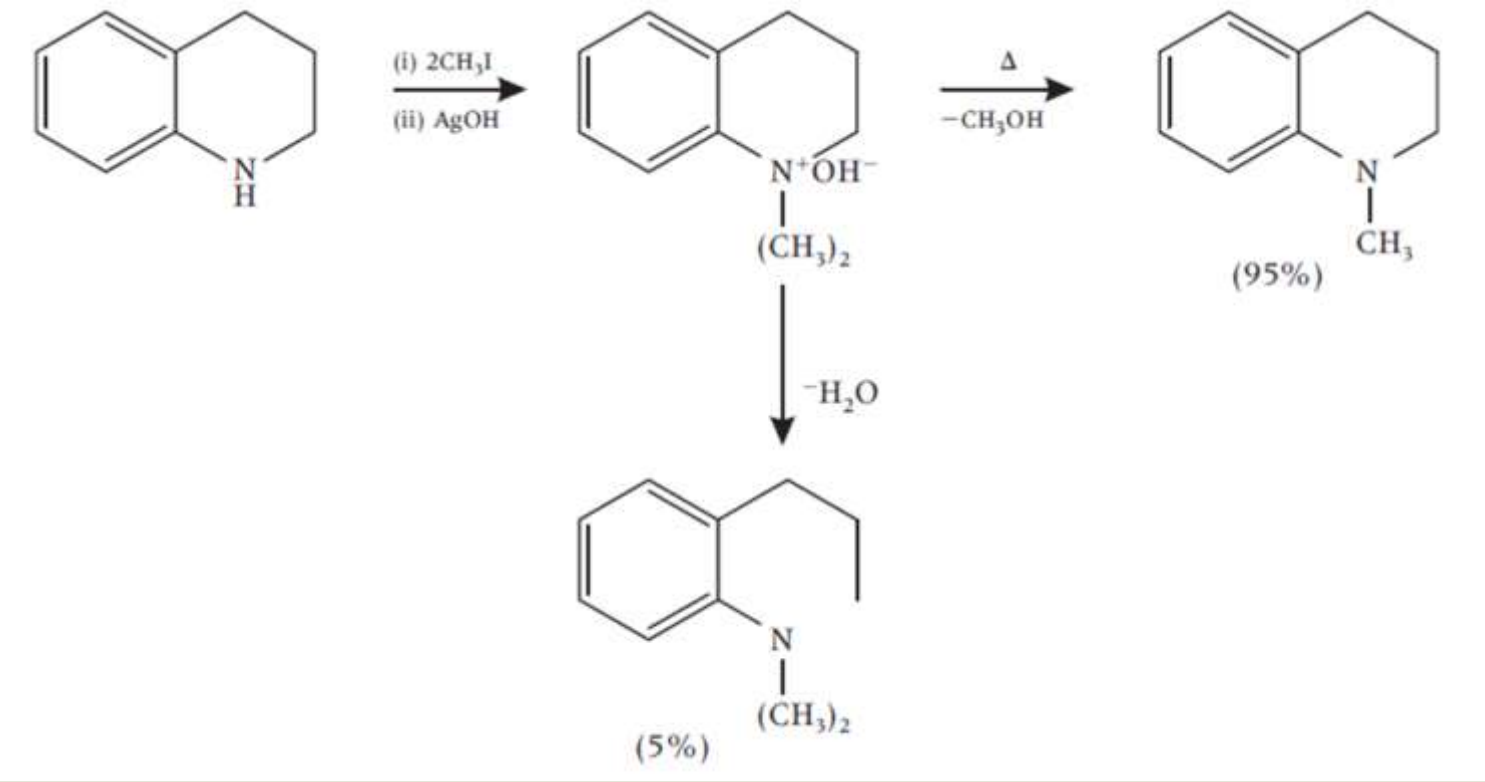
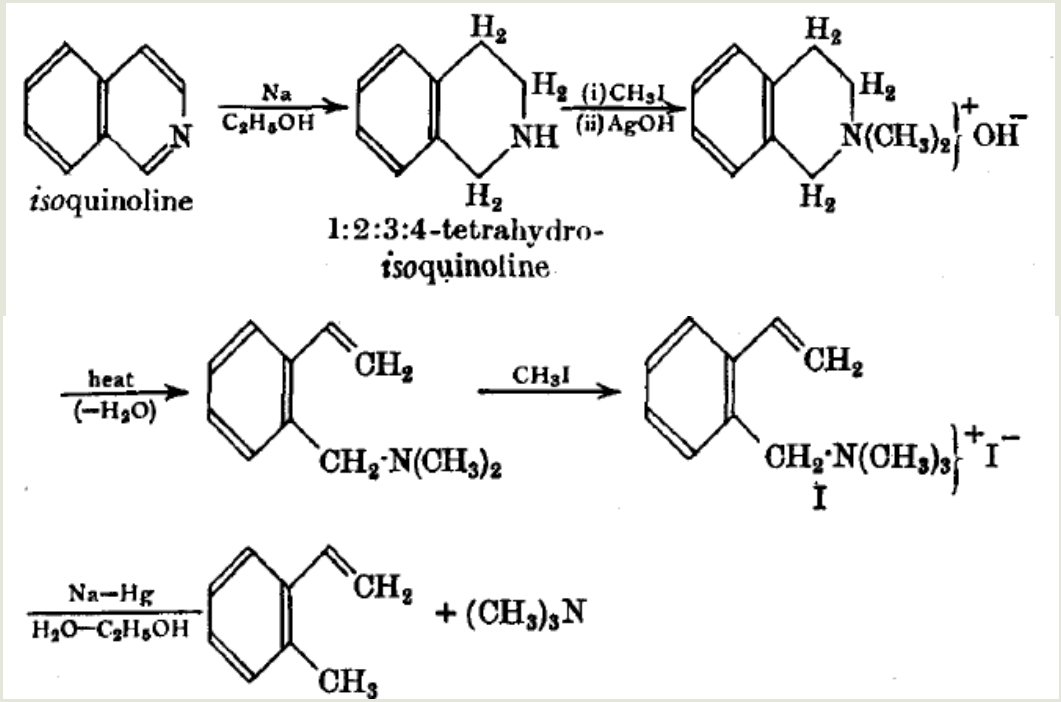
- However, there are some cases in which HEM fails even if the β-hydrogen atom is present.



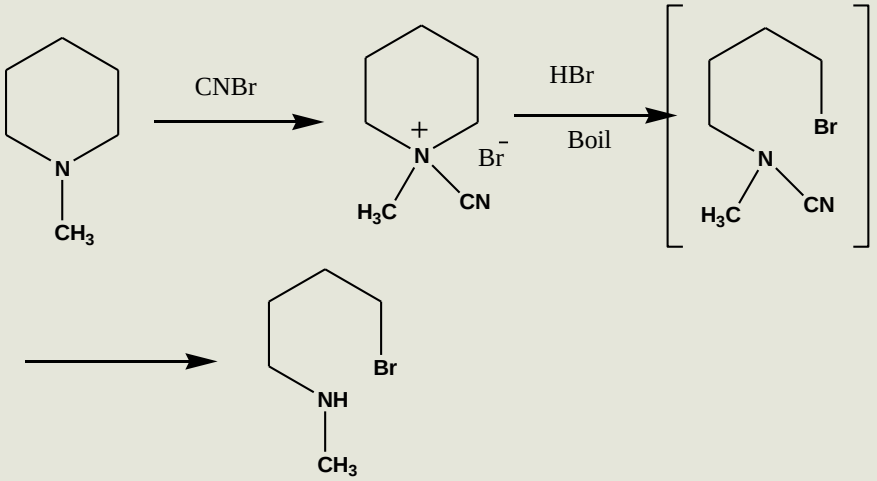
2. Emde's method

- Emde's modification may be used in the above two cases, where HEM failed. In this method, 4° ammonium halide is reduced with sodium amalgam in aqueous ethanol or catalytically hydrogenated.



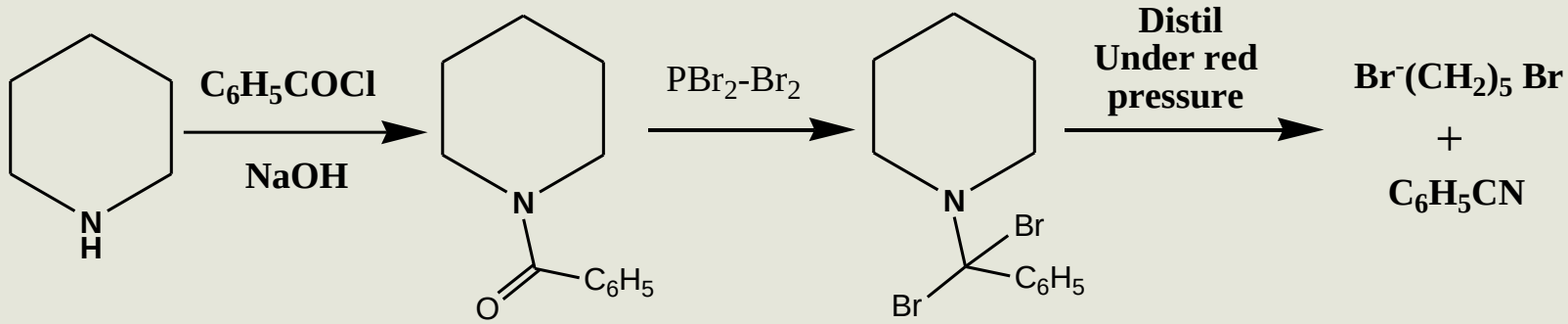
3. Von Braun’s method

- Tertiary amine, which contains at least one-alkyl substituent, is treated with cyanogen bromide.
- The results in cleavage of an alkyls nitrogen bond to give an alkyl halide and a substituted Cyanamide.
- This method is often applicable to such compounds that do not respond to Hofmann's method.

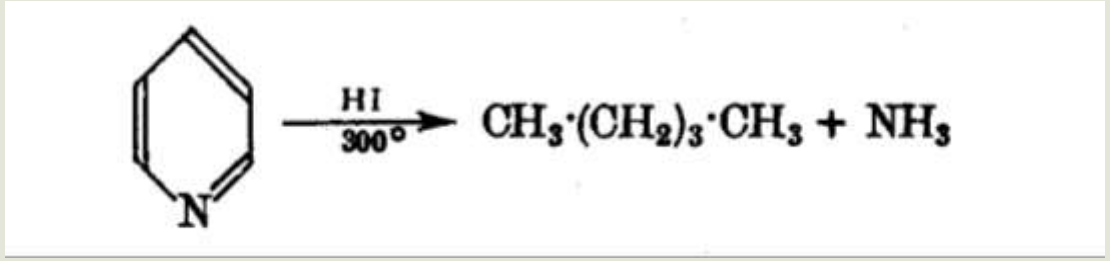


3. Von Braun's method

- Secondary cyclic amine is treated with Benzoyl chloride in presence of NaOH to yield the Benzoyl derivative which on treatment with phosphorus dibromide followed by distillation under reduced pressure yield dihalo compound.

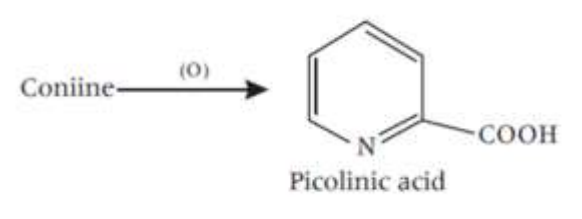


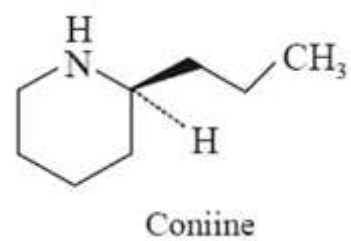
- In number of cases the ring may be opened by heating with hydrochloric acid at 300 ºC



4. Oxidation

- Oxidation gives valuable information about the fundamental structure of alkaloids and the position and nature of functional groups, side chains, etc.
  - For example, picolinic acid obtained upon oxidation of coniine indicates that the coniine is anα-substituted pyridine.

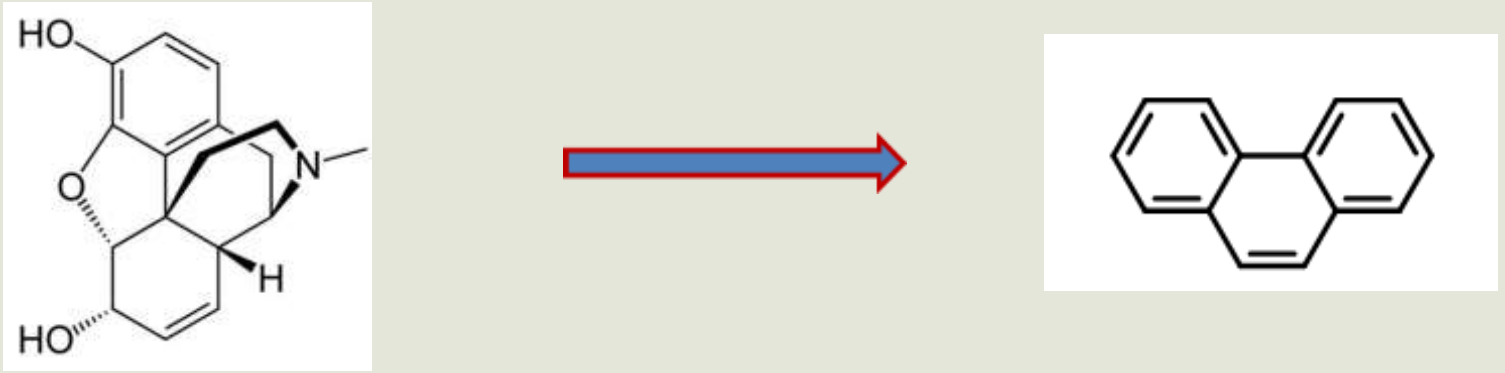




- By varying the strength of oxidizing agents, a variety of products may be obtained. Different types of oxidizing agents used are as follows:
  - For mild oxidation: H_2O_2, O_3, I_2.
  - For moderate oxidation: acid or alkali $KMnO_4$, CrO_3 in CH_3COOH.
  - For vigorous oxidation: $K_2Cr_2O_7$–H_2SO_4, concentrated HNO_3 or MnO_2–H_2SO_4.

5. Zinc distillation

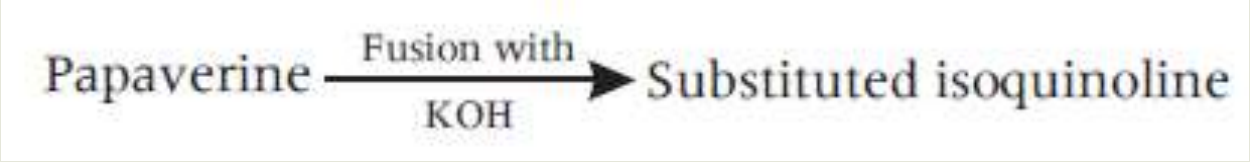
- Distillation of alkaloid over **zinc dust** degrades it into a stable aromatic derivative.



