Unit 3

Alkaloids

1. Coniine
2. Nicotine
3. Quinine
4. Atropine
5. Morphine

ALKALOIDS

Usually, the term Alkaloid (which means alkali like) was given to all organic bases isolated from plants. However, Konigs (1880) suggested that alkaloids are defined as naturally occurring organic baseswhich contains a pyridine ring. This definition was not correct as it included only a limited number of compounds.

Ladenberg again modified and defined alkaloids as natural plant compounds having a basic character and containing atleast one nitrogen atom in a heterocyclic ring. This definition again excludes any synthetic compound and alkaloids obtained from animal sources.

Even today, it is difficult to define an Alkaloid.

The term Alkaloid is generally limited to organic bases found in plants. Alkaloids are very poisonous and are used medicinally in very small quantities. The main character that define plant alkaloids are the basic properties, complex structures, physiological actions and plant origins.

EXTRACTION OF ALKALOIDS

Alkaloids are generally found in the seeds, root, leaves or bark of the plant and generally occur as salts of various plant acids ex acetic, oxalic,citric, maleic , tartaric acid etc.

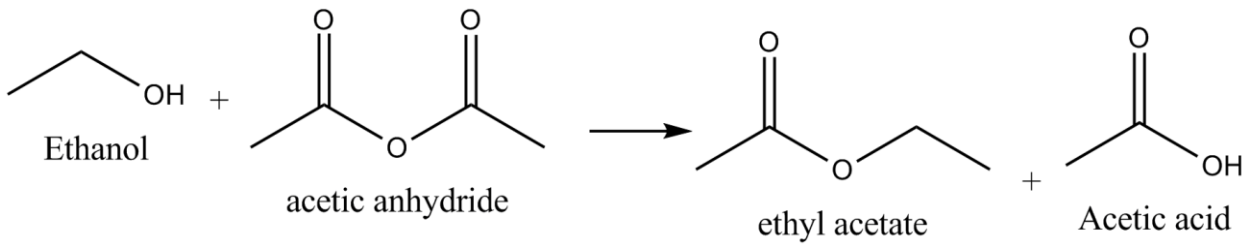
The plant is dried, then finally powdered and extracted with boiling methanol. The solvent is distilled off and the residue is treated with inorganic acids whereupon the bases are extracted as their soluble salts. The free bases are liberated by the addition of Na_2CO_3 and extracted with solvents such as $CHCl_3$, ether etc. The mixture of bases thus obtained are then separated by different chromatographic techniques.

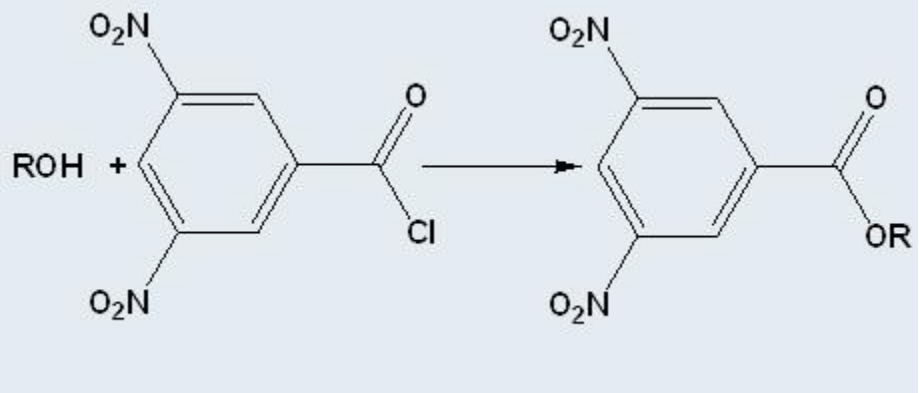
GENERAL METHODS FOR STRUCTURE DETERMINATION OF ALKALOIDS

i) **Molecular formula:** Molecular formula is determined by usual quantitative analysis and mol.wt determination methods and by means of mass spectrometry.

ii) **Nature of oxygen atom present:** If oxygen is present in Alkaloids its functional nature is generally as alcohol, aldehyde, ketone, alkoxy, acetyl or carboxylic groups.

d) **Presence of oxygen atom present:** presence of –OH group can be determined by the formation of acetates with acetic anhydride and benzoyate with 3.5-dinitirobenzoyl chloride.





For one OH group, one molecule of acetic anhydride or 3,5 dinitrobenzoyl chloride is required to form acetates or benzoates.

Now whether the OH group is alcoholic or phenolic is determined using NaOH solution. Phenols are soluble in NaOH whereas alcohols are insoluble in NaOH.

OH + NaOH --→ ONa + H_2O (PHENOL)

OH + NaOH --→ NO REACTION (ALCOHOL)

Whether the OH group is a primary, secondary or tertiary alcohol is determined by oxidation.

Primary alcohols on oxidation give aldehydes which on further oxidation gives carboxylic acid having same number of carbon atoms.

Secondary alcohols on oxidation gives ketones which on further oxidation gives acids with one less carbon atoms.

Tertiary alcohols do not undergo any oxidation and under extreme conditions give alkenes.

$CH_3CH_2OH \xrightarrow{[O]} CH_3CHO \xrightarrow{[O]} CH_3COOH$

Primary alcohols — aldehydes — carboxylic acids with same number of carbon atom

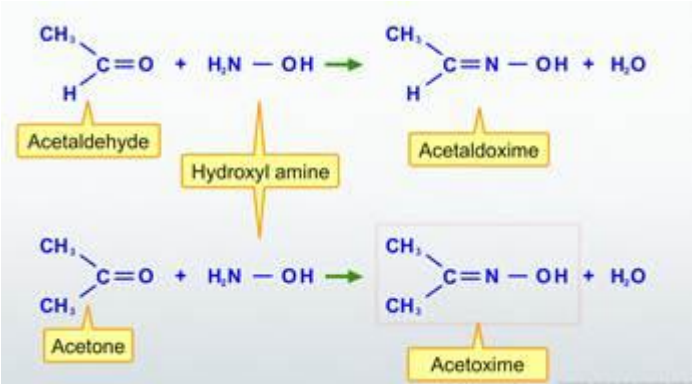
$(CH_3)_2CHOH \xrightarrow{[O]} CH_3COCH_3 \xrightarrow{[O]} CH_3COOH + HCOOH$

Secondary alcohols — ketones — carboxylic acids with one C atom less

$(CH_3)_3COH \xrightarrow{[O]}$ No Reaction

Tertiary alcohols

e) **Presence of >C=O group:** Alkaloids containing carbonyl functional group on reaction with hydroxyl amine, phenyl hydrazine and sodium bi sulphate form crystalline addition products like oxime, phenyl hydrazone and bisulphite etc.



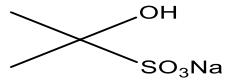
$$CH_3CHO + C_6H_5NHNH_2 \longrightarrow CH_3CH{=}NNHC_6H_5 + H_2O$$

Phenyl hydrazine — Phenyl hydrazones

$$CH_3COCH_3 + C_6H_5NHNH_2 \longrightarrow (CH_3)_2C{=}NNHC_6H_5 + H_2O$$

$$CH_3CHO + NaHSO_4 \longrightarrow CH_3C(OH)(H)SO_3Na$$

bisulphite salts are produced

$$CH_3COCH_3 + NaHSO4 \longrightarrow$$ 

f) Presence of COOH group : Alkaloids containing COOH group on reaction with $NaHCO_3$ (Sodium bicarbonate) gives brisk effervences of CO_2 indicating the presence of COOH group in the compound.

$$COOH + NaHCO_3 \longrightarrow COONa + H_2O + CO_2$$

Now whether the COOH group is primary, secondary or tertiary is checked through esterification reaction.

$$RCOOH + CH_3OH \longrightarrow RCOOCH_3 + H_2O$$

ACID ALCOHOL ESTER

All acids on reaction with alcohol gives esters but the rate of esterification is maximum for primary acids and almost negligible with tertiary acids.

PRIMARY>SECONDARY>TERTIARY

g) **Presence of a $-OCH_3$ group:** Methoxy group in an alkaloid can be detected using Ziesel method.

$$-OCH_3 \xrightarrow[126]{HI} -OH + CH_3I \xrightarrow[AgNO_3]{\text{ethanolic}} AgI\downarrow \text{ weighed}$$

iii) **Nature of Nitrogen atom:** Nitrogen atom in alkaloids is usually present as N-methyl group which can be determined by Herzig Meyer method.

$$=NCH_3 + HI \xrightarrow[\text{pressure}]{150\text{-}300\ C} =NH + CH_3I$$

Distillation of an alkaloid with with aqueous KOH tells about the nature and number of alkyl groups attatched to nitrogen atom. The formation of methyl amine, dimethyl amine or trimethyl amine indicates respectively the attachment of one, two or three methyl groups attached to the nitrogen atom.

The formation of NH_3 shows the presence of an amino group.

Whether the nitrogen atom is primary, secondary or tertiary is determined by the formation of quaternary ammonium salts.

$$CH_3NH_2 \xrightarrow{3CH_3I} CH_3N^+(CH_3)_3I^-$$

Primary amines

$$(CH_3)_2NH \xrightarrow{2CH_3I} (CH_3)_2N^+(CH_3)_2I^-$$

Secondary amines

$$(CH_3)_3N \xrightarrow{CH_3I} (CH_3)_3N^+(CH_3)I^-$$

Tertiary amines

} Quaternary ammonium salts

Degradation of alkaloids: In order to find out the structural system of alkaloids following degradation methods are used ……

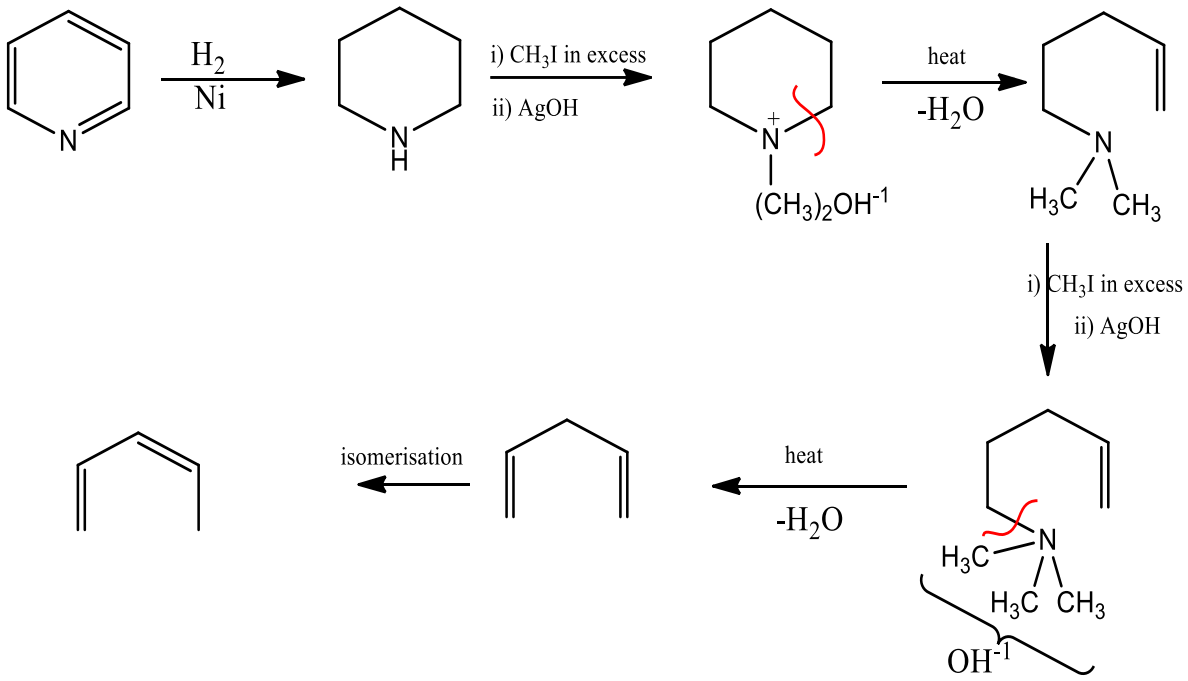
1. HOFFMANN EXHAUSTIVE METHYLATION METHOD:

This is an important step in alkaloid chemistry because by this heterocyclic rings are opened with the elimination of nitrogen. From the nature of the remaining carbon skeleton, the nature of the heterocyclic ring can be determined.