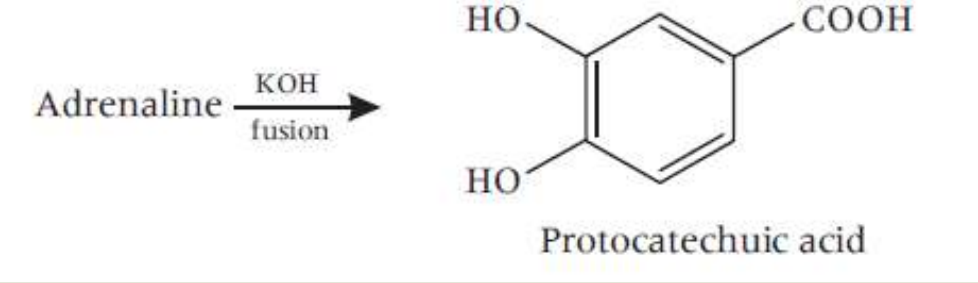
- The reaction indicates that morphine is possessing phenanthrene nucleus.

6. Alkali fusion

- Fusion of alkaloids with solid KOH gives simple fragments from which the nature of alkaloid can be derived.



  - The reaction indicates papaverine is containing isoquinoline nucleus.



  - The reaction indicates adrenaline is a monosubstituted catechol derivative.

7. Dehydrogenation

- Distillation of alkaloid with catalysts such as S, Se and Pd yields simple and recognizable products from which the gross skeleton of the alkaloid may be derived.
- Thus with the help of degradation, nature of various fragments obtained, nature of nucleus and type of linkages are established.
- The fragments obtained are arranged in the possible ways with the possible linkages and the one that will explain all the properties is selected and confirmed by synthesis.
- Optical activity of an alkaloid helps greatly in establishing the structure of alkaloid

8. Physical Methods

- The important physical methods used in structural elucidation of alkaloids are as follows:
  - IR spectroscopy: Identify functional groups
  - UV spectroscopy: Characteristic of chromophoric system
  - NMR spectroscopy: Detect protons
  - Mass spectroscopy: Know molecular weight and fragments
  - X-ray analysis: Distinguish the various possible structures
  - Optical rotatory dispersion (ORD) and circular dichroism : Optically active stereoisomers.
  - Conformational analysis: Stereochemistry

9. Synthesis

- The above-mentioned chemical and analytical work helps to propose a tentative structure (or structures) of the alkaloid under investigation.
- Synthesis always gives additional evidence for the assigned structure even though the physical methods (mentioned above) provide final proof of the proposed structure.

Structural elucidation

- Morphine
- Reserpine
- Emetine

Morphine

- It was the first alkaloid to be isolated from Sertuner plant (1806). In opium, it is present in a quantity of 10-23 percent along with other substances.
- Codeine and thebaine are the other closely related alkaloids to morphine.
- It is a colourless prismatic substance which melts at 247°C.
- It has a bitter taste & is laevorotatory having a specific rotation of -131°.
- It has little solubility in water, ether, benzol and chloroform but has sufficient solubility in alcohol and alkali solution.
- It acts as a monoacid base and forms well defined salts with acids.

Constitution

1. Molecular formula: This has been found to be $C_{17}H_{19}O_3N$.
2. Nature of nitrogen atom: As morphine adds on one molecule of methyl iodide to form quaternary salt, this shows that it contains tertiary nitrogen atom. The tertiary nature of nitrogen is further confirmed by Hoffmann degradation of codeine derivative which also reveals the presence of nitrogen in the ring. By Herzig-Mayer method, it is shown that $>N\text{-}CH_3$ group is present in morphine.
3. Nature of the oxygen atoms:
   i. Morphine when acetylated or benzylated yields the diacetyl or benzoyl derivative, indicating that morphine contains two hydroxyl group.
   ii. With ferric chloride morphine yields characteristic colour. Morphine is also soluble in aq. Sodium hydroxide solution to form mono sodium salt. All these facts reveal that one of the two hydroxyl group is phenolic in nature.

Constitution

iii. When morphine is treated with halogen acids, it yields monohalogeno derivative, i.e., one hydroxyl group is replaced by halogen acid. This reaction is characteristic of alcohol. Therefore second hydroxyl group is alcoholic in nature.

iv. From unreactivity of the third oxygen atom and the degradation product of morphine, indicating that third oxygen atom of morphine is present as an ether linkage.

4. Presence of ethylenic bond: When codeine (i.e., methylated morphine) is reduced catalytically in the presence of palladium, it takes up one molecule of hydrogen, suggesting that both codeine and morphine contain one ethylenic bond.

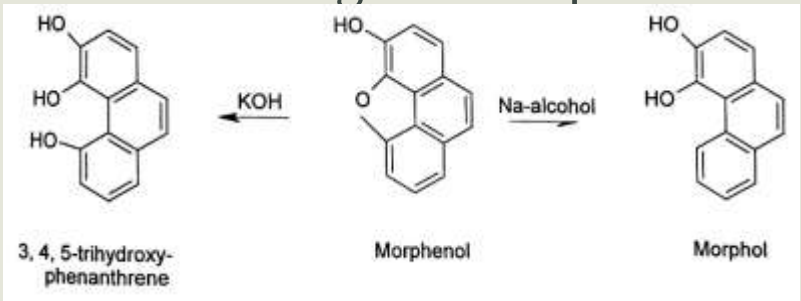
5. Presence of benzene nucleus: Morphine when brominated yields a mono-bromo derivative along with the evolution of a molecule of hydrogen bromide, suggesting that morphine possesses a benzene nucleus.

Constitution

6. <u>Presence of phenanthrene:</u> When morphine is distilled with zinc dust, it yields phenanthrene and a number of bases, suggesting that morphine may contain a phenanthrene nucleus.

   Codeine when treated with methyl iodide it yield codeine methiodide which on further treatment with alkali to get alkali codeimethine.

   Alpha codeimethine on alkali treatment gives beta codeimethine. Either of these two isomer is treated with methyl iodide followed by alkali yield methyl morphenol which is treated with hydrogen bromide gives morphenol which on reduction with sodium and alcohol gives morphol.

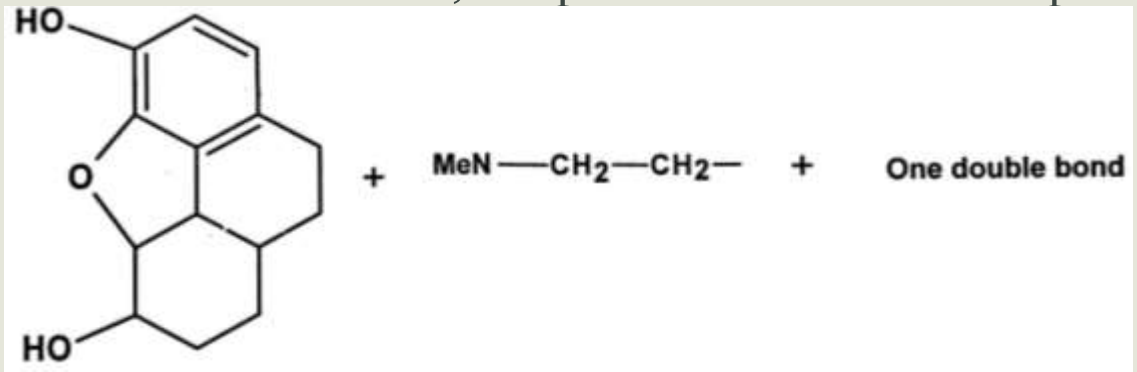


Constitution

7. Structure of morphine:
   i. As pointed out earlier that morphine forms monobromo derivative with bromine and monosodium salt with sodium hydroxide, indicating that morphine contains one benzenoid structure. Further as ethylene is formed as one of the product in the exhaustive methylation of alpha codeimethine and dimethyl amino ethanol is formed so CH_2-CH_2-N-CH_3 must be present in morphine.

   As it also contains double bond and tertiary nitrogen atom partial structure for morphine was given.

   On taking all these facts in view, the partial structure of morphine may be written as follows:



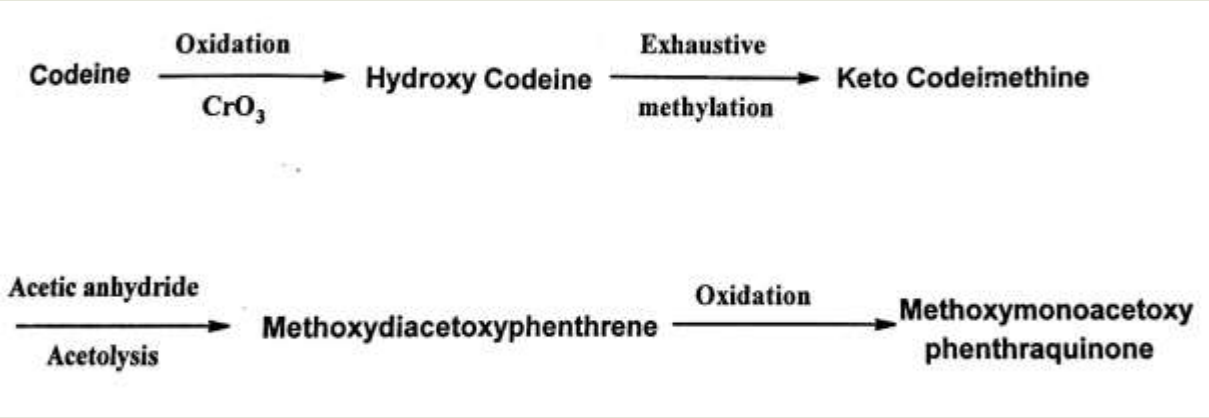
Constitution

ii. Point of linkage of the $-CH_2-CH_2-N-CH_3$ chain: Codeine (methylated morphine) when oxidized gently with chromic acid yields some hydroxyl codeine along with codeinone.

The hydroxy codeine when subjected to exhaustive methylation yields keto-codeimethine which on heating with AcO yields methoxy diacetoxy phenanthrene.

The latter when oxidized further yields a quinine with loss of acetoxy group.

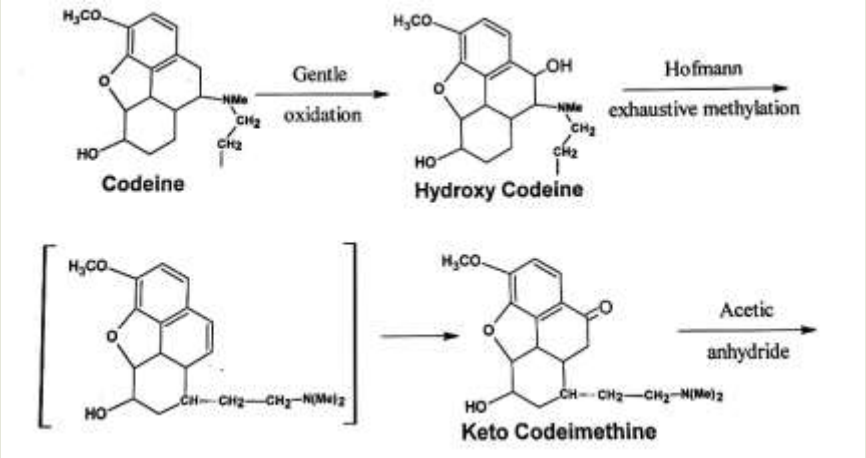
Thus, all these reaction may be summarized as follows:



Constitution

- As there occurs the loss of an acetyl group in the oxidation of methoxy diacetoxy phenanthrene to methoxy monoacetoxy phenanthraquinone, this reveals that one of the acetoxy groups in the former compound must be present either C_9 or at C_{10}.
- Now since the acetoxyl group, which is lost in the oxidation is inserted in position via the ketonic group during the acetolysis, it means that the keto group in keto codemethine and therefore the new hydroxyl group in hydroxy codeine should be present at C9 or C10. On the basis of steric consideration., the attachment at C9is most probable. From this we can conclude that the point of linkage of nitrogen is at C9.
- All the above reactions can be explained if the partial structure of codeine is taken as follows:

Constitution

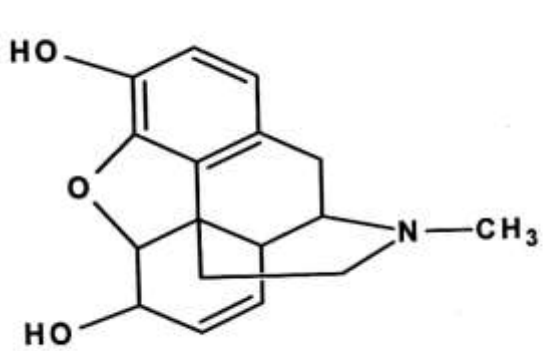


- We have seen that the side chain having nitrogen atom is always eliminated during the aromatization of the phenanthrene nucleus.
- According to Gulland and Robinson, there can't take place the formation of the phenanthrene derivative for structural reasons unless the ethamine chain is displaced.
- But we have already shown that the nitrogen end of side chain is linked to C_9. Therefore the carbon end of the side chain must be located at angular position and the possible positions are C_{13} and C_{14}.

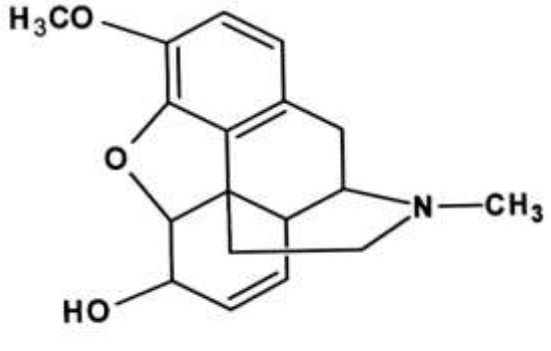
Constitution

- The former is selected on the basis that such structure is only able to explain the re arrangement of thebaine to thebenine.

iii. Position of double bond: Codeine when treated with PCl_5, yields chlorocodide which on hydrolysis gives the mixture of codeine, isocodeine, pseudocodeine and allopseudocodeine. First two and last two are configurational isomers of the hydroxyl group at C_6. These changes can be explained if the double bond is in between C_7 and C_8.