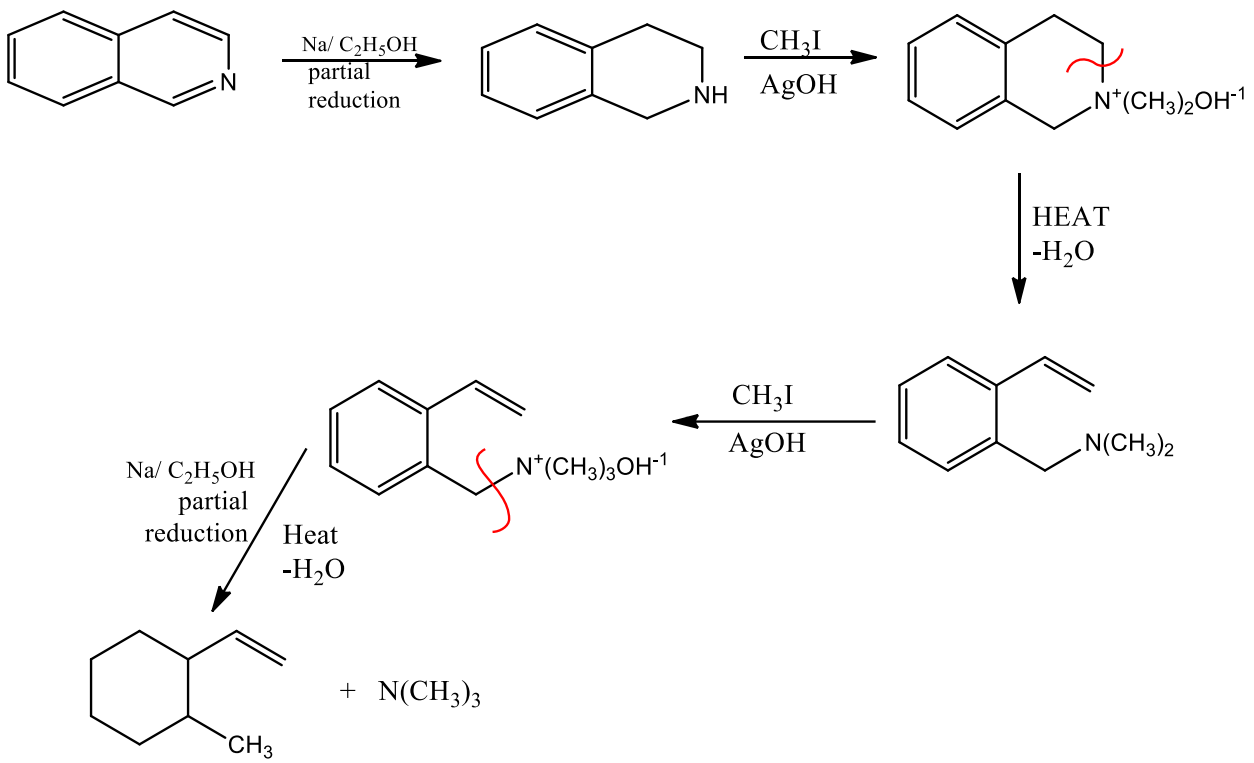
The principle of this method is that compounds which contain the structural unit $-CH_2-CH_2-NR3OH$ eliminates a trialkyl amine on pyrolysis at 300^0C or above to yield an alkene.

The main requirement for the above reaction is the presence of a β-hydrogen atom.

Hoffmann exhaustive methylation fails in the case of unsaturated heterocyclic rings, in case of the absence of β-hydrogen atom and with tetrahydroquinoline.

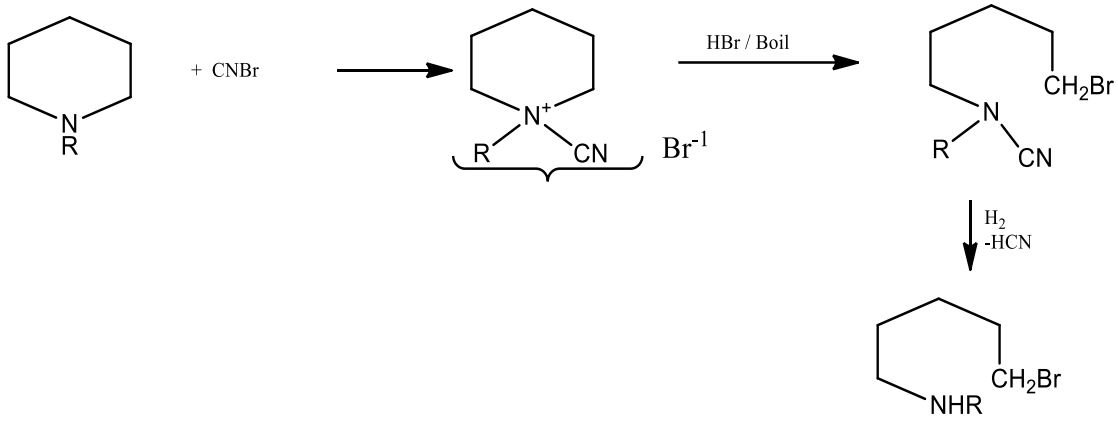


2. EMDE'S DEGRADATION: When the base does not contain a β-hydrogen atom, the exhaustive methylation method fails. In such cases, Emde's degradation method is used. In this method the quaternary ammonium salt is reduced with Na amalgam in aqueous ethanol or with Na in liquid NH_3, or is catalytically hydrogenated.

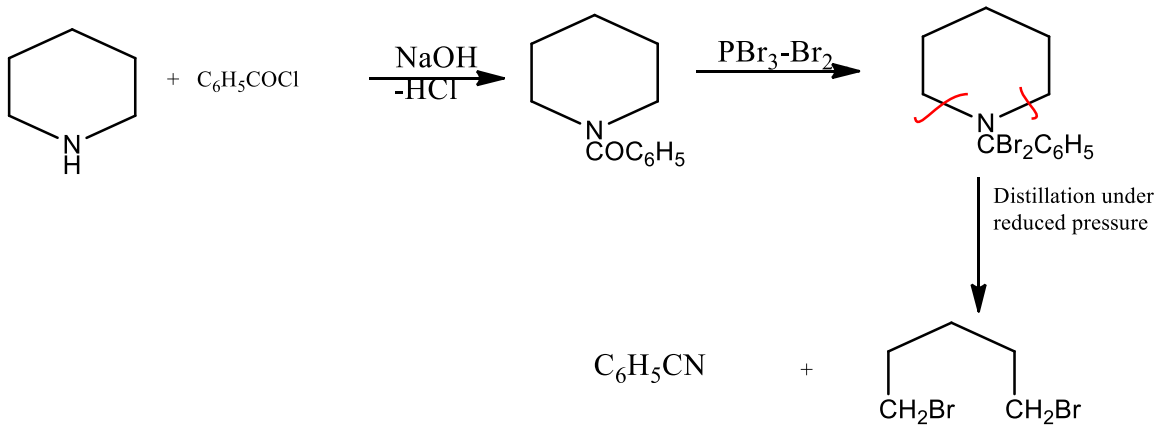


3. VON BRAUN'S METHOD: is applicable to compounds which do not respond to Hoffmann method. It is of two types

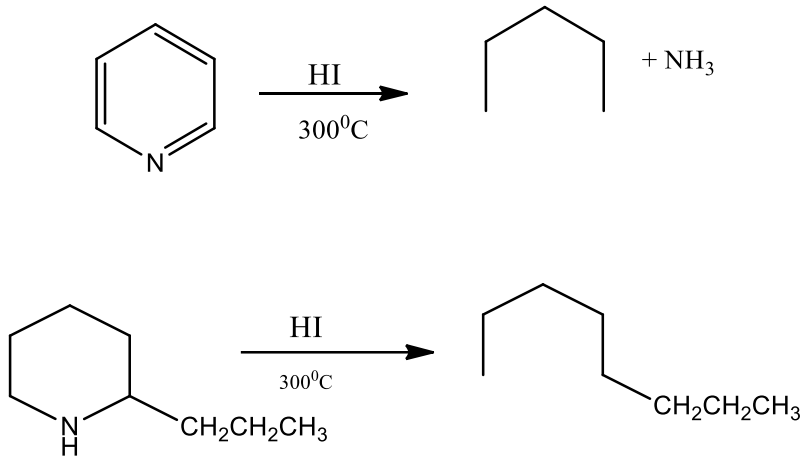
   a) With cyanogen bromide: In this method, the tertiary amine which contains at least one alkyl substituent is treated with cyanogen bromide. This results in the cleavage of an alkyl-nitrogen bond to give an alkyl halide and a substituted cyanamide.



   b) With Benzoyl chloride: In this method, the secondary amines is treated with Benzoyl Chloride in the presence of NaOH to give benzoyl derivatives which on treatment with PBr_3 –Br_2 followed by distillation under reduced pressure gives 1,5 dihalo compounds with the elimination of Benzonitrile.



4. REDUCTIVE DEGRADATION AND ZINC DUST DISTILLATION: In some cases the ring opening may take place by heating with HI at 300^0C.



CONIINE

Pyridine-Piperidine Alkaloid (Hemlock Alkaloid)

Coniine is a poisonous chemical compound, an alkaloid present in and isolable from poison hemlock .

Its ingestion and extended exposure are toxic to humans and all classes of livestock; its mechanism of poisoning involves disruption of the central nervous system, with death caused by respiratory paralysis.

It was the first Alkaloid to be synthesized due to its simple structure.

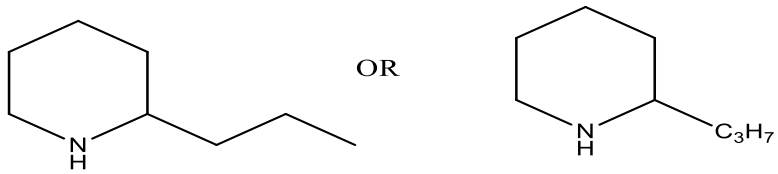
Hemlock contains a poisonous piperidine alkaloid, coniine, and related alkaloids, *N*-methyl-coniine, conhydrine, pseudoconhydrine, and gamma-coniceine.

The symptoms of hemlock poisoning are effects on the nervous system (stimulation followed by paralysis of motor nerve endings and nervous system stimulation and later depression), vomiting, trembling, difficulty in movement, an initially slow and weak and later a rapid pulse, rapid respiration, salivation, urination, nausea, convulsions, coma, and death.

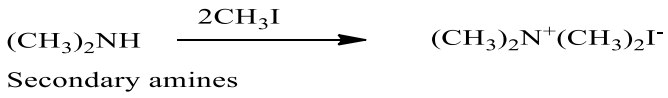
The most famous hemlock poisoning occurred in 399 BCE, when the philosopher Socrates is believed to have consumed a liquid infused with hemlock to carry out his death sentence, his having been convicted of impiety toward the gods, and the corruption of youth. Hemlock juice was often used to execute criminals in ancient Greece.

Hemlock has had a limited medical use throughout history. The Greeks used it not just as capital punishment, but also as an antispasmodic and treatment for arthritis.

STRUCTURE ELUCIDATION OF CONIINE:

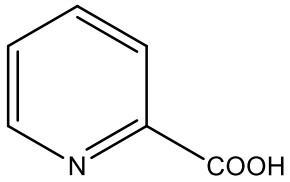


1. **Molecular Formula :** $C_8H_{17}N$
2. **Nature of the Nitrogen atom:** Coniine has a secondary amino group in its structure as it takes up two moles of Methyl iodide to form a Quaternary ammonium salt.



$C_8H_{17}N$ (Coniine) $\xrightarrow{2CH_3I}$ Quaternary ammonium salts

3. **Presence of a Piperidine ring:** When coniine is distilled with Zn Dust, it yields Conyrine $C_8H_{11}N$, which on further oxidation with KMnO4 yields Pyridine-2-carboxylic acid (α-Picolinic acid)

$C_8H_{17}N$ (Coniine) $\xrightarrow[-3H_2]{\text{Zn Dust}}$ $C_8H_{11}N$ (Conyrine) $\xrightarrow[KMnO_4]{[O]}$ 

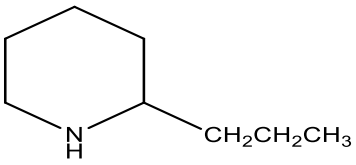
Pyridine-2-carboxylic acid

The formation of Pyridine-2-carboxylic acid suggests that Conyrine must be a Pyridine derivative with a side chain C_3H_7 at α-position. (in conyrine 8C atoms, five present in the pyridine ring and three present in the side chain)

But Coniine is a secondary amine and on distillation with zinc dust it loses 6 hydrogen atoms to form Conyrine, indicating that it must be a Piperidine derivative.

4. **Probable structure**: From the above points it is clear that Coniine has a Piperidine ring with a side chain C3H7 at the α-position. Now, the only question left is whether the side chain is n-propyl or isopropyl.

On the basis of the side chain, the structure of Coniine can be either I or II



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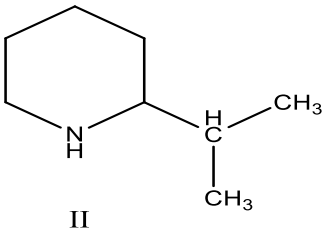
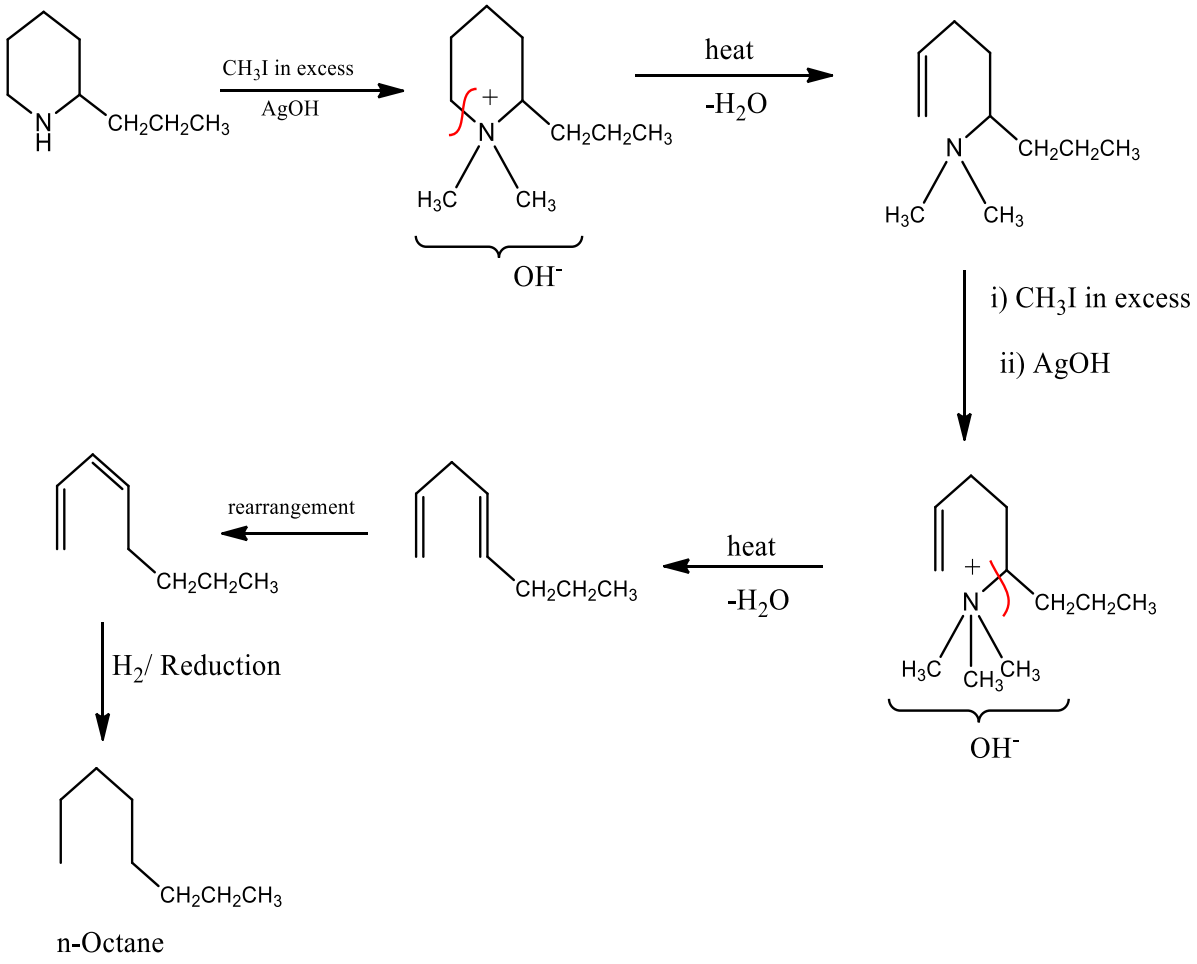


II

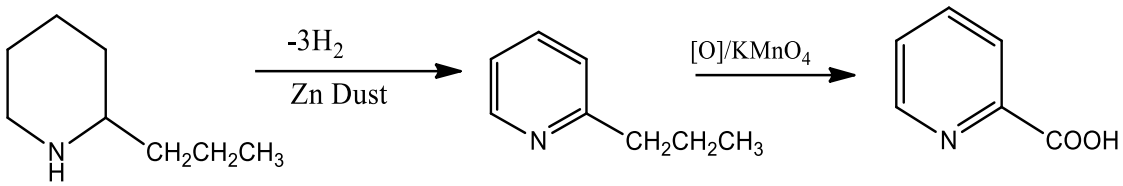
5. **Evidence in favour of Structure I :** The following reactions prove that Coniine must have structure I.

   i) Coniine on heating with HI at about 300^0C under pressure yields n-Octane and not Iso Octane which would have been formed if structure II was correct.

ii) Complete Hoffmann Exhaustive methylation of Coniine followed by reduction also gives Octane and not Isooctane.



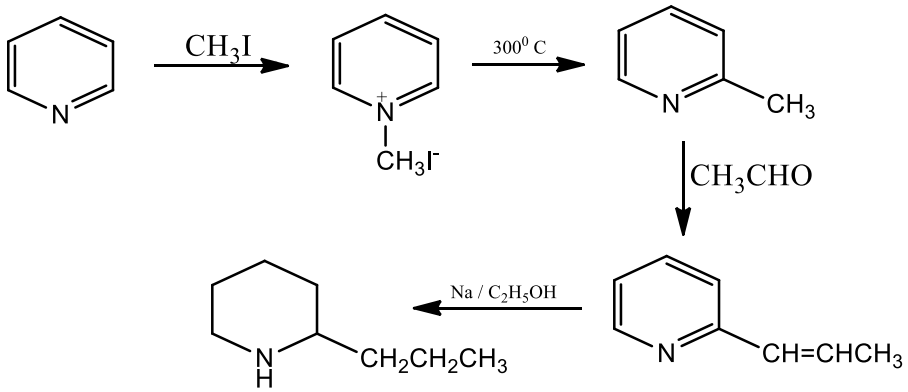
Thus, structure I is the correct structure for coniine as it explains the formation of conyrine as well as pyridine-2-carboxylic acid too.



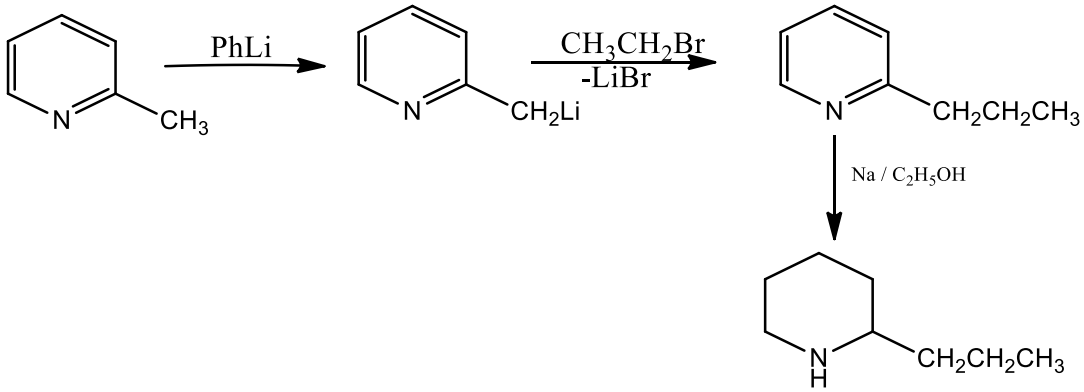
Coniine

6. Synthesis: Finally, the above structure of Coniine is confirmed by its synthesis.

LADENBERG SYNTHESIS



BERGMANN SYNTHESIS



NICOTINE

Pyridine-Pyrrolidine Alkaloid

Nicotine is a widely used stimulant alkaloid that is naturally produced in the nightshade family of plants (most notably in tobacco).

It is used for smoking cessation to relieve withdrawal symptoms.

Nicotine constitutes approximately 0.6–3.0% of the dry weight of tobacco.

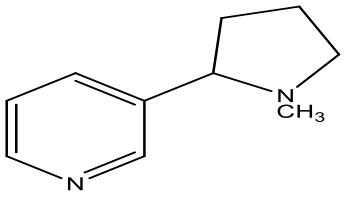
Nicotine is also present at concentrations of millionths of a percent in the edible family Solanaceae, including potatoes, tomatoes, and eggplants though sources disagree on whether this has any biological significance to human consumers.

It functions as an antiherbivore chemical; consequently, nicotine was widely used as an insecticide in the past.

Nicotine is highly addictive, unless used in slow-release forms.

An average cigarette yields about 2 mg of absorbed nicotine. The estimated lower dose limit for fatal outcomes is 500–1,000 mg of ingested nicotine for an adult (6.5–13 mg/kg).

STRUCTURE ELUCIDATION OF NICOTINE:



Nicotine

1. Molecular Formula : $C_{10}H_{14}N_2$
2. Number of double bonds: On catalytic reduction it takes up three molecules of hydrogen to give a hexa hydro compound indicating the presence of three double bond in its structure.

$$C_{10}H_{14}N_2 + 3H_2 \xrightarrow{Ni} C_{10}H_{20}O_2$$

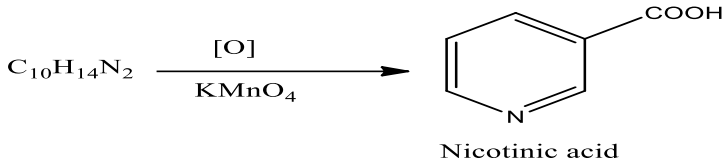
3. Presence of two nitrogen atoms: Nicotine undergoes Herzig Meyer test indicating the presence of Nitrogen in its structure.

$$=NCH_3 + HI \xrightarrow[\text{under pressure}]{150\text{-}300^0C} =NH + CH_3I$$

Both the nitrogen atoms in Nicotine are found to be in a tertiary state because Nicotine takes up two molecules of CH_3I to form a dimeth iodide.

$$C_{10}H_{14}N_2 + 2CH_3I \longrightarrow {}^{-1}ICH_3{}^{+}N[C_{10}H_{14}]N^{+}CH_3I^{-1}$$

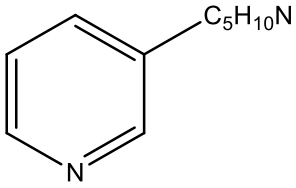
4. Presence of a Pyridine Ring: On oxidation with CrO_3/ $KMnO_4$, Nicotine gives Nicotinic acid (Pyridine-β-carboxylic acid) showing that Nicotine is a pyridine derivative containing a side chain at the β-position.



Nicotinic acid

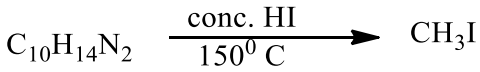
This reaction shows that

a) Nicotine has a Pyridine nucleus.
b) The side chain $C_5H_{10}N$, obtained by subtracting the molecular formula of substituted Pyridine (C_5H_4N) from the molecular formula of Nicotine , $C_{10}H_{14}N_2$, must be present in the β-position of the pyridine nucleus. Thus, the structure of Nicotine maybe

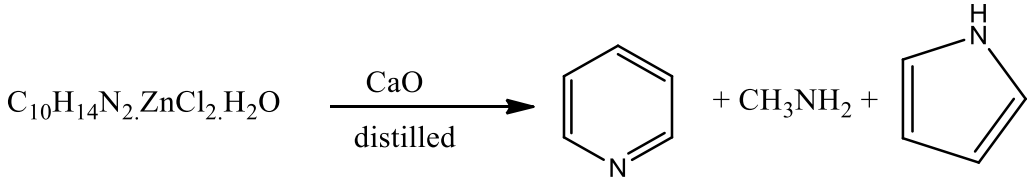


5. Nature of the side chain : As the formula of the side chain $C_5H_{10}N$ is similar to the piperidyl group, therefore it was thought that Nicotine was Piperidyl-pyridine alkaloid. However, this was found to be incorrect due to the following rasons:

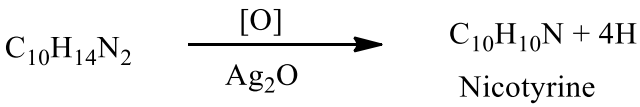
a) On heating with Conc HI at 150^0C , Nicotine gives CH_3I (Herzig Meyer Test), indicating that the side chain must have an N-CH_3 group .



b) Nicotine zinc chloride when distilled with soda lime, gives pyridine, methyl amine and pyrrole. This reaction shows that Nicotine might contain a five membered heterocyclic ring having an N-CH_3 group.



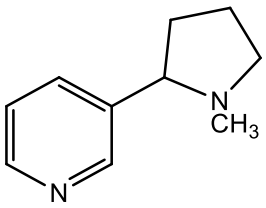
c) Nicotine when oxidized mildly with silver oxide yields Nicotyrine by the loss of four carbon atoms.



All the above points prove that Nicotine contains a Pyrrolidine ring and therefore the side chain in Nicotine must be an N-Methyl Pyrrolidine.

6. Point of attachment of the side chain N-METHYL PYRROLIDINE to the Pyridine nucleus:

The pyrrolidine side chain maybe attached to the Pyridine nucleus in two possible ways i.e. either through position 2 or 3 (α or β) resulting in two possible structures for Nicotine.