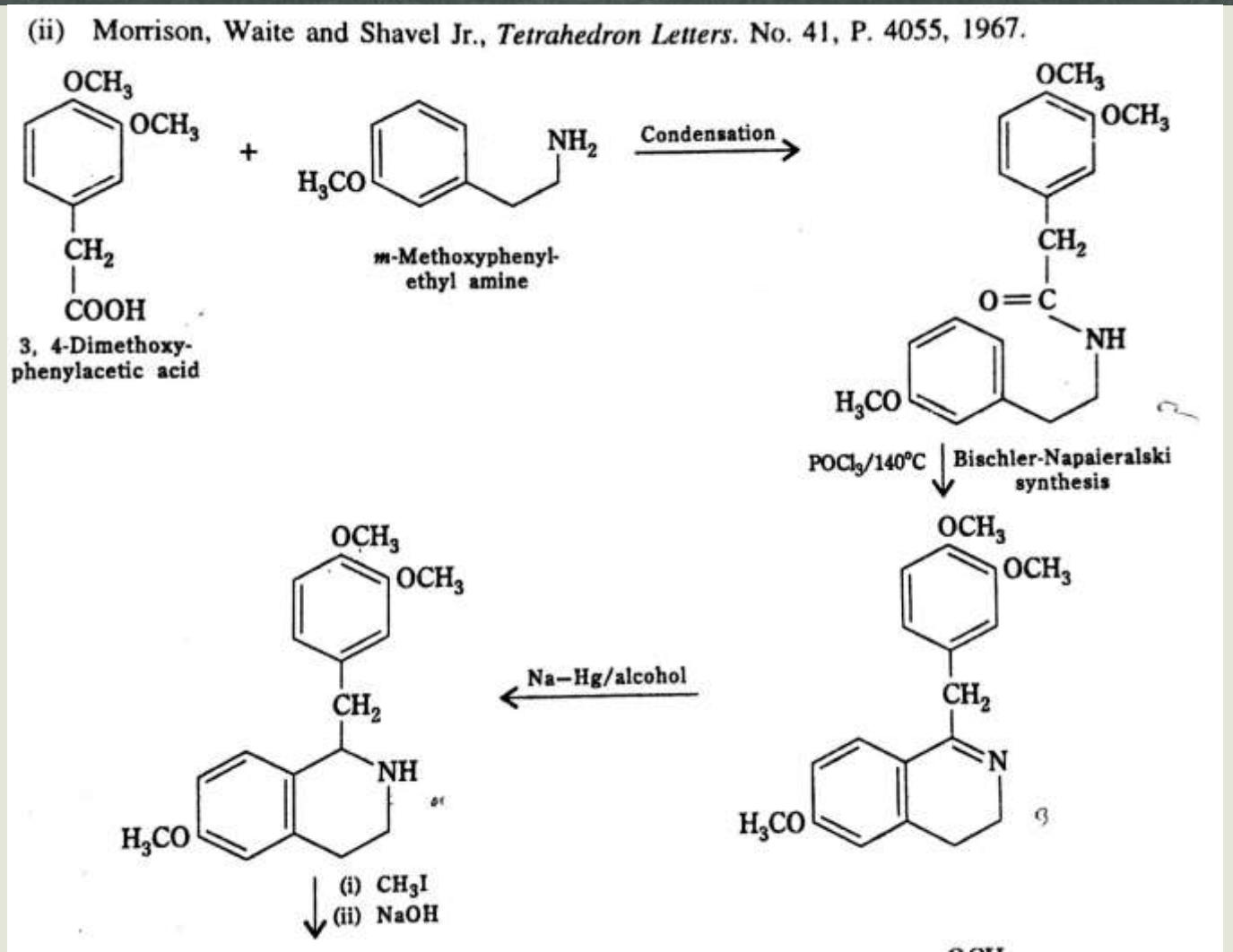
MORPHINE



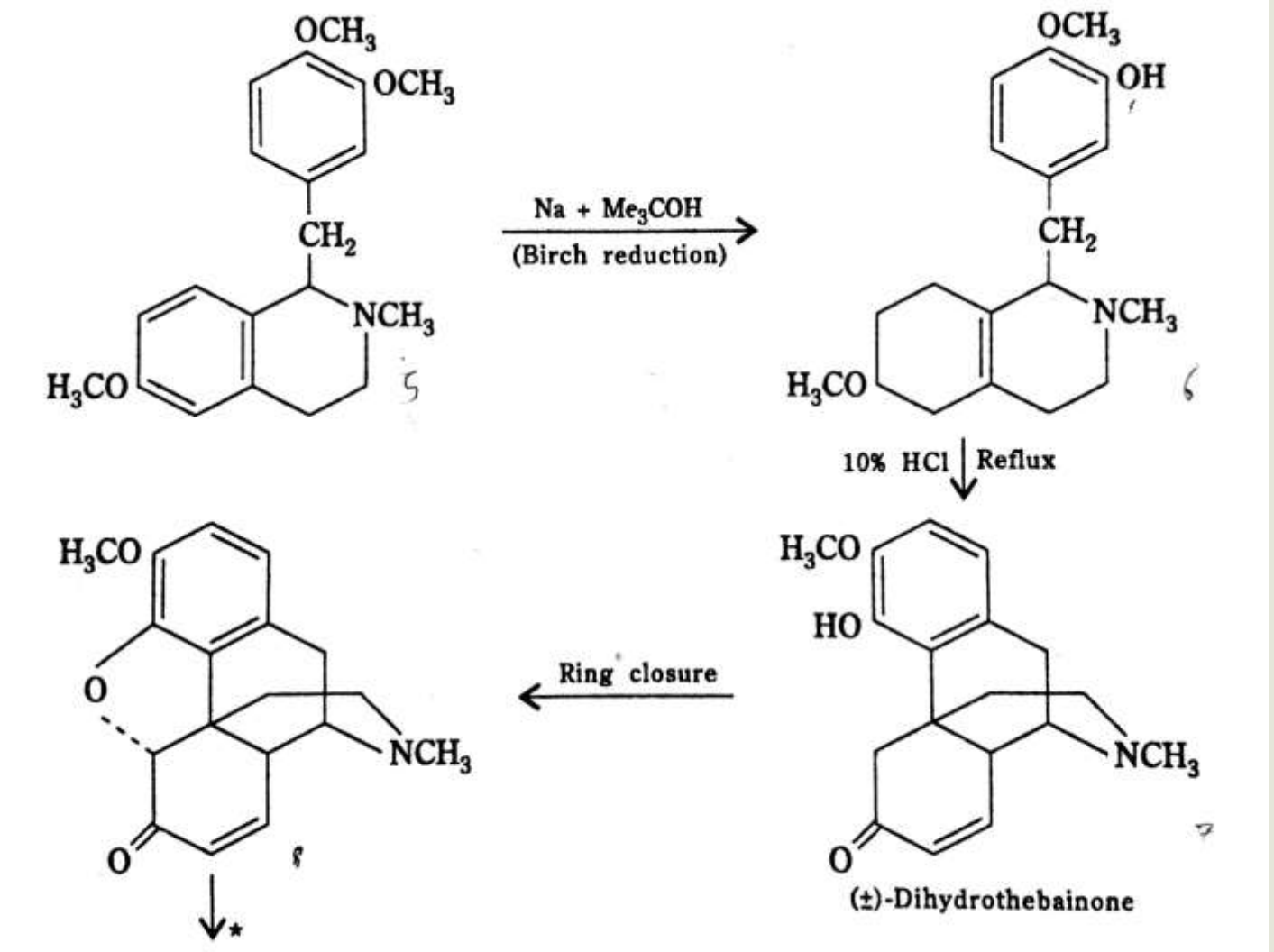
CODEINE

Morrison's synthesis

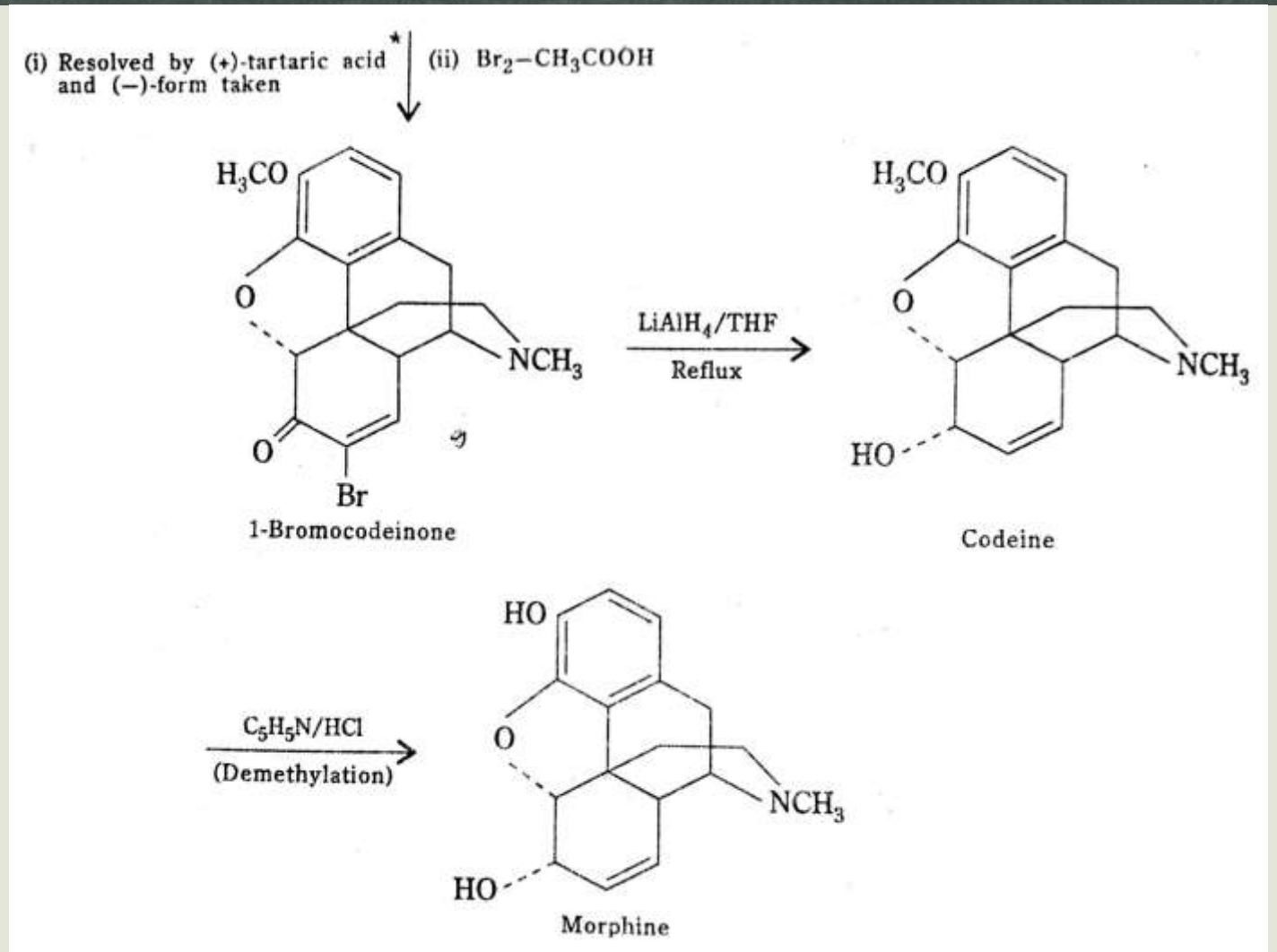
The above structure of Morphine has been confirmed by it's synthesis



Continue..


OCH3
OCH3
CH2
NCH3
H3CO
Na + Me3COH
(Birch reduction)
OCH3
OH
CH2
NCH3
H3CO
10% HCl
Reflux
H3CO
HO
NCH3
O
(±)-Dihydrothebainone
Ring closure
H3CO
O
NCH3
O

Continue..

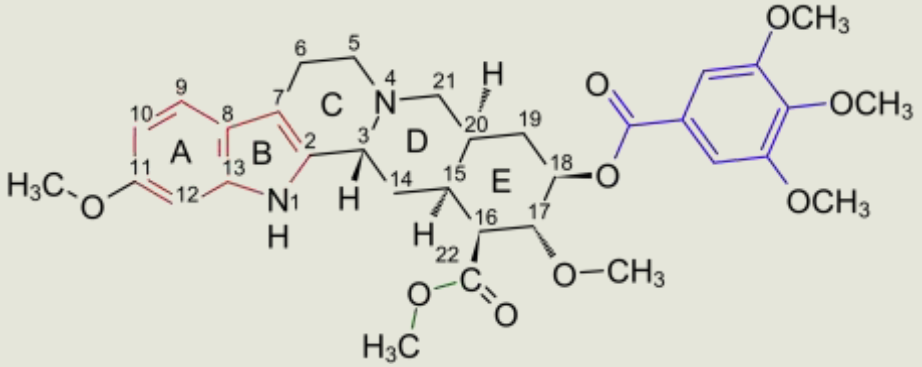

(i) Resolved by (+)-tartaric acid and (−)-form taken
(ii) Br_2-CH_3COOH
H_3CO
O
NCH_3
O
Br
1-Bromocodeinone
$LiAlH_4$/THF
Reflux
H_3CO
O
NCH_3
HO
Codeine
C_5H_5N/HCl
(Demethylation)
HO
O
NCH_3
HO
Morphine

Reserpine

- Synonym: Sarpagandha.
- Biological source: It is obtained from dried roots of Rauwolfia serpentine & Rauwolfia vomitoria.
- Family: Apocynaceae.
- Parts used: Roots.
- Chemical constituent: Alkaloids- reserpine, yohimbmine, ajmaciline & ajmaline.

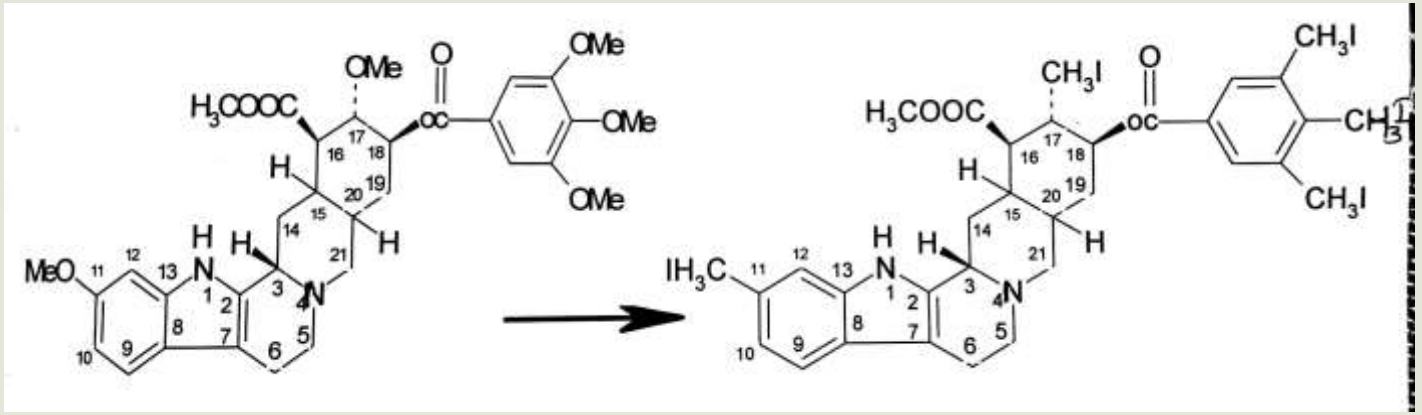
Constitution

1. Molecular formula: $C_{33}H_{40}N_2O_9$



2. Presence of five methoxyl group:

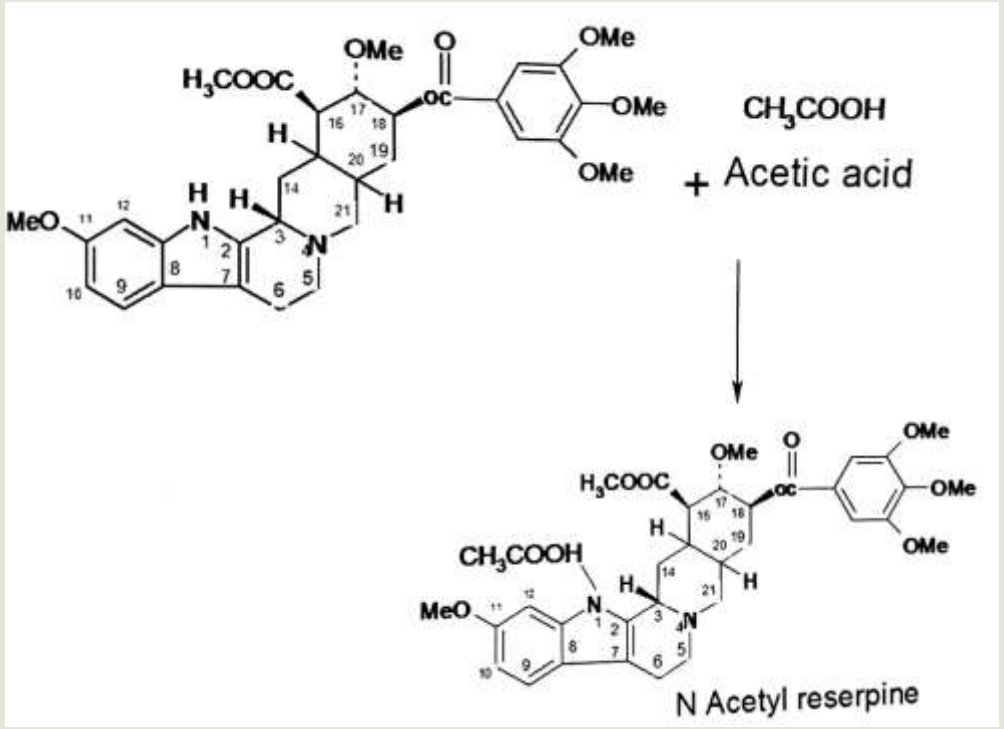
   When treated with Hl yields five molecules of methyl iodide indicating the presence of five methoxy groups.