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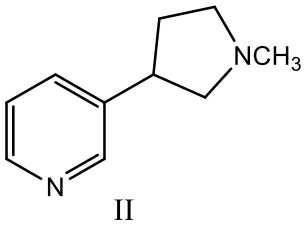

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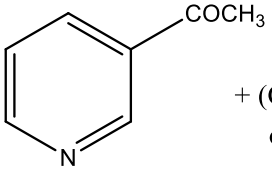
The exact nature of the side chain is proved on the basis of the following points

1. $C_{10}H_{14}N_2$ (Nicotine) $\xrightarrow{Br_2 \text{ in acetic acid}}$ $C_1OH_{10}Br_2.N_2O.HBr.Br_2$ (Nicotine Hydrobromibe per bromide) $\xrightarrow{aq\ H_2SO_5}$ $C_{10}H_{10}Br_2.N_2O$ (Dibromo Nicotine)

$\downarrow$ heat with mix. of $H_2SO_3 + H_2SO_4$ 130-140^{0C}

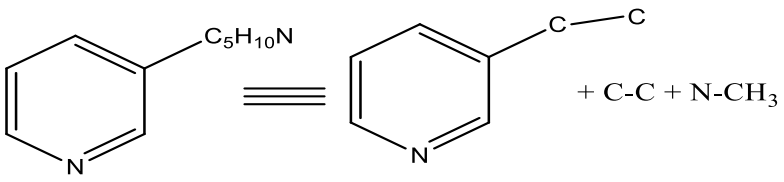


3-acetyl pyridine

$+ (COOH)_2 + CH_3NH_2$

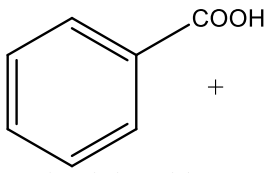
oxalic acid methyl amine

This reaction shows that the structure of Nicotine undergoes the following fragmentation.



+ C-C + N-CH3

2. $C_{10}H_{14}N_2$ (Nicotine) $\xrightarrow[HBr]{Br_2}$ $C_{10}H_8Br_2.N_2O_2$ (Dibromo nicotine) $\xrightarrow[Ba(OH)_2]{heat}$

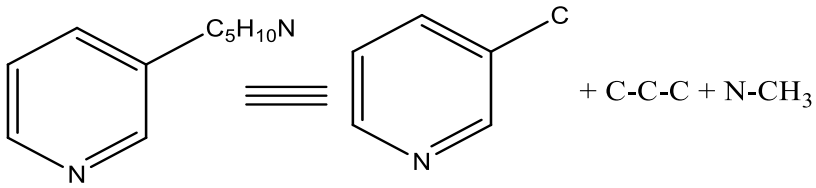


nicotinic acid +

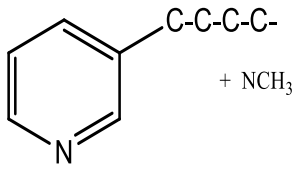
$COOHCH_2COOH + CH_3NH_2$

malonic acid methyl amine

This reaction shows that the structure of Nicotine undergoes the following fragmentation

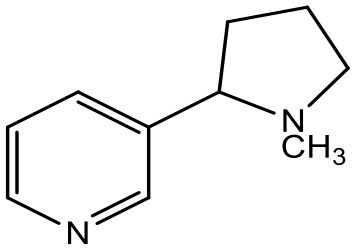


From the above two points it is clear that in Nicotine the N-methyl pyrrolidine group is linked to the pyridine β position by its α position and the nicotine has the following structure-



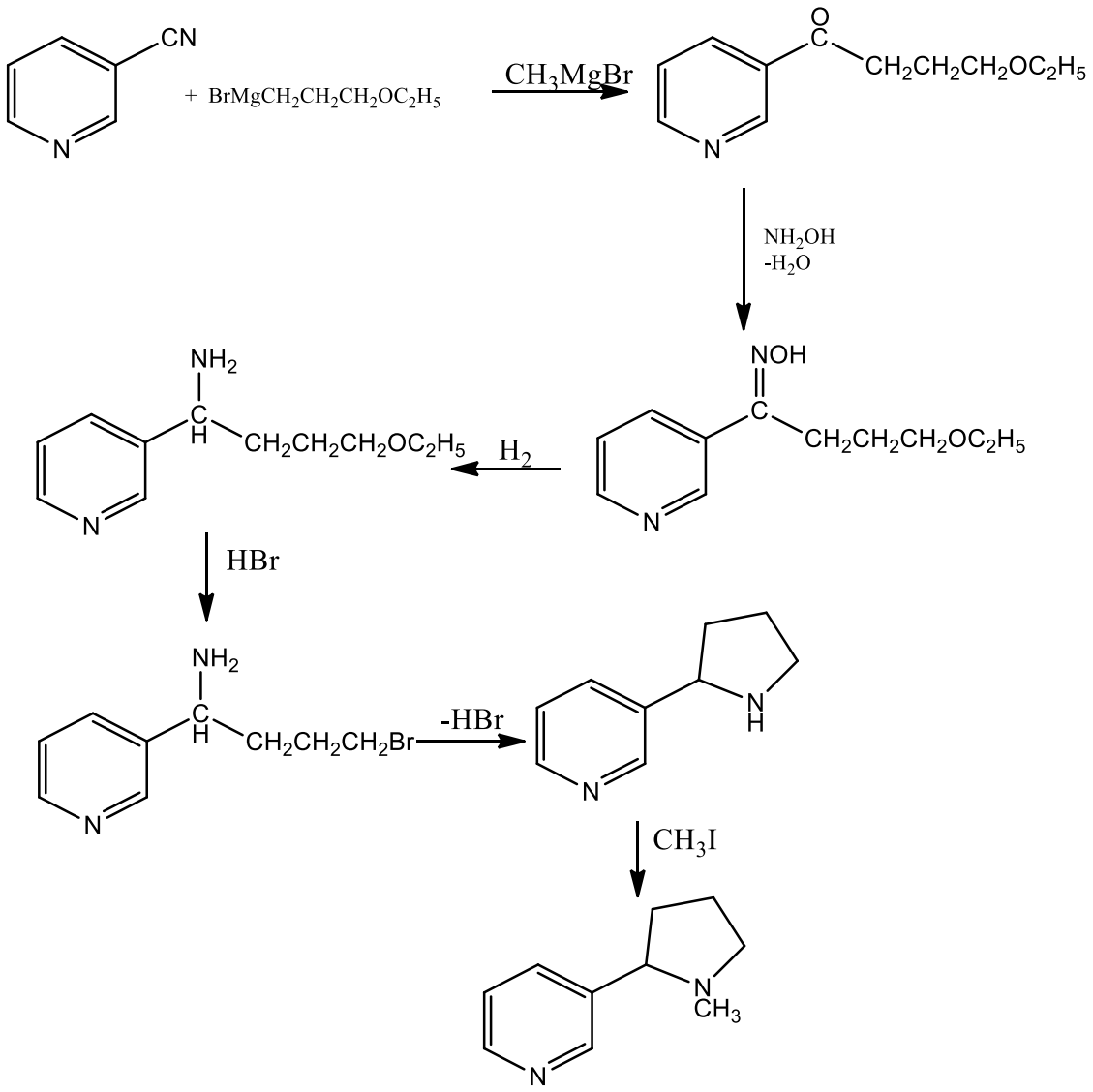
As nicotine takes up only three molecule of hydrogen to form hexahydro nicotine, it means that the side chain is saturated and this is only possible if the side chain is cyclic and has a tertiary Nitrogen atom with N-CH3 group, i.e. side chain should be N-methyl pyrrolidine $C_5H_{11}N$.

And so, the structure of Nicotine is



I

7. Synthesis : Finally the above structure is confirmed by its synthesis.

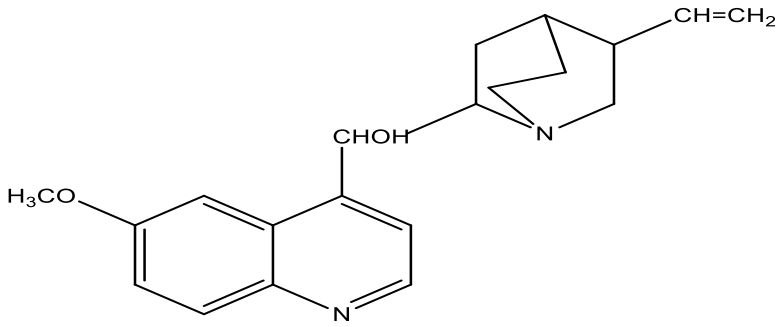

CN
+ BrMgCH2CH2CH2OC2H5
CH3MgBr
O
C
CH2CH2CH2OC2H5
N
NH2OH
-H2O
NOH
C
CH2CH2CH2OC2H5
N
H2
NH2
C
H
CH2CH2CH2OC2H5
N
HBr
NH2
C
H
CH2CH2CH2Br
N
-HBr
N
H
N
CH3I
N
CH3
N

QUININE
(Quinoline Alkaloid)

It is a well-known bitter antimalarial drug which occurs among the alkaloids of Cinchona bark and Ramijia. Cinchona bark contains about 30 alkaloids but its anti-malarial activity is mainly due to Quinine, quinidine, cinchonine and cinchonidine.

ISOLATION: The bark of cinchona is dried and powdered and then treated with lime and caustic soda solution for several hours and finally extracted with petroleum ether. The extract is then washed with dilute sulphuric acid. The acid aqueous layer while still hot is neutralized and allowed to stand when the neutral sulphates of the alkaloids (quinine, cinchonine and cinchonidine) crystallizes out. The mixture of sulphates of three alkaloids is recrystallized when quinine sulphate having maximum solubility crystallizes out first while the sulphates of the remainining alkaloids remain in the mother liquor.

STRUCTURE ELUCIDATION OF QUININE:



1. Molecular Formula : $C_{20}H_{24}N_2O_2$
2. Number of double bonds: On catalytic reduction it takes up one molecule of hydrogen to give a di hydro compound indicating the presence of one double bond in its structure.

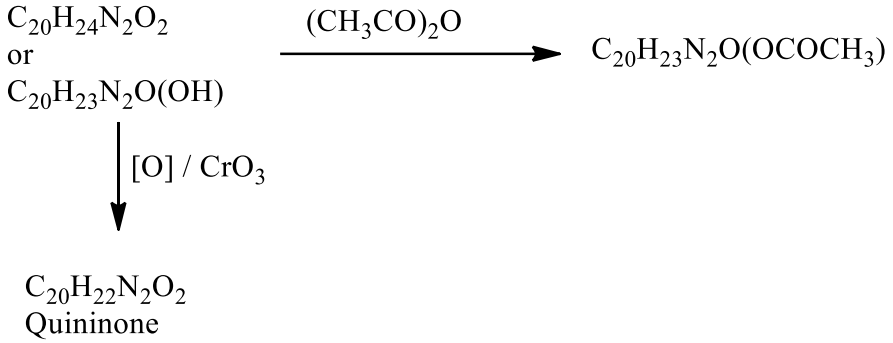
$$C_{20}H_{24}N_2O_2 + H_2 \xrightarrow{Ni} C_{20}H_{26}N_2O_2$$

3. Nature of two nitrogen atoms: Quinine undergoes Herzig Meyer test indicating the presence of Nitrogen in its structure. The two nitrogen atoms are found to be tertiary in nature as it takes up two molecules of CH_3I to give a di quaternary ammonium salt.

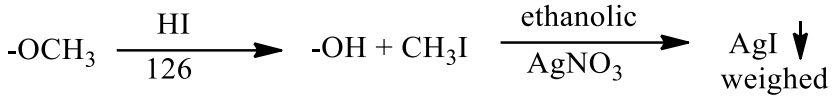
$$C_{20}H_{24}N_2O_2 + 2CH_3I \longrightarrow {}^{-1}ICH_3N^{+}[C_{20}H_{24}O_2]\,N^{+}CH_3I^{-1}$$

4. Nature of oxygen atoms: Out of the two oxygen atoms present in Quinine, one is found to be present as a secondary alcoholic OH group as it takes up one molecule of acetic anhydride to form monoacetate.

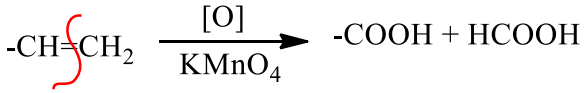
Also Quinine on oxidation gives a ketone Quininone indicating that the OH group is secondary in nature.



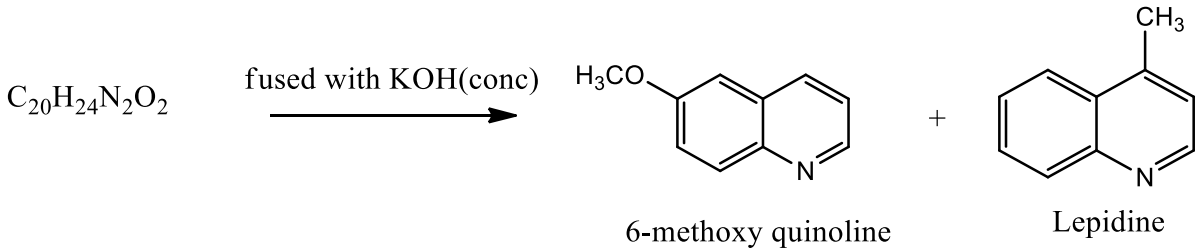
The second oxygen atom is found to be a methoxyl ($-OCH_3$) group as quinine undergoes Ziesel test to confirm the presence of a $-OCH_3$ group in its structure.



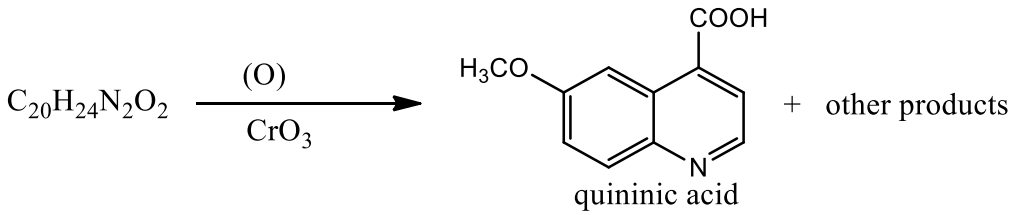
5. Presence of a Vinyl group: When controlled oxidation of quinine is done with $KMnO_4$, it gives a monocarboxylic acid and Formic acid. This reaction indicates the presence of a Vinyl group in its structure.



6. Presence of a Quinoline ring in its structure: Quinine on fusion with KOH gives 6-methoxy quinoline and Lepidine (4-methyl quinoline) indicating the presence of a Quinoline ring in its structure.



7. Oxidative degradation: Quinine on oxidation with CrO_3 gives Quininic acid and other products.



On the other hand controlled oxidation of Quinine with CrO_3 gives Quininic acid and Meroquinine .

$$C_{20}H_{24}N_2O_2 \xrightarrow[\text{controlled oxidation with } CrO_3]{(O)} \underset{\text{Quininic acid}}{C_{11}H_9NO_3} + \underset{\text{Meroquinine}}{C_9H_{15}NO_2}$$

In order to find the structure of Quinine we have to first establish the structure of Quininic acid and Meroquinine.

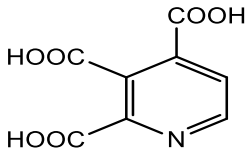
STRUCTURE OF QUININIC ACID

A. Molecular formula : $C_{11}H_9NO_3$

B. Presence of a COOH group: On reaction with $NaHCO_3$, it gives brisk effervesces indicating the presence of a COOH group in its structure.

$$\text{-COOH} + NaHCO_3 \longrightarrow \text{-COONa} + H_2O + CO_2$$

Quininic acid on oxidation with CrO3 gives Pyridine 2,3,4 – tricarboxylic acid indicating that the COOH group is present in the nitrogen containing ring of Quinoline at position number 4.

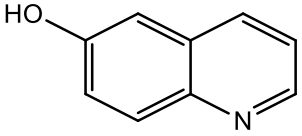
$$C_{11}H_9NO_3 \xrightarrow{(O)/\ CrO_3}$$ 

Pyridine-2,3,4-tricarboxylicacid

C. Presence of a $-OCH_3$ group : Quininic acid undergoes Ziesel test indicating the presence of a –OCH3 group in its structure.

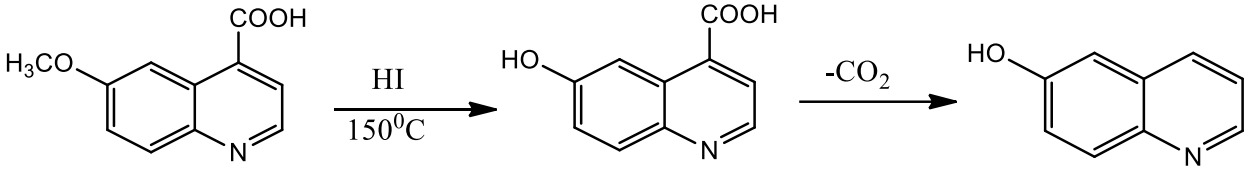
$$\text{-}OCH_3 \xrightarrow[126]{HI} \text{-OH} + CH_3I \xrightarrow[AgNO_3]{\text{ethanolic}} \underset{\text{weighed}}{AgI\downarrow}$$

The position of the –OCH3 group is confirmed to be at position 6 as quininic acid on undergoing Ziesel test followed by decarboxylation gives 6-hydroxy quinoline indicating that the methoxyl group was present at 6-position.

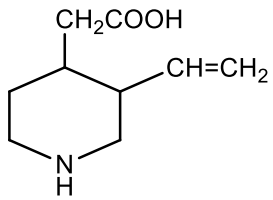
$$C_{11}H_9NO_3 \xrightarrow[150^0C,\ Heat,\ -CO_2]{HI}$$ 

$+ CH_3I$

From all the above points, the structure of quininic acid is following which explains all the reactions.



STRUCTURE OF MEROQUININE:



Meroquinine

A. Molecular Formula : $C_9H_{15}NO_2$

B. Presence of a –COOH group: Meroquinine on reaction with $NaHCO_3$ gives a monosodium salt and brisk effervences of CO_2 indicating the presence of a –COOH group in its structure.

$$\text{-COOH} + NaHCO_3 \longrightarrow \text{-COONa} + H_2O + CO_2$$

C. Presence of one double bond: On catalytic reduction it takes up one molecule of H2 to give a dihydro compound indicating the presence of a double bond in its structure.

$$C_9H_{15}NO_2 + H_2 \longrightarrow C_9H_{17}NO_2$$

The double bond is found to be present as a Vinyl group as on oxidation with KMnO4 it gives formic acid HCOOH along with another acid Cincholoiponic acid. The formation of HCOOH as a product of oxidative degradation is a proof of compound having a Vinyl group in its structure.

$$\text{-CH=CH}_2 \xrightarrow[KMnO_4]{[O]} \text{-COOH} + HCOOH$$

$$C_9H_{15}NO_2 \xrightarrow[KMnO_4]{(O)} C_8H_{13}NO_4 + HCOOH$$

cincholoiponic acid

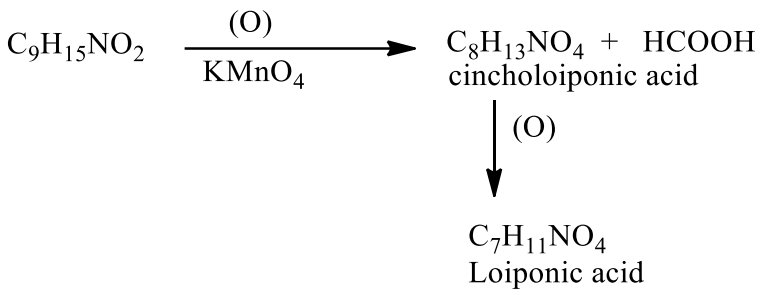
D. Presence of a secondary amino group: Meroquinine take up two molecules of CH_3I to give a quaternary ammonium salt indicating the presence of a secondary amino group in its structure.

$$C_9H_{15}NO_2 \xrightarrow{2CH_3I} C_9H_{15}O_2N^+CH_3I^-$$

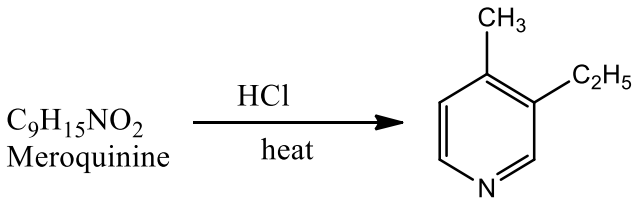
Quaternary ammonium salt

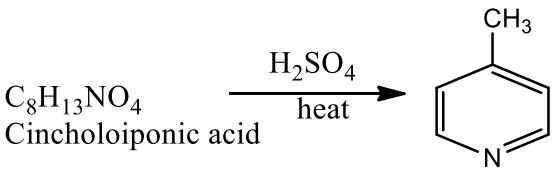
E. Presence of a $–CH_2COOH$ side chain: Meroquinine on oxidation gives Cincholoiponic acid along with HCOOH. This Cincholoiponic acid on further oxidation gives Loiponic acid.

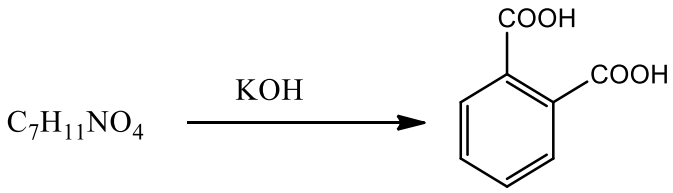
As this Loiponic acid is a dicarboxylic compound and contains one –CH2 less than Cincholoiponic acid, it means that Meroquinine as well as Cincholoiponic acid has a –CH2COOH side chain in its structure.



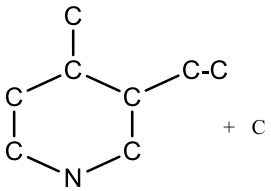
F. Presence of a Piperidine ring: The following dehydrogenation reactions indicate the presence of a Pyridine and finally a saturated Piperidine ring in the structure of Meroquinine.



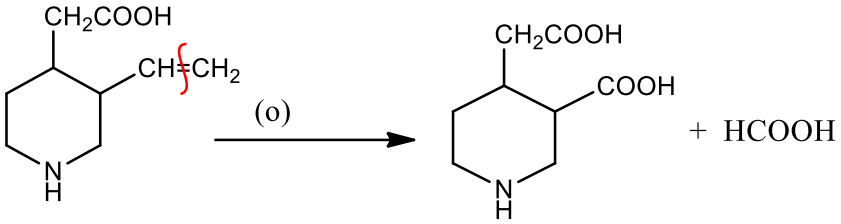




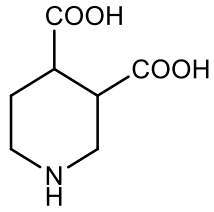
From the above reactions , it is clear that the partial carbon skeleton for Meroquinine will be



Out of 9 carbon atoms of Meroquinine, position of 8 carbon atoms is confirmed and the extra carbon atom cannot be present as a $–NCH_3$ group as the N atom is secondary in nature. So the ninth C atom is present at position 4 as –CH2COOH group. This explains all the reactions.



Meroqunine Cincholoiponic acid

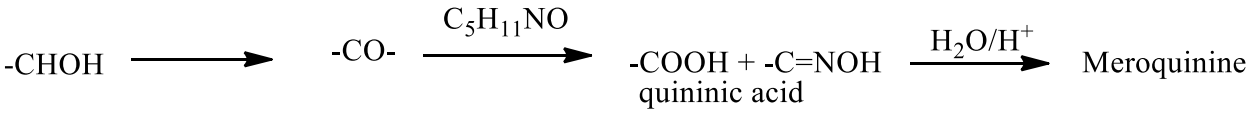


Loiponic acid

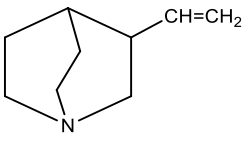
POINT OF LINKAGE BETWEEN QUININIC ACID & MEROQUININE:

In the Quinine molecule, carboxylic groups are not present but its oxidation products i.e. Quininic acid & Meroquinine posess free COOH groups indicating that the two fragments are linked with each other by means of the COOH carbon atoms.

As we know that Quinine is having a Secondary OH group in its structure which on oxidation gives a ketone Quininone, which on treatment with amyl nitrite gives quininic acid and an oxime which on hydrolysis gives Meroquinine .

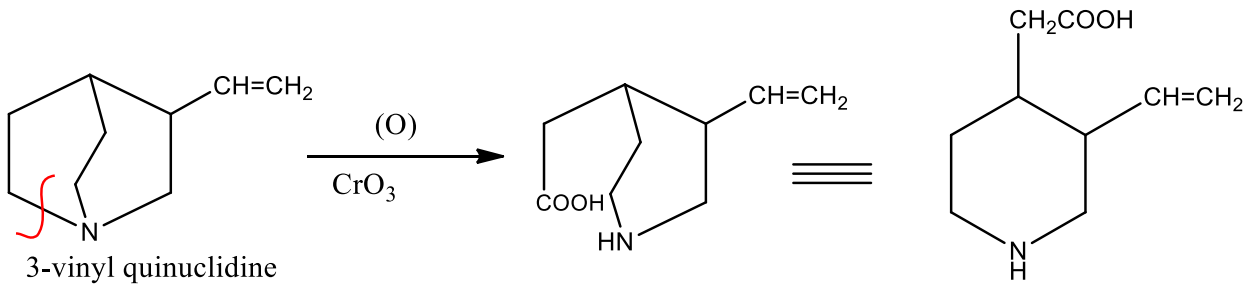


Also, Quinine is a di tertiary base whereas Meroquinine has a secondary N atom which indicates that in the formation of Meroquinine a tertiary N atom is converted into a sec N atom and at the same time a COOH group is produced. This is only possible if N forms a part of the condensed ring system. Therefore, the precursor of Meroquinine has the following structure:



3-vinyl quinuclidine

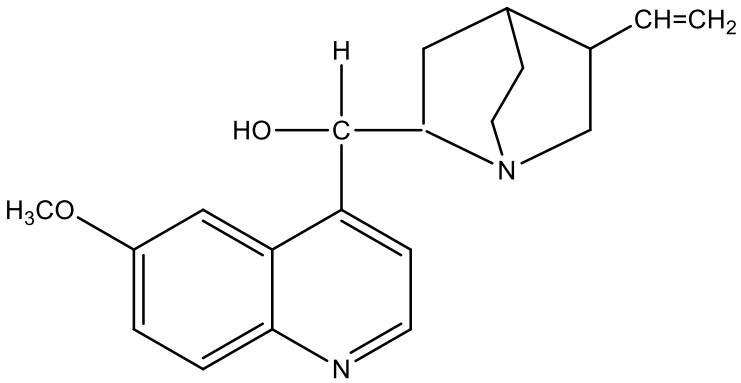
When 3-vinyl quinuclidine is oxidized with CrO_3, one C-N bond is ruptured thereby producing a secondary N atom from a tertiary N atom and a COOH group.