Constitution

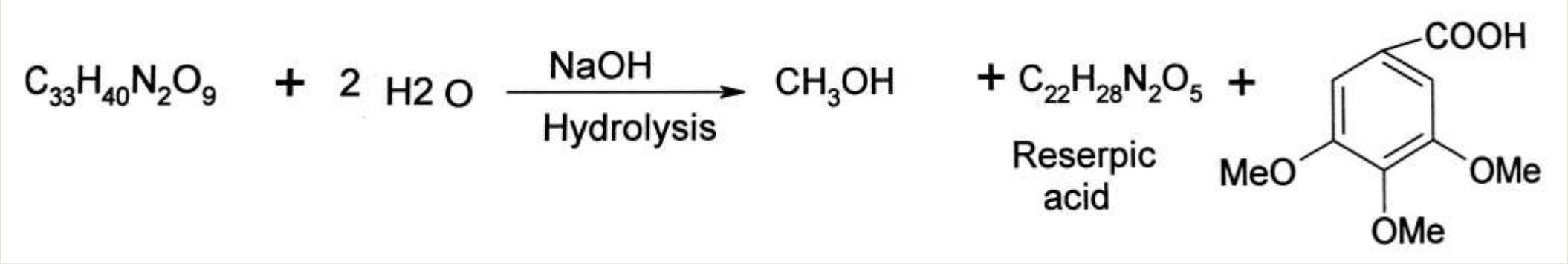
3. Nature of ‘N’ atom:

   It is weak base. Both N atoms are inside the ring system. it does not have any hydroxyl group but forms monoacetyl derivative one N atom is present as NH group.



Constitution

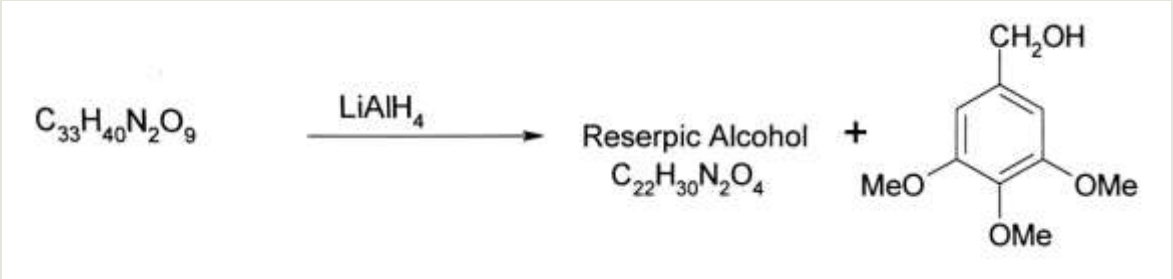
4. Hydrolysis: Hydrolysis of reserpine with alkali yields mixture of
   i) Methyl alcohol
   ii) 3,4,5-trimethoxy benzoic acid
   iii) Reserpic acid.



- As reserpine does not contain -COOH & -OH groups, hence its hydrolysis product proves that reserpine is a di-ester.

Constitution

5. Reduction:



6. Oxidation:

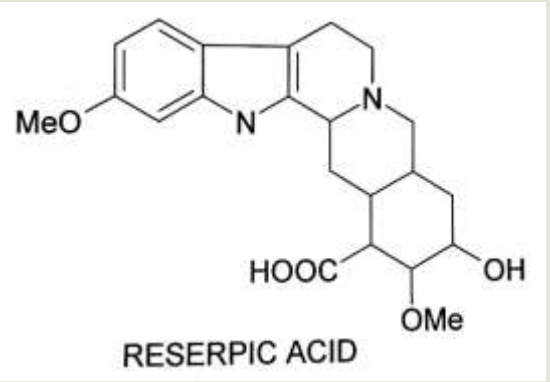
   It is the major route of degradation of reserpine. On oxidation it gives

   i. 3,4-Didehydroreserpine

   ii. 3,4,5,6-Tetradehydroreserpine

Constitution

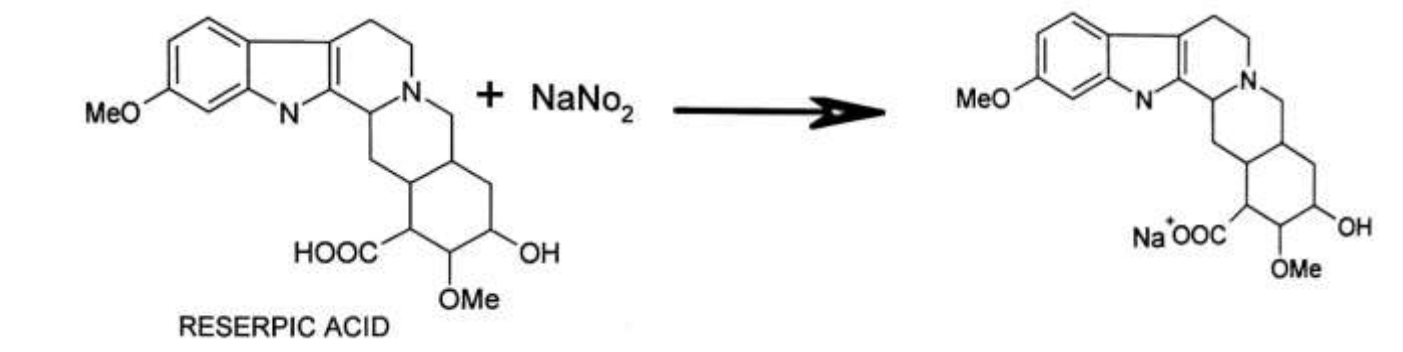
7. Structure of Reserpic acid:



a) <u>Molecular formula</u>- $C_{22}H_{28}N_2O_5$

b) <u>Presence of one carboxyl group</u>

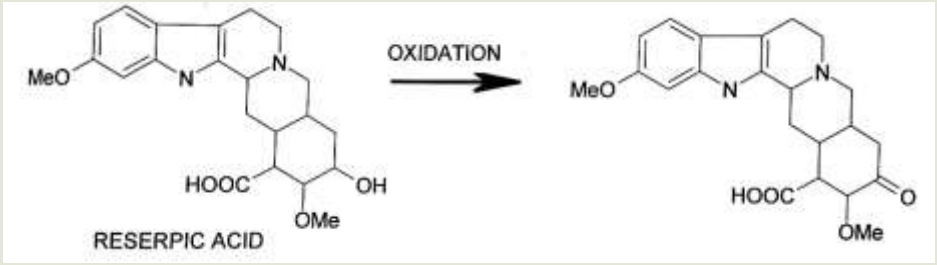
By usual tests e.g. silver salt method. Reserpic acid is shown to posses one carboxyl group.



Constitution

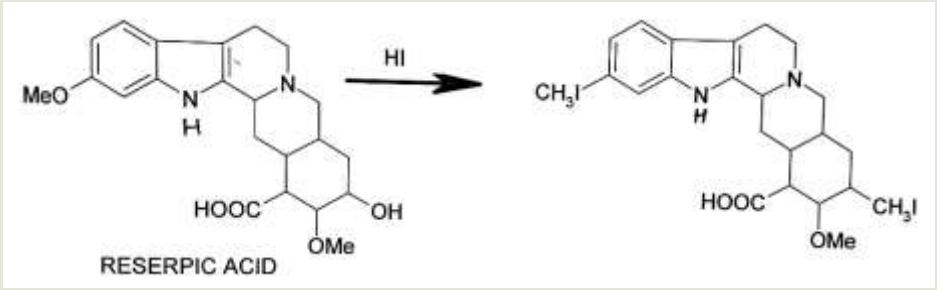
c) Presence one -OH group

Reserpic acid on oxidation yields a ketone that means it has secondary alcoholic group.



d) Nature of two methoxy groups

By zeisels method. It shows that reserpic acid contains 2 methoxy groups.



Constitution

e) Nature of two ‘N' atom

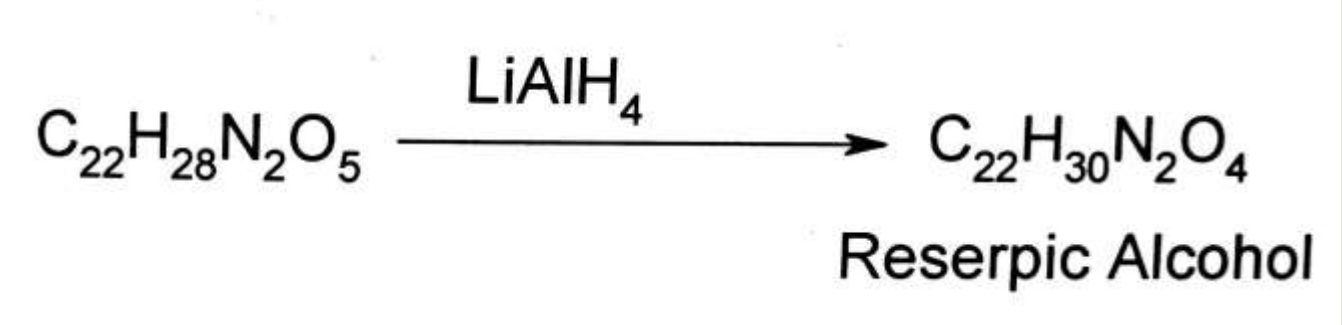
lt shown that it contains two ‘N’ atoms in heterocyclic ring in the form of

i. Secondary ‘N’

ii. Tertiary amino group

f) Reduction of reserpic acid

On reduction with LiAlH4 yields reserpic alcohol.



Constitution

g) <u>Oxidation of reserpic acid</u>

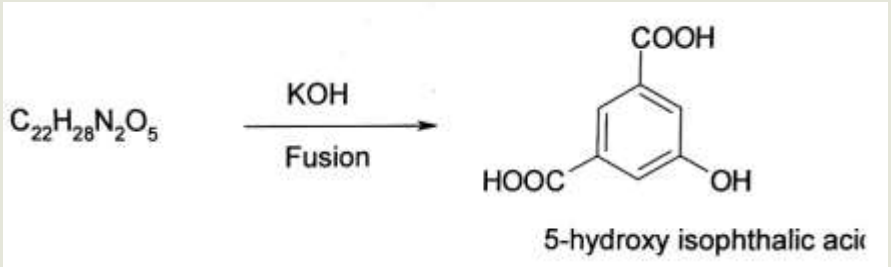
On oxidation with KMnO4 it gives 4-methoxy N-oxalyl anthranilic acid.

Thus one of the methoxyl group is present in meta position to -NH group

h) <u>Fusion with KOH</u>

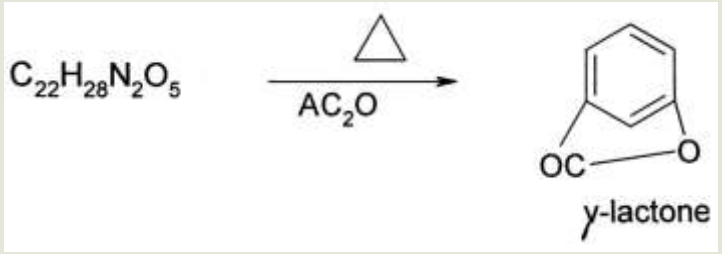
When reserpic acid is fused with KOH it yields 5-hydroxy isophthalic acid.

One of the acidic groups of isophthalic acid must be



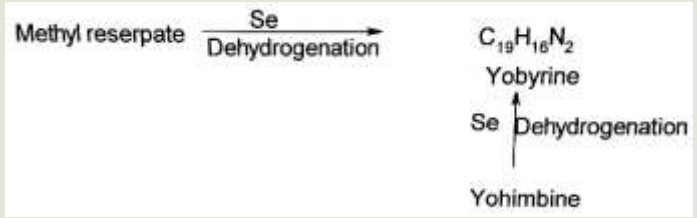
Constitution

Present in m-position to each other this confirm by the fact that reserpic acid when heated with acetic anhydride yields a gamma Iactone.



i) <u>Dehydrogenation</u>

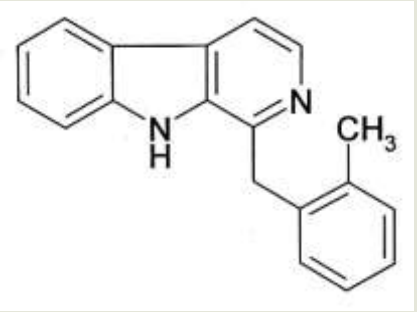
When methyl reserpate is dehydrogenated with selenium it yields a yobyrine of Molecular formula $C_{19}H_{16}N_2$



This yobyrine is also obtained by dehydrogenation of Yohimbine with seleniUm & was therefore named as Yobyrine.

Constitution

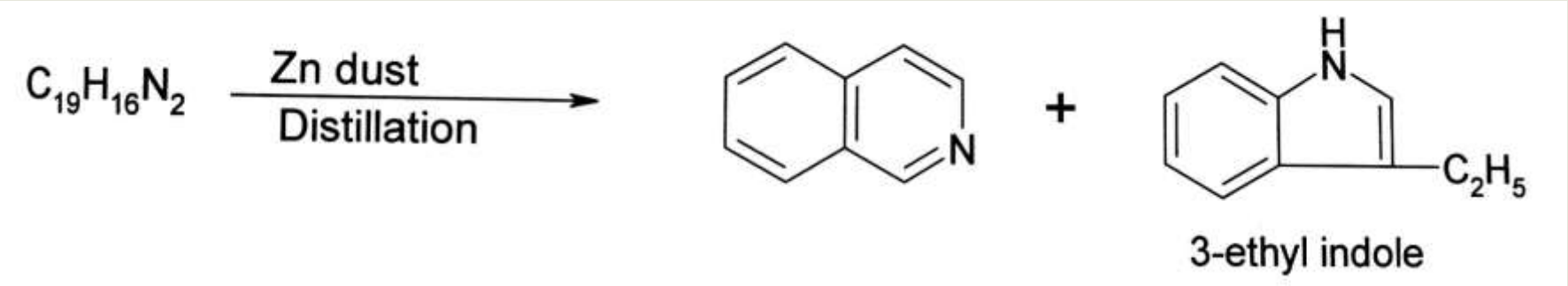
8. Structure of Yobyrine



   a) Molecular formula: C19H16N2

   b) Zinc Distillation

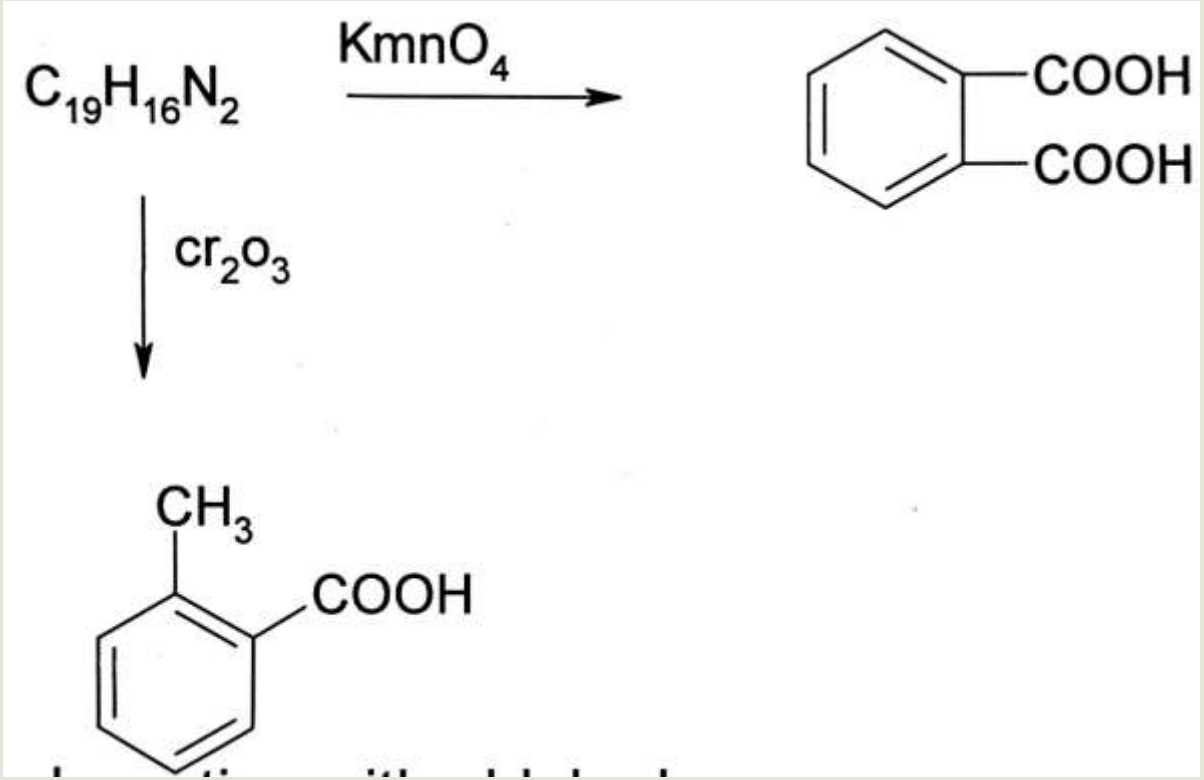
      When distilled with zinc it yields 3ethyl indole & isoquinoline.



Constitution

c) <u>Oxidation</u>

When yobyrine is oxidized with pot. permangnate it yields phthaiic acid.

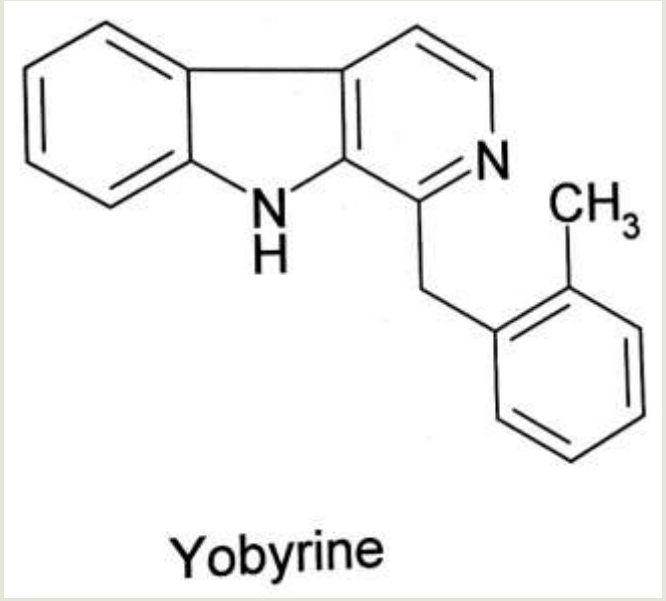


Constitution

d) <u>Condensation with aldehydes</u>

Yobyrine gives condensation products suggesting the presence of pyridine ring with a -CH2 substitution adjacent to the nitrogen.

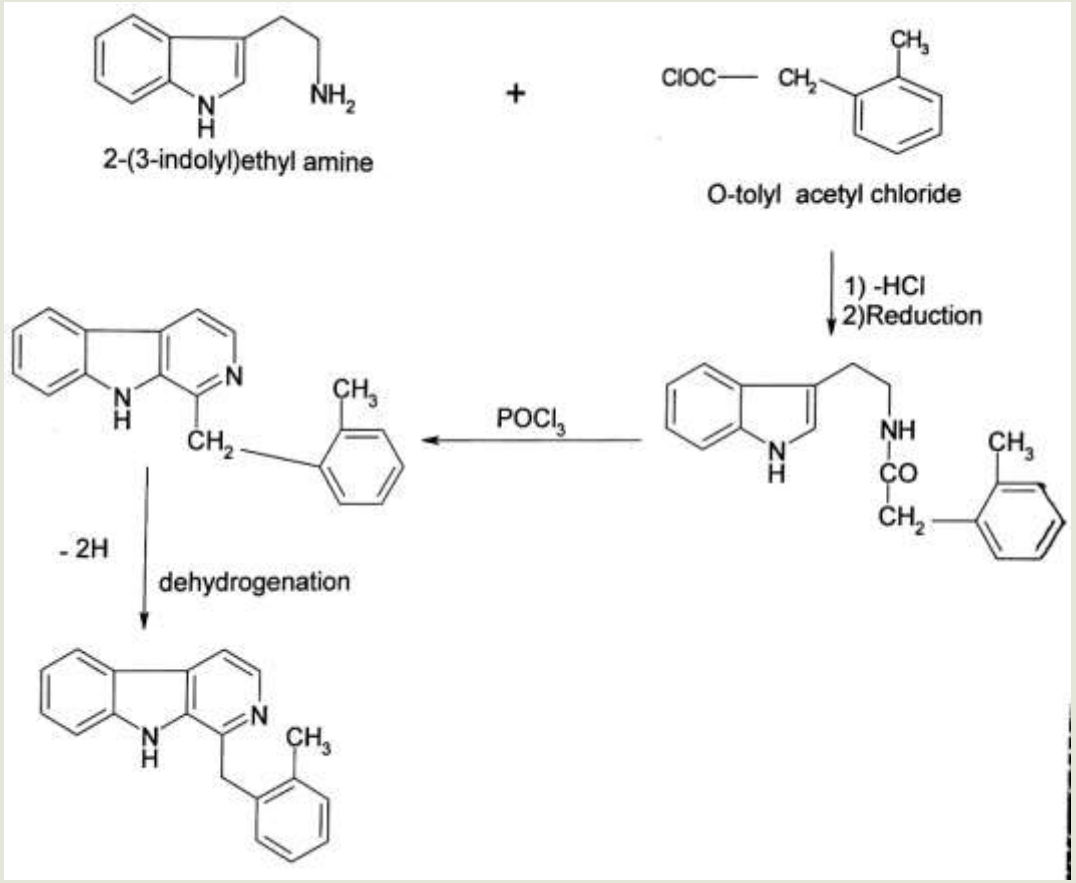
On the basis of above facts following structure has been postulated for yobyrine.



Yobyrine

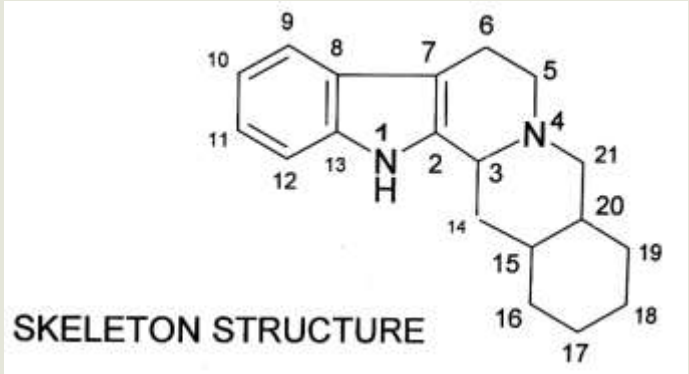
Constitution

e) Synthesis of yobyrine



Constitution

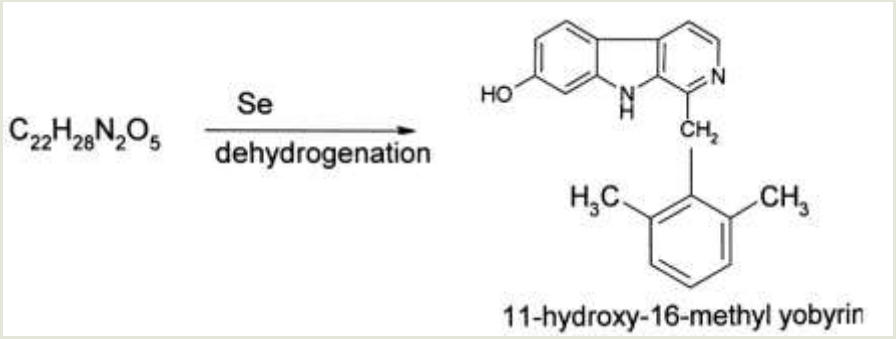
f) As yobyrine is formed from reserpic acid it means that reserpic acid may possesses the following types of skeleton structures.



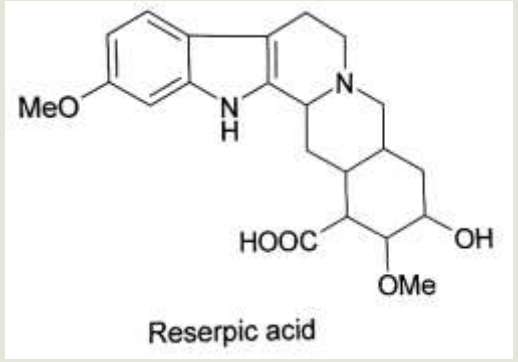
SKELETON STRUCTURE

g) From the step (g) it follows that one of the methoxyl group is present in m-position to the NH group of indole i.e. on C-11. Reserpic acid when dehydrogenated yields 11-hydroxy-16-methyl yobyrine,this may be only formed if -COOH group is present on C-16

Constitution



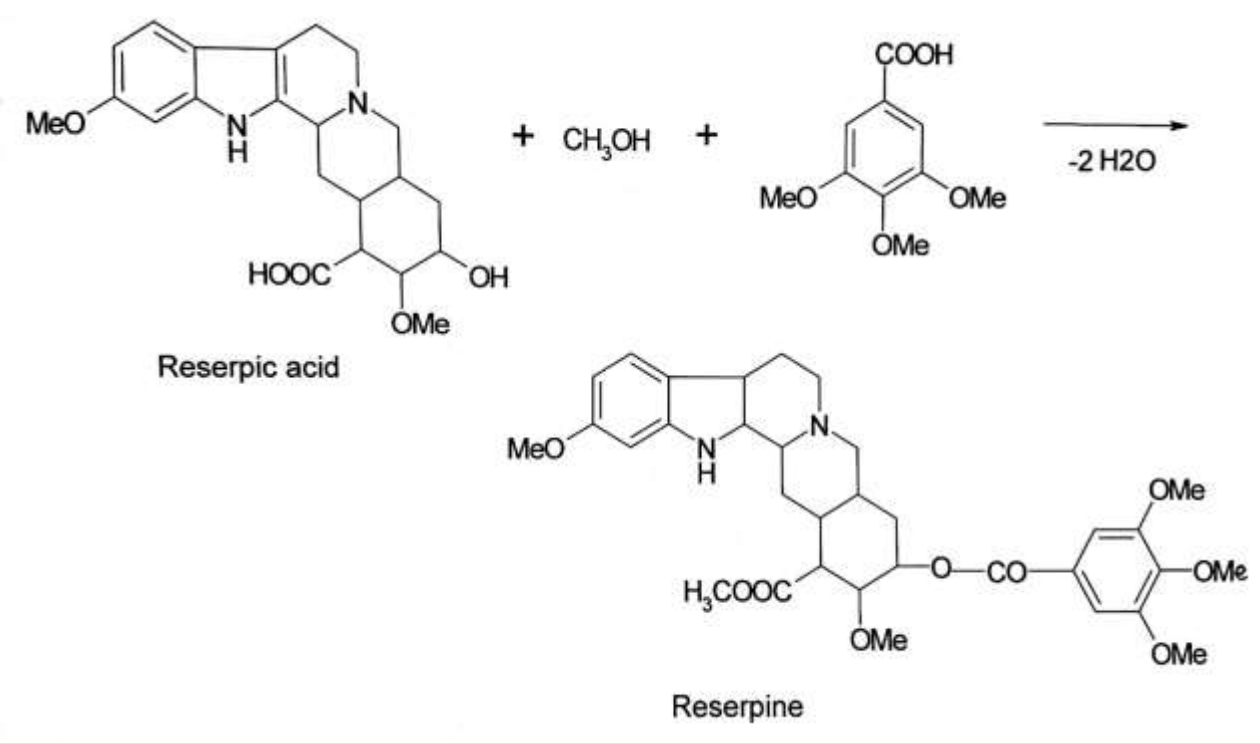
- From the step (h) it follows that -COOH & -OH group are in m-position to each other but -COOH group is present at C-16 therefore -OH group must be at C-18.
- From purely biogenic reasons, the 2nd methoxyl group has been assigned position C-17.
- On the basis above mentioned facts the structure of reserpic acid may be