3-vinyl quinuclidine

STRUCTURE OF QUININE:

Finally, the structure of Quinine can be represented as



QUININE

FINALLY, THE ABOVE STRUCTURE IS CONFIRMED BY ITS SYNTHESIS.

ATROPINE

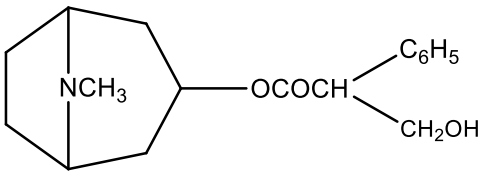
(TROPANE ALKALOIDS) (SOLANACEOUS ALKALOIDS)

This is the most important alkaloid of the tropane group and occurs in the roots of deadly nightshade (Atropa Belladona), thorn apple (Datura stramonium) etc.

ISOLATION: Atropine is extracted either from Belladona roots or from the juice of Datura plant. In general, the juice which also contains hyocyamine is heated with K2CO3 and then hyocyamine is racemised to ATROPINE. Then this atropine is extracted with CHCl3. The CHCl3 is recovered by evaporation and the residue is extracted with dil. H2SO4. The solution is made alkaline with K2CO3, when Atropine is crystallized out. The precipitated Atropine is extracted with ether and purified by converting into an oxalate or sulphate.

Uses: It dilates the pupils of the eyes. Therefore, it finds extensive use in ophthalmology.

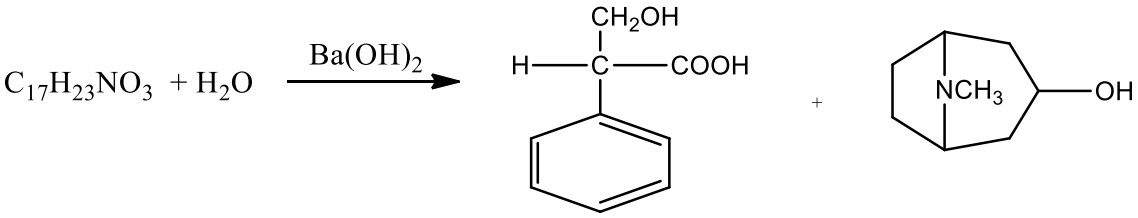
STRUCTURE ELUCIDATION OF ATROPINE



$C_{17}H_{23}NO_3$
ATROPINE

1. **Molecular Formula :** $C_{17}H_{23}NO_3$
2. **Atropine as an ester:** When Atropine is warmed with $Ba(OH)_2$ solution, it undergoes hydrolysis to yield a racemic mixture of an acid Tropic acid and an optically inactive alcohol Tropine.
   This reaction shows that Atropine is the Tropine ester of Tropic acid i.e. it is a Tropine Tropate.

$$C_{17}H_{23}NO_3 + H_2O \xrightarrow{Ba(OH)_2} \underset{\text{Tropic acid}}{C_9H_{10}O_3} + \underset{\text{Tropine}}{C_8H_{15}NO}$$



Tropic acid
$C_9H_{10}O_3$

Tropine
$C_8H_{15}NO$

Ladenberg further confirmed that Atropine is a Tropine Tropate ester by evaporating a mixture of tropine & tropic acid in presence of an acid to get Atropine.

$$\underset{\text{Tropic acid}}{C_9H_{10}O_3} + \underset{\text{Tropine}}{C_8H_{15}NO} \xrightarrow{HCl} \underset{\text{Atropine}}{C_{17}H_{23}NO_3} + H_2O$$

In order to establish the structure of Atropine, we have to first determine the structure of Tropine & Tropic acid.

STRUCTURE OF TROPIC ACID

1. Molecular Formula : $C_9H_{10}O_3$
2. Presence of a COOH group: Tropic acid on reaction with NaHCO3 gives a sodium salt and brisk effervences of CO2 gas indicating the presence of a COOH group in the structure.

$$\text{-COOH} + NaHCO_3 \longrightarrow \text{-COONa} + H_2O + CO_2$$

3. Presence of one OH group: Tropic acid on reaction with acetic anhydride forms a monoacetate and also it is insoluble in NaOH indicating the presence of an alcoholic OH group in its structure.

$$\underset{\text{or } C_9H_9O_2(OH)}{C_9H_{10}O_3} \xrightarrow{(CH_3CO)_2O} \underset{\text{Monoacetate}}{C_9H_9O_2(OCOCH_3)} + CH_3COOH$$

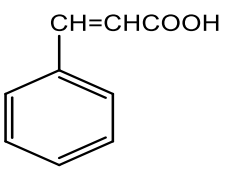
4. Dehydration: When Tropic acid is heated strongly, it loses a molecule of water to give an unsaturated acid called Atropic acid.

$$C_9H_{10}O_3 \xrightarrow[-H_2O]{P_2O_5 \,/\, Heat} \underset{\text{Atropic acid}}{C_9H_8O_2}$$

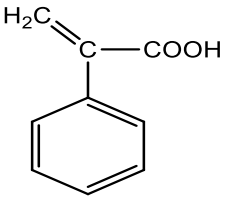
5. Presence of a Benzene nucleus: Atropic acid on oxidation gives Benzoic acid. The formation of Benzoic acid indicates that Atropic acid and hence, Tropic acid contains Benzene nucleus with a 3C atom side chain having a COOH group in its structure.

$$\underset{\text{Tropic acid}}{C_9H_{10}O_3} \xrightarrow{-H_2O} \underset{\text{Atropic acid}}{C_9H_8O_2} \xrightarrow{(O)} \underset{\text{Benzoic acid}}{\text{C}_6\text{H}_5\text{COOH}}$$

As Atropic acid is an unsaturated acid having a Benzene ring and three carbon atoms in its side chain, its structure cab be either I or II



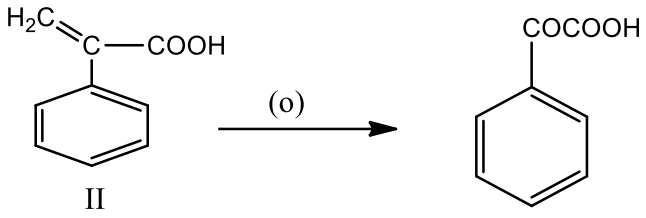
I



II

Structure I is found to be the structure for Cinnamic acid so str II is the correct structure.

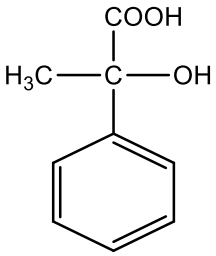
This is further proved by the fact that Atropic acid on oxidation with KMnO4 gives Phenyl glyoxalic acid.



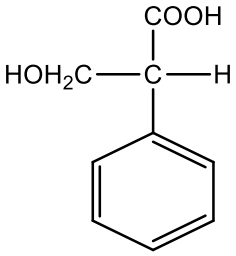
II

Phenyl glyoxalic acid

As Atropic acid is obtained by the dehydration of Tropic acid, it means by adding a molecule of water to Atropic acid we can get the structure for Tropic acid. This structure can again be of two types



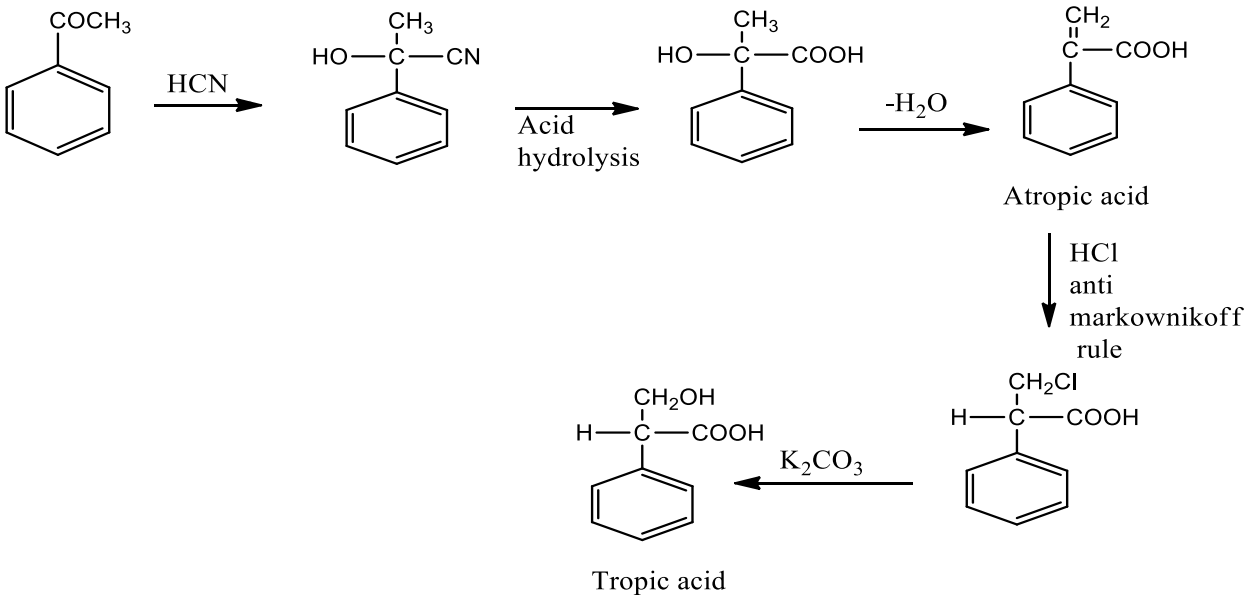
III



IV

The structure of Tropic acid was found to be IV on the basis of its synthesis.

Mackenzie and Wood synthesized Tropic acid from acetophenone



Tropic acid

STRUCTURE OF TROPINE

1. **Molecular Formula:** $C_8H_{15}NO$
2. **Presence of a tertiary Nitrogen atom:** Tropine takes up one molecule of CH_3I to give a quaternary ammonium salt indicating the presence of a Tertiary nitrogen atom in its structure.

$$\underset{\text{Tropine}}{C_8H_{15}NO} + CH_3I \xrightarrow{NaOH} \underset{\text{Quaternary ammonium salt}}{C_8H_{15}ON^+CH_3I^-}$$

3. **Presence of an N-CH3 group:** Tropine undergoes Herzig Meyer Test on heating with HI it give CH_3I indicating the presence of an N-CH_3 group in its structure.

$$C_8H_{15}NO \xrightarrow[150^0C]{HI} CH_3I + C_7H_{12}ONH$$

4. **Presence of an OH group:** On acetylation it forms a mono acetate indicating the presence of a OH group in its structure.

$$\underset{\text{or } C_8H_{15}N(OH)}{C_8H_{15}NO} \xrightarrow{CH_3COCl} \underset{\text{monoacetate}}{C_8H_{14}N(OCOCH_3)} + HCl$$

This OH group is found to be a secondary OH group as on oxidation it gives a ketone, Tropinone.

$$\underset{\text{Tropine}}{C_7H_{13}N(CHOH)} \xrightarrow{(o)} \underset{\text{Tropinone}}{C_7H_{13}N(CO)}$$

5. **Presence of a –CH2-CHOH-CH2- group in the ring:** Tropine on reaction with HNO2 forms a Dioxime and on reaction with Benzaldehyde gives a Dibenzylidine derivative. These two reactions are typical for a compound having a –CH2-CHOH-CH2- chain in its structure.

$$\underset{\text{Tropinone}}{C_7H_{13}N(CO)} \xrightarrow{2HNO_2} \text{Dioxime derivative}$$