Constitution

9. Structure of reserpine

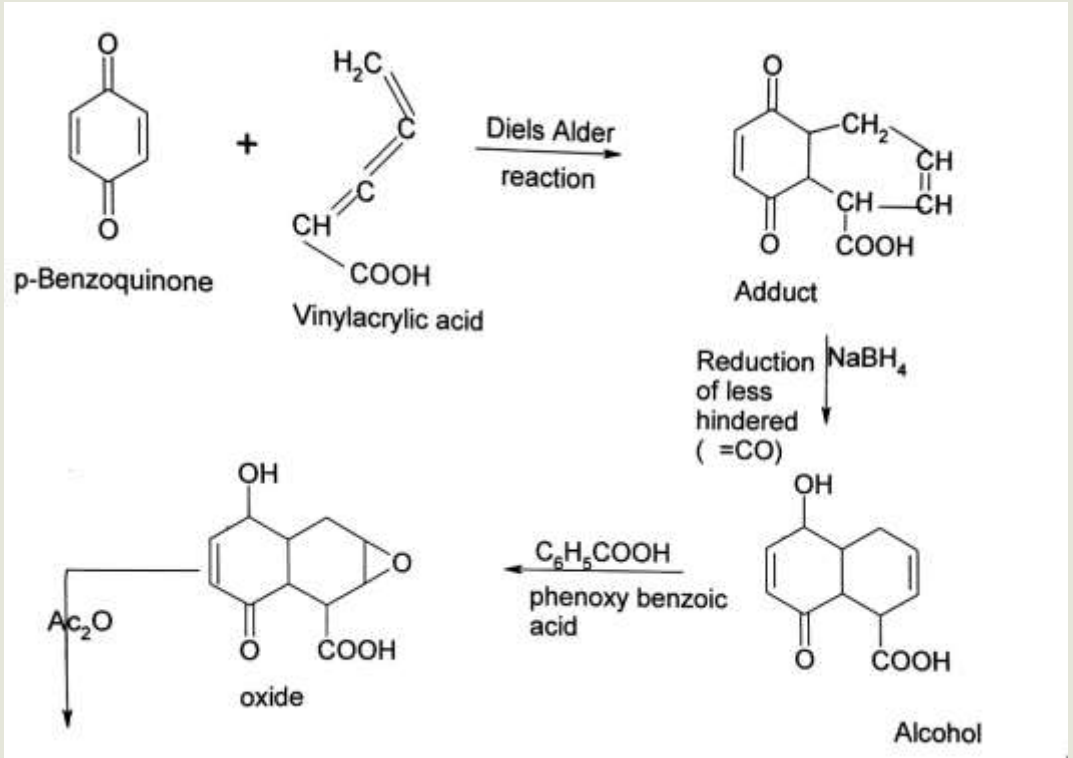
As reserpine is di-ester of reserpic acid, the structure of reserpic acid is written as follows

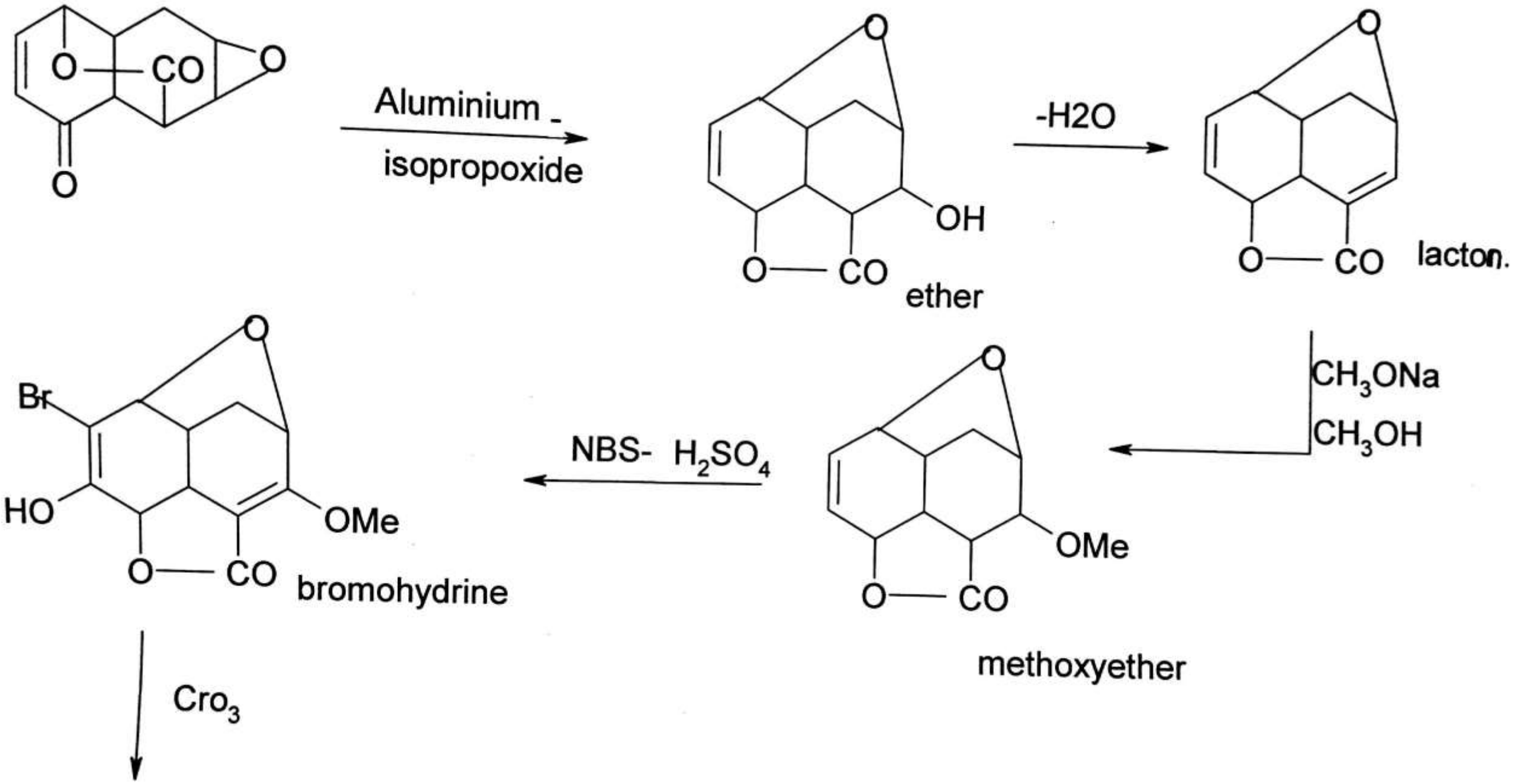


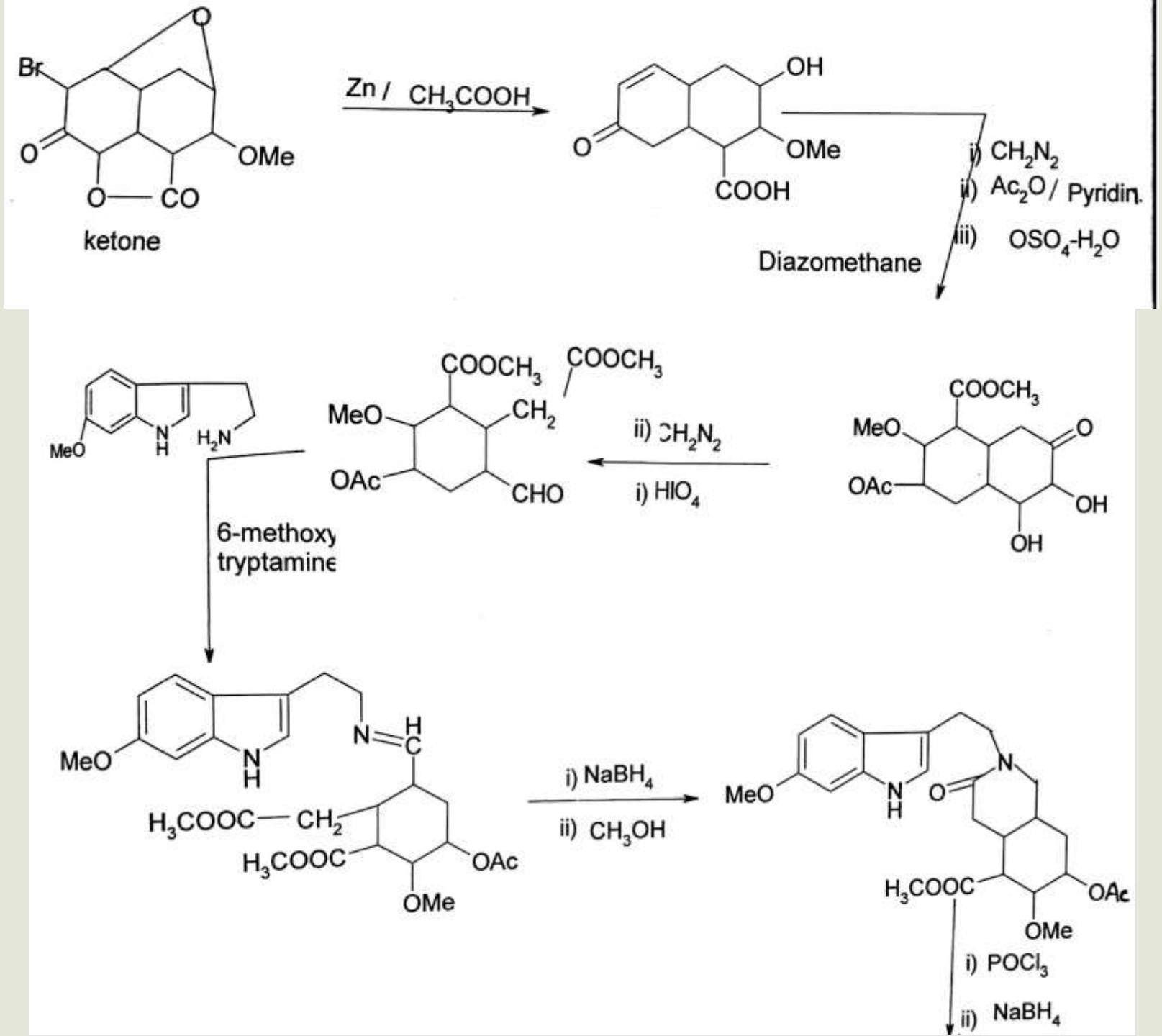
Constitution

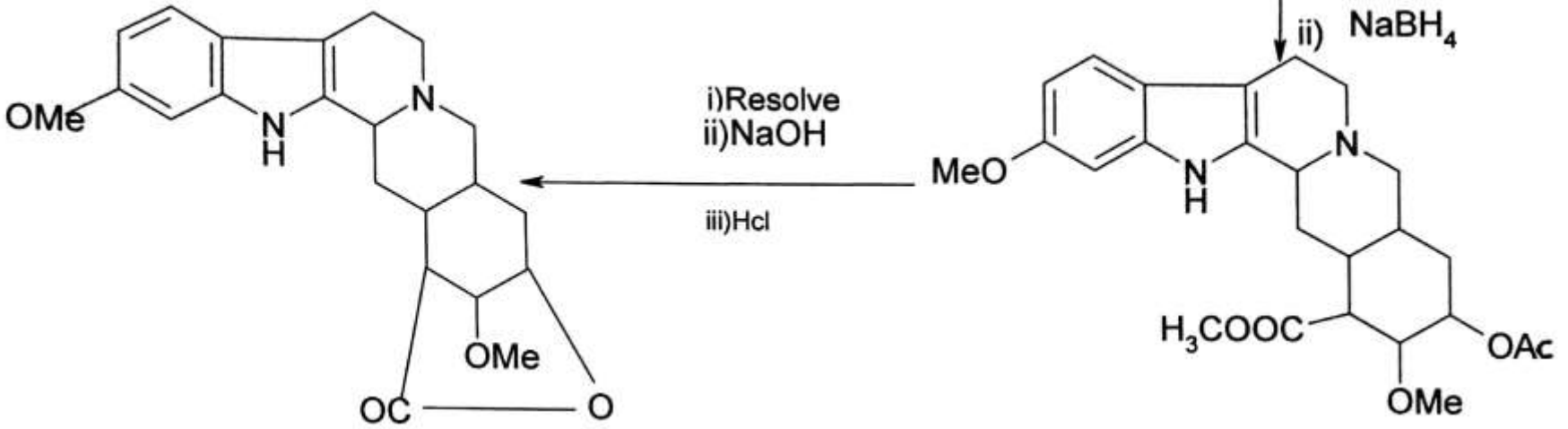
10. Synthesis of Reserpine

The structure of reserpine has been confirmed by its synthesis given by Woodward et. Al., (1956, 1958)

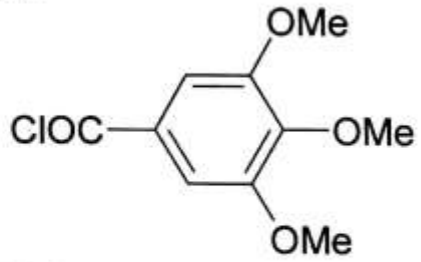



Aluminium -
isopropoxide
-H2O
lacton.
ether
CH3ONa
CH3OH
NBS- H2SO4
methoxyether
bromohydrine
Cro3


Br
O
O
OMe
O — CO
ketone
Zn / CH3COOH
OH
O
OMe
COOH
i) CH2N2
ii) Ac2O / Pyridin.
iii) OSO4-H2O
Diazomethane
COOCH3
COOCH3
MeO
CH2
OAc
CHO
ii) CH2N2
i) HIO4
COOCH3
MeO
O
OAc
OH
OH
MeO
N
H
H2N
6-methoxy
tryptamine
MeO
N
H
N
H
C
H3COOC — CH2
H3COOC
OAc
OMe
i) NaBH4
ii) CH3OH
MeO
N
H
N
O
H3COOC
OAc
OMe
i) POCl3
ii) NaBH4

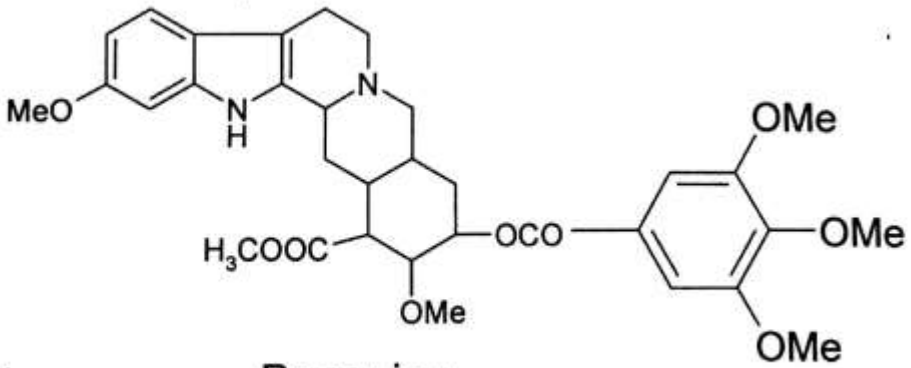


Reserpic acid Lactone



ISOMERIZATION

CH_3OH



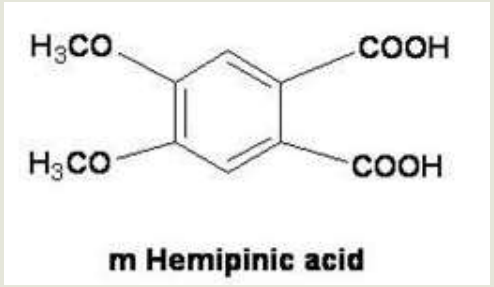
14 Reserpine

Emetine

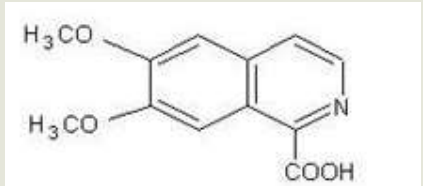
- Emetine being an alkaloid was first isolated by Pelletier and Magendie in the year 1817 from roots of Cephalis ipecacuanha belonging to the family Rubiaceae.
- White amorphous powder.
- Melting point 70 C
- Sparingly soluble in Water.
- Completely miscible in organic solvents like alcohol, chloroform and ether.
- Uses: Emetic, expectorant and amoebic dysentry.

Constitution

- Molecular formula- By analytical data it is found to be $C_{29}H_{40}N_2O_4$
- Emetine does not contain N -methyl groups but has a secondary and a tertiary nitrogen atoms.



m Hemipinic acid



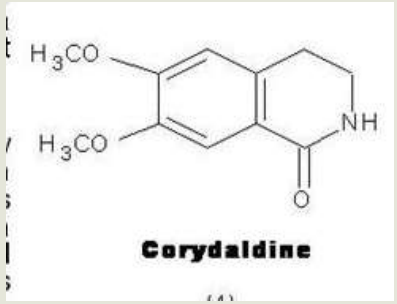
6,7 Dimethyl isoquinoline 1 carboxilic acid

- Presence of 4 methoxyl group- it is given by Zeisel Method where in on treating with hydroiodic acid this yields 4 molecules of methyl iodide showing presence of methoxyl groups.

Constitution

- Presence of one unit of 6.7-dimethoxy Isoquinoline
  i. Oxidation with potassium permanganate in presence of acetone to give m-hemipinic acid with small amounts of 6.7-dimethoxy.isoquinoline-1-carboxylic acid.
  ii. Oxidation with chromic acid it yields 4,5—dimethoxy phthalonimide.

4,5 Dimethyl phthalonimi



Corydaldine

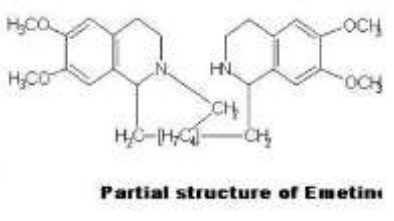
- Derivative of tetrahydro isoquinolinethis is shown by the UV -spectra of cephaline and emetine which resembles that of 1,2,3,4-tetrahydro isoquinoline

Constitution

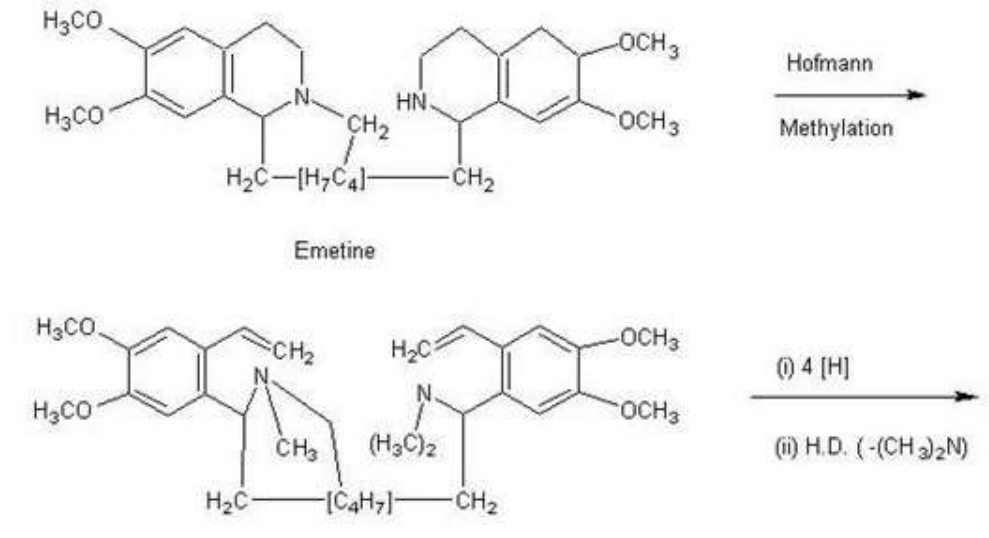
- Presence of o-dimethoxy benzene units. This is shown by the UV –spectra of emetine which closely resembles that of tetra hydro papaverine
- Further proof for 6,7-dimethoxy isoquinoline-
  i. Gentle oxidation with alkaline potassium permanganate, this yields firstly Corydaldine then when the remaining mother liquor is oxidized further with the permanganate it gives m-hemipinic acid.
  ii. Cephaline another ipecac alkaloid on ethylation gives ethyl ether of cephaeline which yielded a mixture of corydaldine and ethoxy methoxy isoquinoline.
  iii. Oxidation of emetine gives 96% yield of m-hemipinic acid which is higher when compared to papaverine this shows the presence of 2 isoquinoline units.

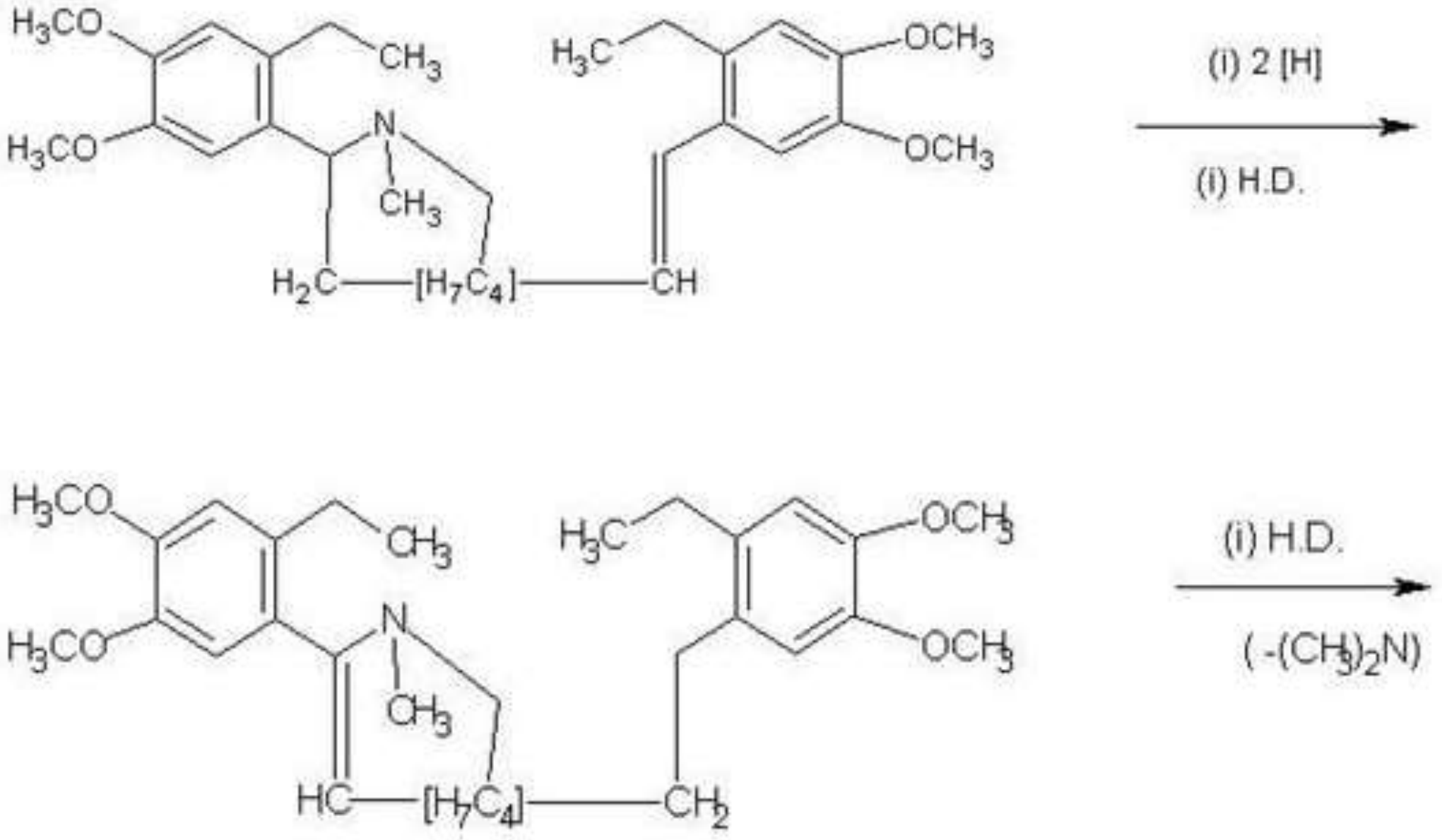
Constitution

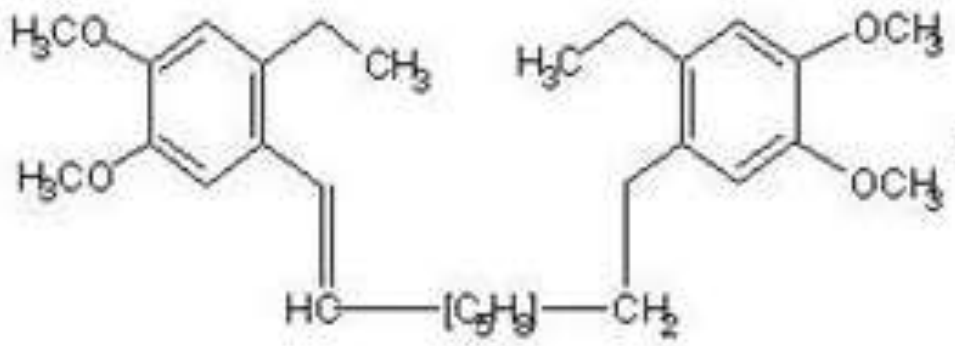
- Partial structure of Emetine.



- The nature of [C_4H_7] Fragment this is given by Hoffmann degradation of emetine which removes the nitrogen atoms completely, it is given in the following steps.

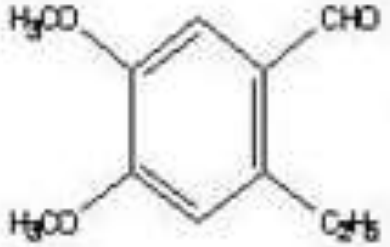



H3CO
CH3
H3CO
N
CH3
H2C—[H7C4]—CH
H3C
OCH3
OCH3
(i) 2 [H]
(i) H.D.
H3CO
CH3
H3CO
N
CH3
HC—[H7C4]—CH2
H3C
OCH3
OCH3
(i) H.D.
(-(CH3)2N)



(6)

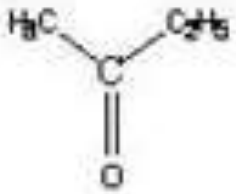
Ozonolysis



6-ethyl veratraldehyde

+ unsaturated aldehyde

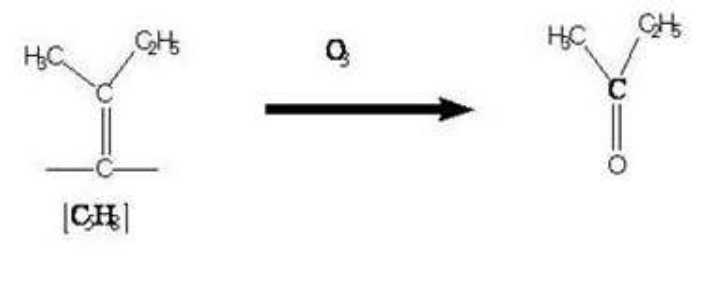
Ozonolysis



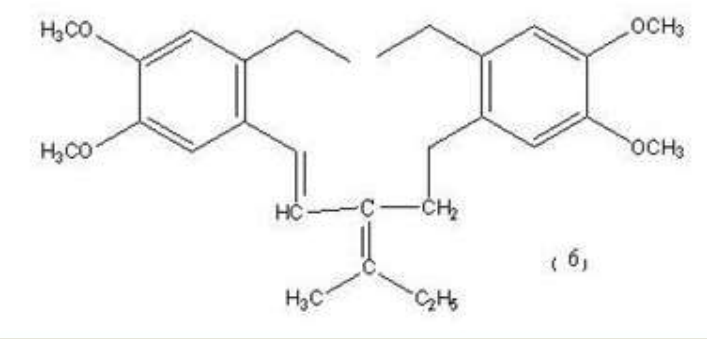
Ethyl methyl ketone

Constitution

- The formation of ketone is also shown as;

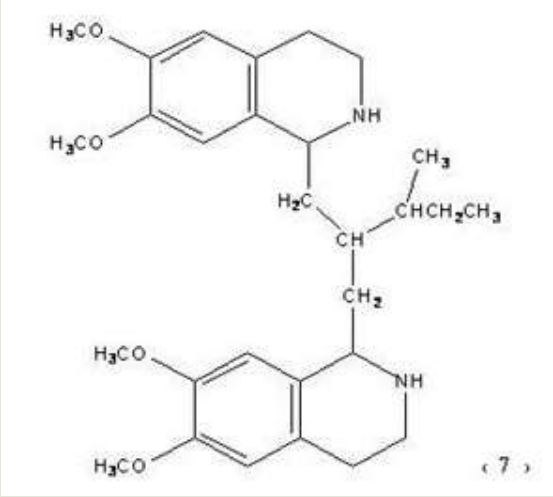


- The structure of (6) can also be given as;

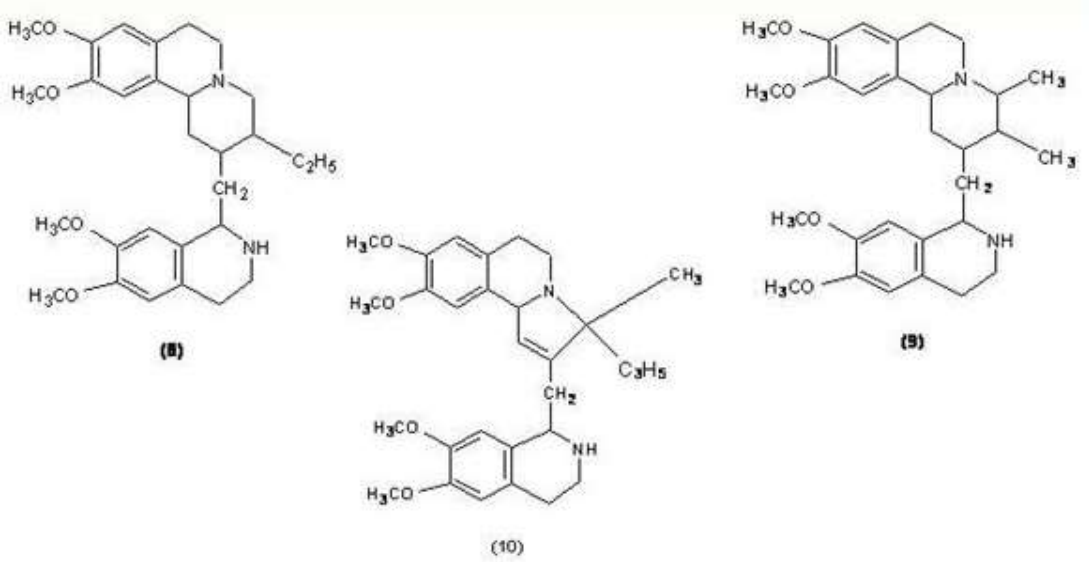


Constitution

- From the structure (6) structures (7),(8),(9) and (10) were proposed. Based on (7) the structure of emetine was given.