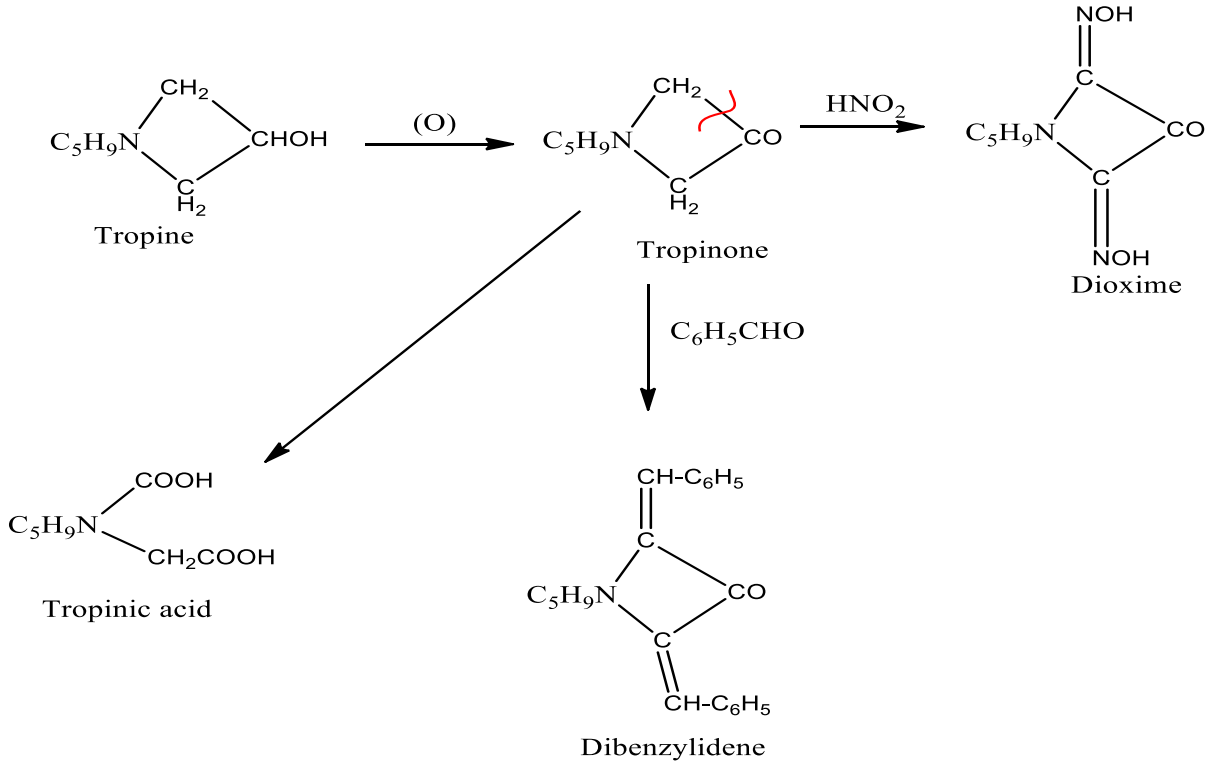
$$\underset{\text{Tropinone}}{C_7H_{13}N(CO)} \xrightarrow{2C_6H_5CHO} \text{Dibenzylidene derivative}$$

$$\underset{\text{Tropinone}}{C_7H_{13}N(CO)} \xrightarrow{(O)} \text{Dicarboxylic acid } C_8H_{13}NO_4$$

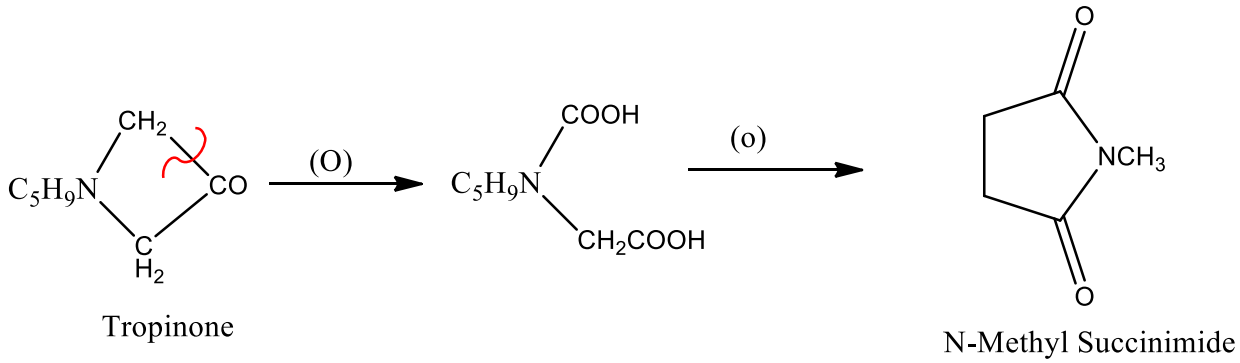
Tropine on oxidation is converted to a ketone Tropinone which on further oxidation is converted into a dicarboxylic compound without any loss of carbon atom indicating that the -CH2-CO-

CH2- group of Tropinone must be present in a ring as cyclic ketones on oxidation are converted into a dicarboxylic acid without the loss of a carbon atom.

The overall reaction can be written as

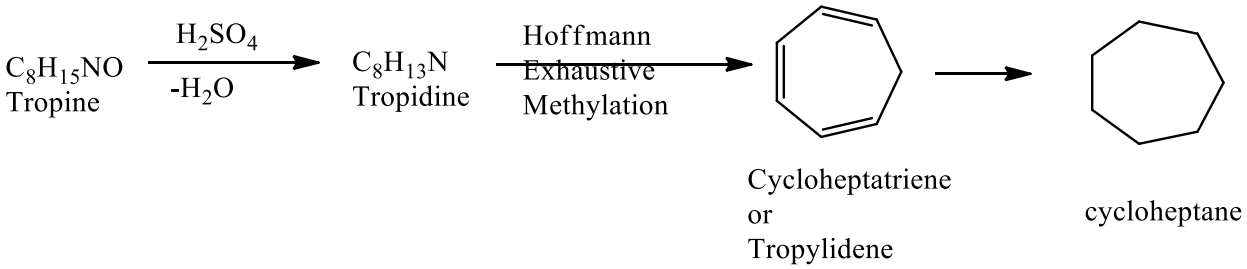


6. Presence of N-CH3 Pyrrolidine Ring: Tropinone on oxidation with CrO_3 gives Tropinic acid which on further oxidation gives N-Methyl succinimide.
   This reaction indicates the presence of N-METHYL PYRROLIDINE ring in the structure of Tropinone and hence in Tropine.



Out of the 8 carbon atoms present in Tropine , 5C atoms are found to be present as N-Methyl pyrrolidine ring and the remaining three Carbon atoms can be present as COOH & CH2COOH group in Tropinic acid. These two groups are found to be present at the α, α' position of N-METHYL SUCCINIMIDE as it undergoes oxidation at this position.

Tropine has a cycloheptanone structure , this is proved by Hoffmann exhaustive methylation.

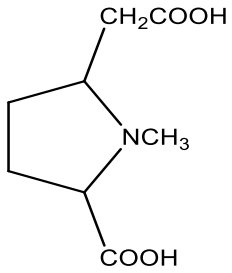


From all the above points, one can draw the following points:

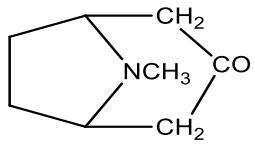
a. Tropine possess a seven membered carbon ring system having –CH2-CHOH-CH2- group.
b. Tropine posess a reduced pyrrole (pyrrolidine) ring in its structure.
c. Tropine posess a reduced pyridine (piperidine) ring in its structure.
d. Tropine posess a N-CH3 group.

As Tropine contains only one N atom, it means that it is common to boh pyrrolidine and piperidine ring and it should be present as –N-CH3 group.

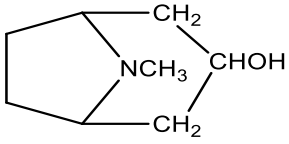
On the basis of the above facts, the structure of Tropine, tropinic acid and tropinone can be