Constitution

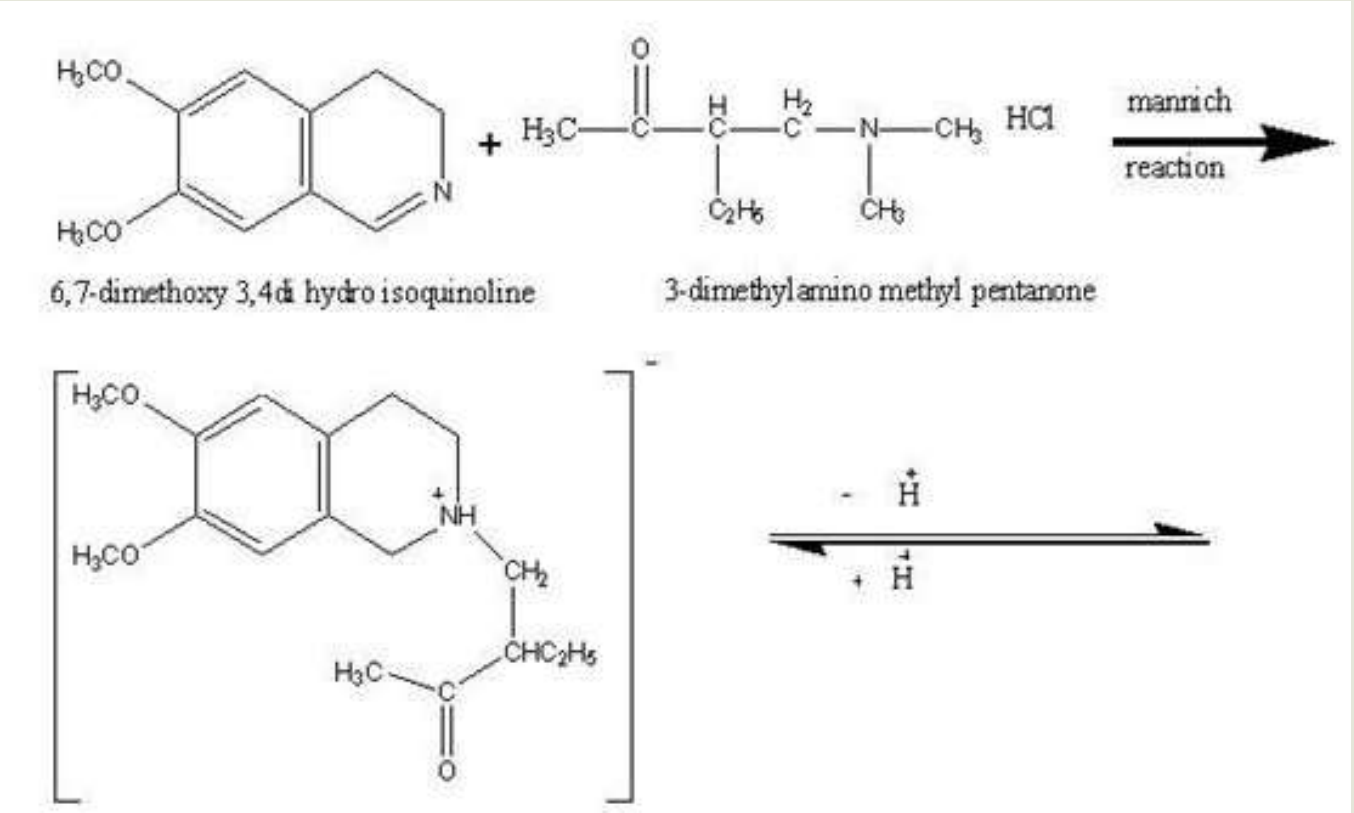


- Emetine is found to contain only one C-alkyl group hence structures (9) and (10) are ruled out as they contain 2 alkyl groups.
- For biogenetic reasons structure (8) is said to be structure of emetine.

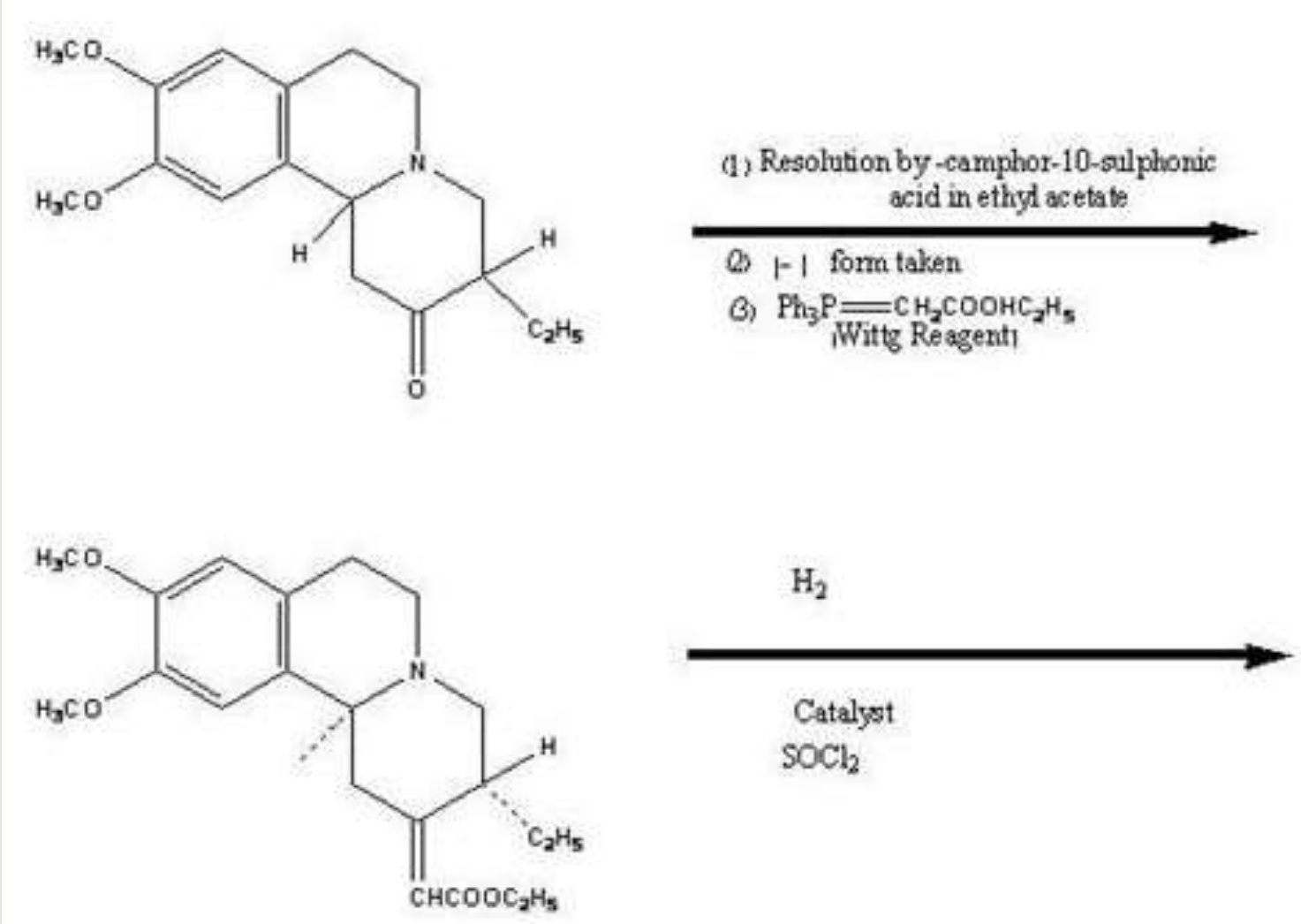
Constitution

- Synthesis

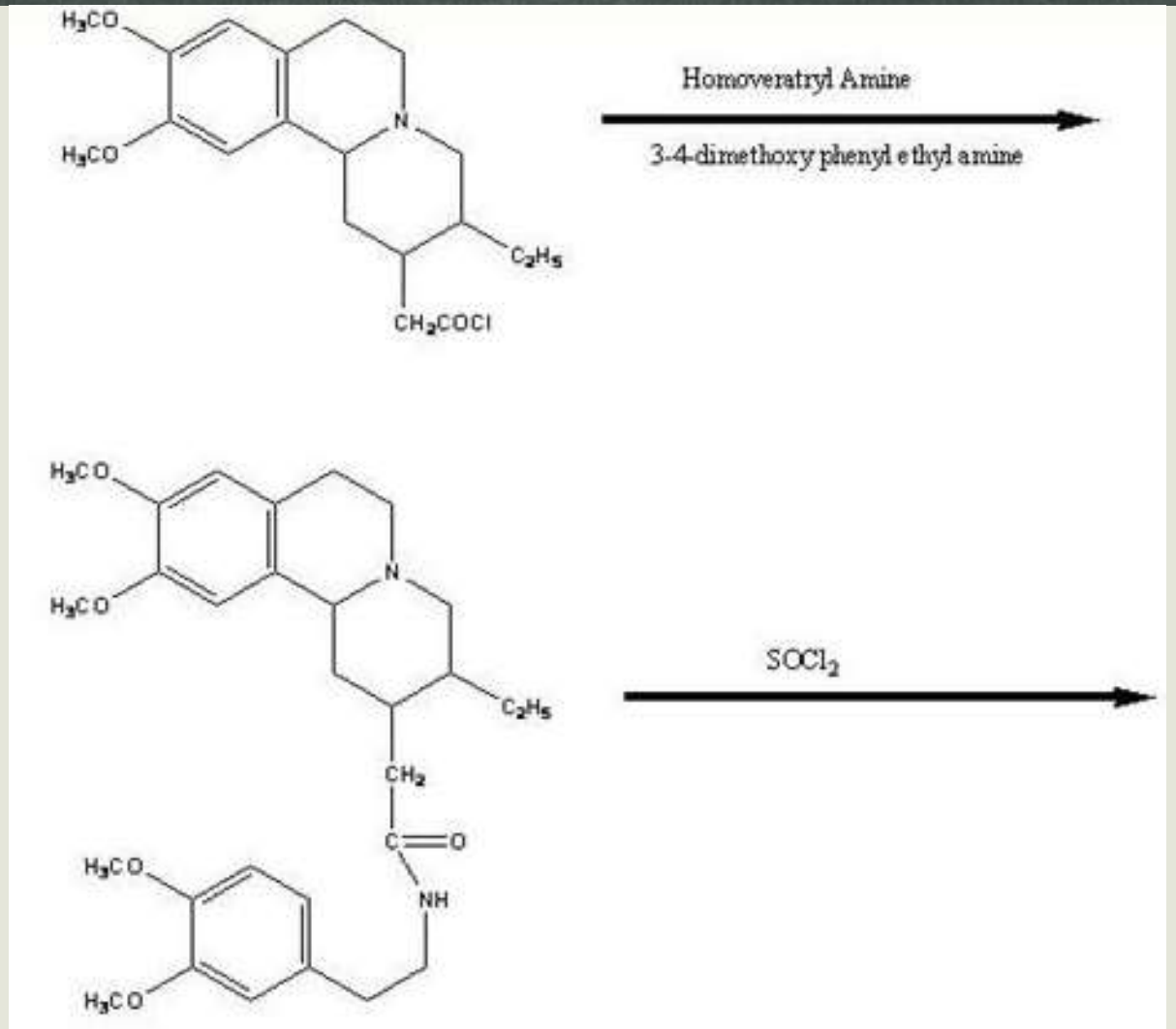
  Openshaw and Whittaker synthesis



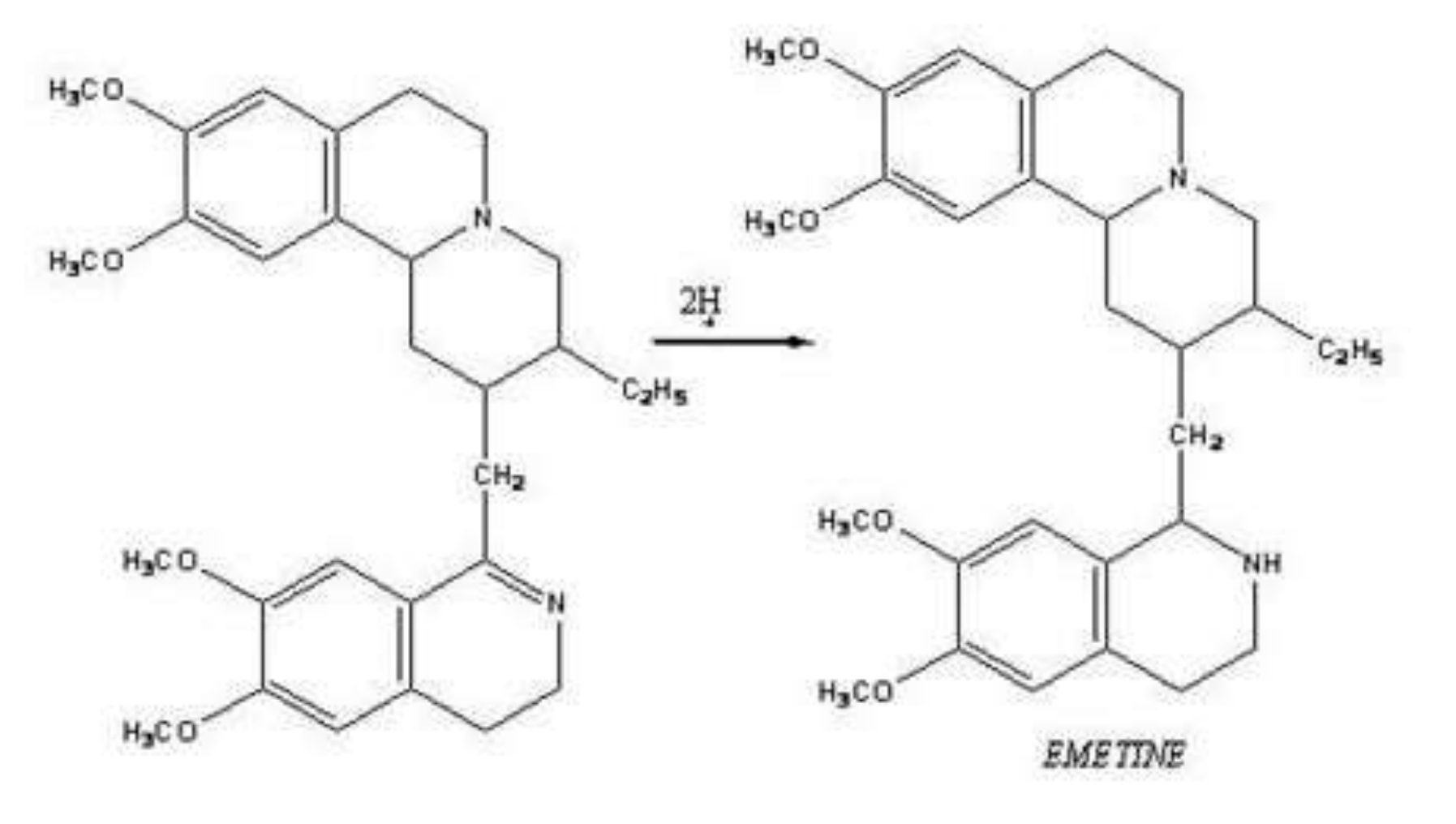
Constitution



Constitution



Constitution



Reference

- Chemistry of natural products, Vol. 1, O. P. Agarwal, Goel publishing house. Meerut., Page No. 193-311.
- Organic chemistry of natural products, Vol. 1, Gurdeep R. Chatwal, Edited by M. Arora, Page No. 3.1 – 3.154


thank you!