TROPINIC ACID

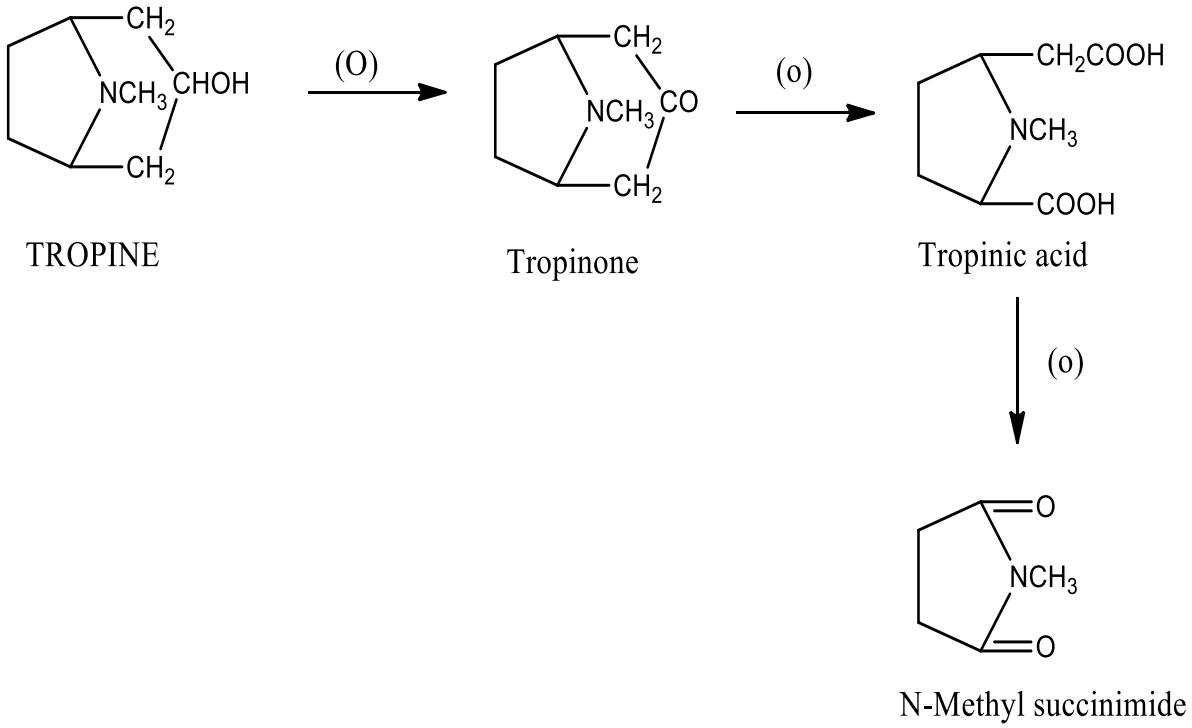


TROPINONE



TROPINE

This structure explains all the reactions

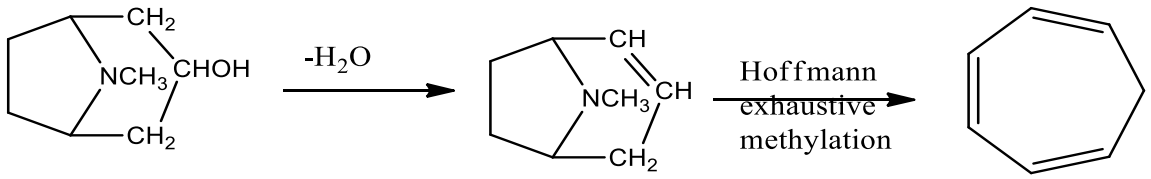


TROPINE

Tropinone

Tropinic acid

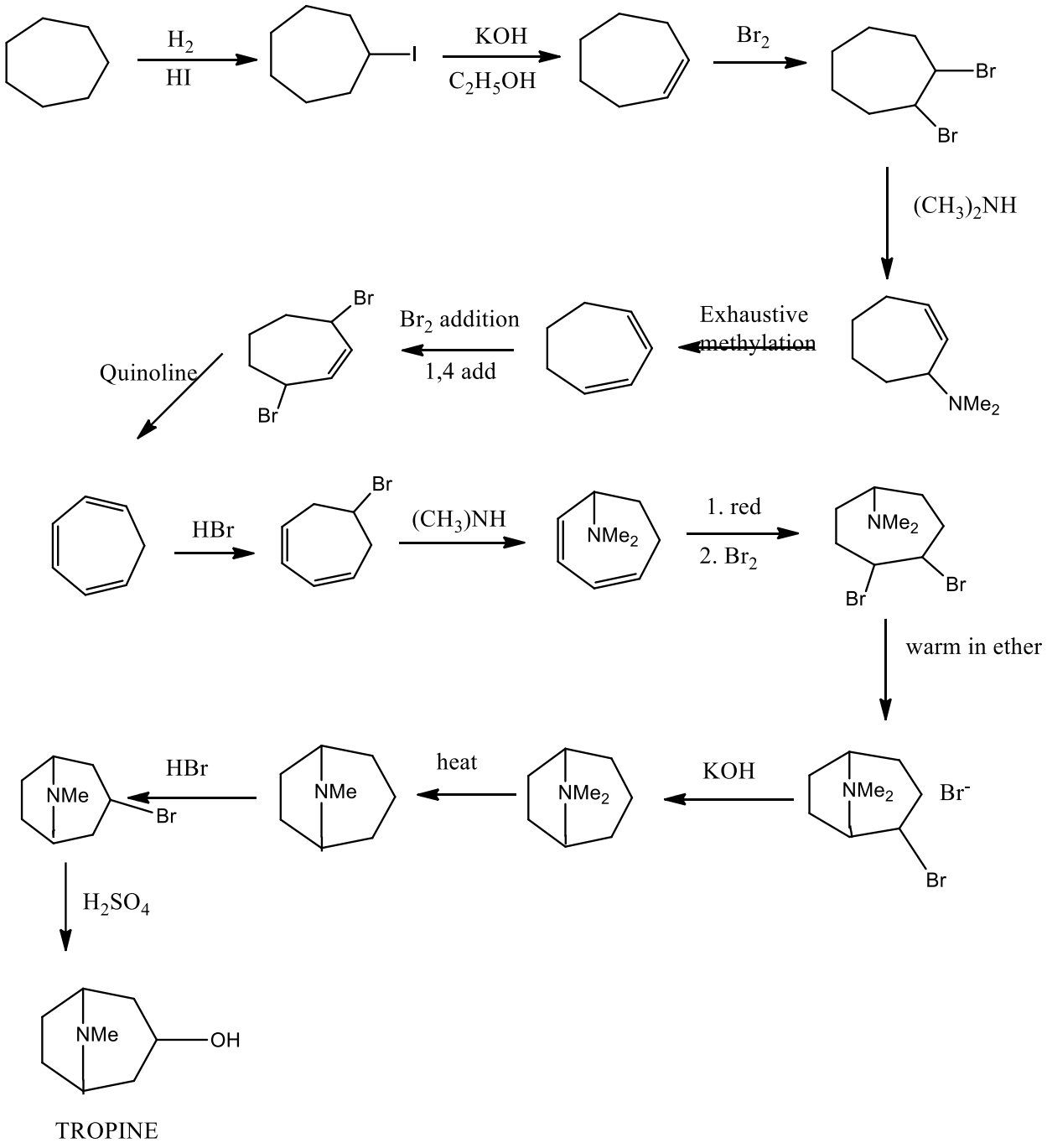
N-Methyl succinimide



TROPINE

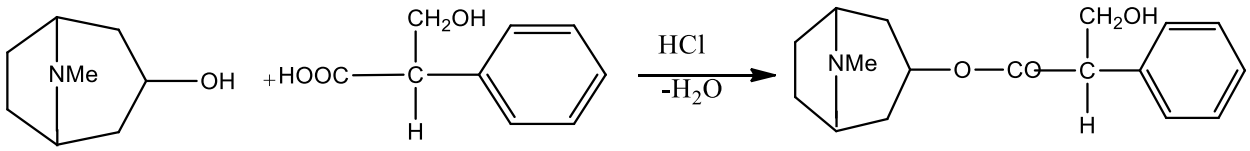
Tropilidene

Synthesis: Finally, the above structure of Tropine is confirmed by its synthesis



STRUCTURE OF ATROPINE

Now as Atropine is a Tropine Tropate ester so it is given the following structure



Tropine

Tropinic acid

Atropine

MORPHINE
(OPIUM ALKALOID) (PHENANTHRENE ALKALOIDS)

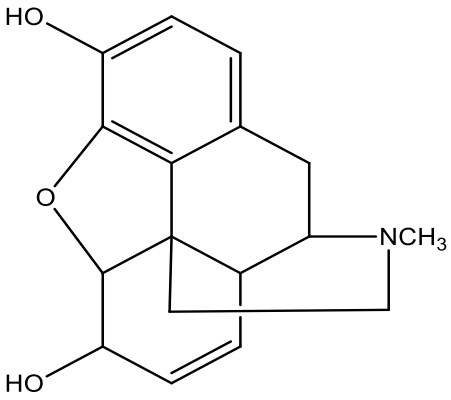
It was the first alkaloid to be obtained from Serturner plant(1806). It is found in Opium with a percentage of 10-23% along with other substances.

Codeine, Thebaine and Morphine are closely related alkaloids and are commonly called as MORPHINE alkaloidsand they form a sub-group of the opium alkaloids.

In all Morphine alkaloids, Phenanthrene nucleus is present. Due to this they are known as Phenanthrene alkaloids also.

USES: They are widely used as analgesic agents. Trade name of Morphine is Heroin.

STRUCTURE ELUCIDATION OF MORPHINE



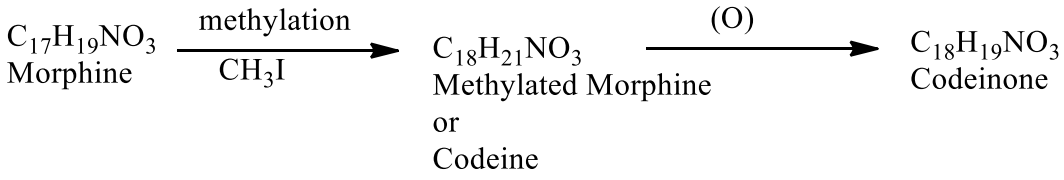
MORPHINE

1. **Molecular Formula:** $C_{17}H_{19}NO_3$
2. **Nature of Oxygen atom:** Out of the three oxygen atoms present in Morphine two are found to be present as an OH group as on acetylation it gives a diacetyl compound indicating the presence of two OH group in its structure.

$$\underset{\text{or } C_{17}H_{17}NO(OH)_2}{C_{17}H_{19}NO_3} \xrightarrow{2CH_3COCl} \underset{\text{Diacetate}}{C_{17}H_{17}NO(OCOCH_3)_2} + 2HCl$$

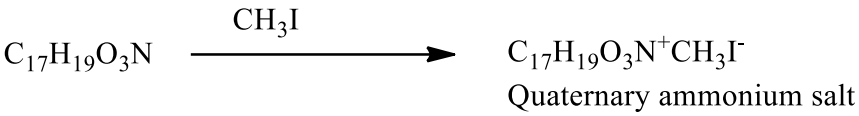
Out of the two OH groups in Morphine, one is found to be Phenolic in nature as it is soluble in NaOH and it gives test with FeCl3 solution too.

The second OH group is found to be present as a secondary alcoholic OH group as on oxidation of Methylated Morphine, we get a ketone, Codeinone.

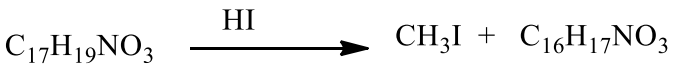


Nature of the third oxygen atom: The third oxygen atom due to its unreactive nature and due to the degradation products of Morphine is found to be present as ether linkage.

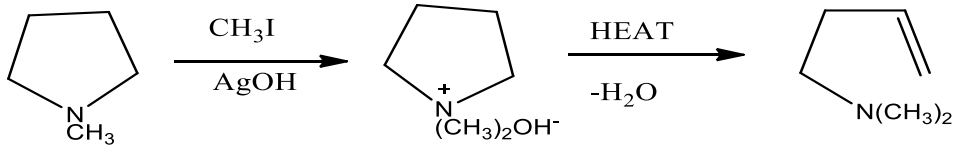
3. **Nature of the Nitrogen atom:** The Nitrogen atom in Morphine is found to be present as a tertiary Nitrogen atom as on methylation it takes up one molecule of CH3I to give a Quaternary ammonium salt.



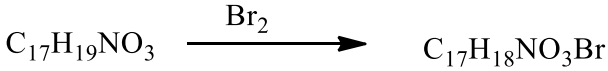
The nitrogen atom is found to be present as a N-CH3 group as it undergoes Herzig Meyer test



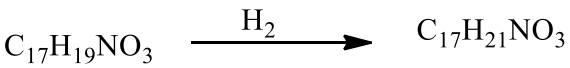
4. **Presence of a cyclic tertiary nitrogen base:** Morphine on methylation gives Codeine. When Codeine undergoes Hoffmann exhaustive methylation once, it gives α-codiemethine, which has one more –CH2 group than Codeine and the nitrogen atom is not lost. This reaction is a typical of t-cyclic nitrogen base system because if the codeine possess an acyclic t-amine system then on Hoffmann exhaustive methylation, then the product would have one C atom less and the Natom would also have been lost.
Thus, Codeine and hence, Morphine has a cyclic tert. Base system



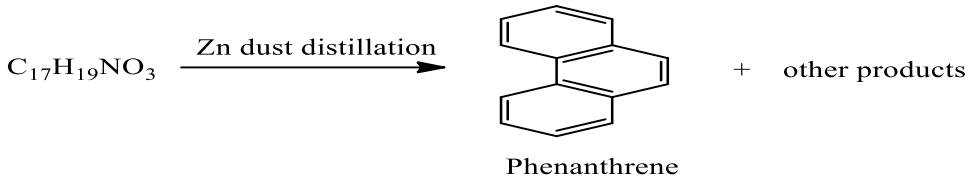
5. **Presence of a Benzene ring:** UV spectra of Morphine supports a benzene ring in its structure. Also, it undergoes electrophilic substitution reaction which is typical for compounds having an aromatic ring in its structure.



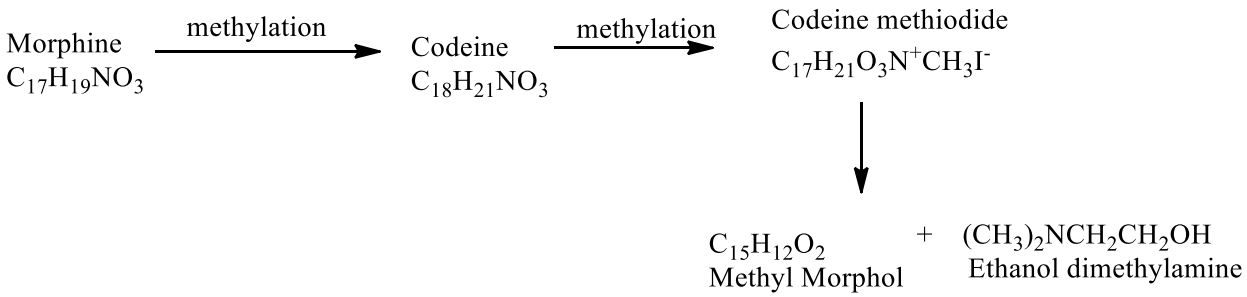
6. **Presence of one double bond:** on catalytic reduction it takes up one molecule of hydrogen to give a dihydro compound, indicating the presence of a double bond in its structure.



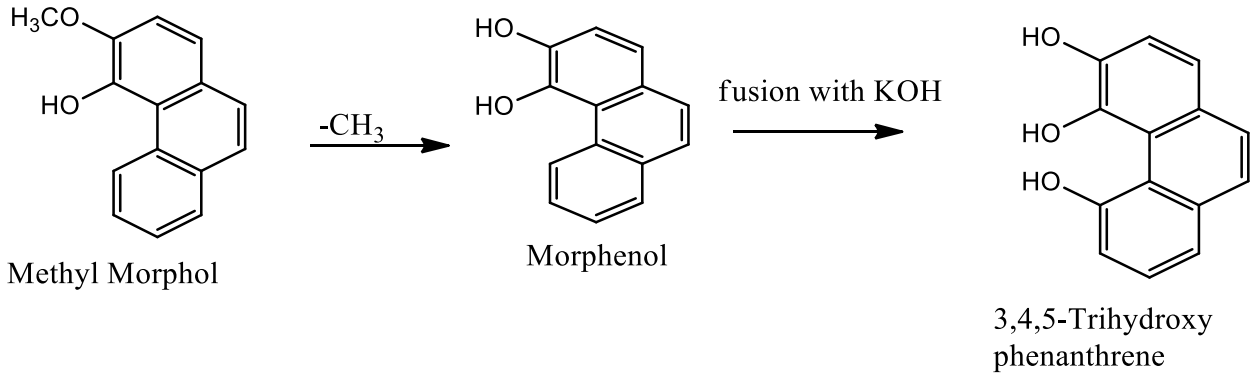
7. **Presence of a Phenanthrene nucleus:** Morphine on Zinc dust distillation gives Phenanthrene indicating the presence of a Phenanthrene ring in its structure.



8. Confirmation of a Phenanthrene ring, -NCH3 group and position of three oxygen atoms:
When Codeine or Methylated Morphine is treated with CH_3I, it gives Codeine methiodide which on further reactions give two compounds, Ethanoldimethylamine and Methyl morphol.



The structure of Methyl Morphol was found to be 4-hydroxy-3-methoxy phenanthreneby its synthesis.



Methyl Morphol on demethylation gives Morphenol which on fusion with KOH gives 3,4.5-trihydroxy phenanthrene.

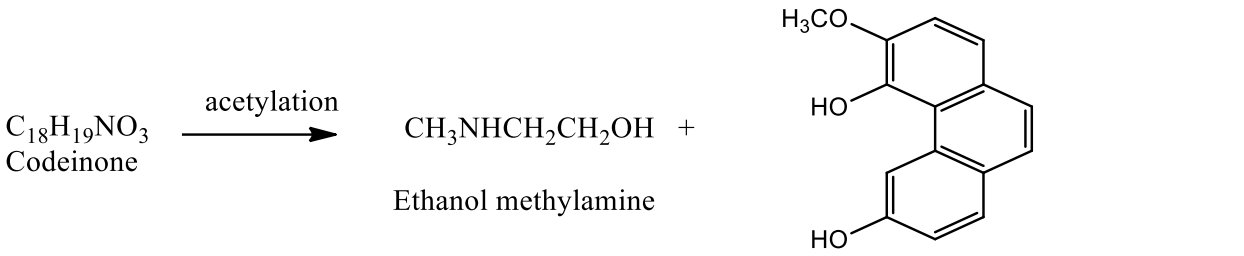
All these reactions explain the following points:

1. Formation of methyl morphol confirms the presence of one phenanthrene ring in morphine
2. Formation of ethanol dimethylamine indicates that there is one NCH3 group in morphine having two more carbon atoms as side chain.
3. Methylation of morphine gives codeine whose phenolic OH group is converted to methoxyl group and its position in methyl morphol was at position 3. Hence, the phenolic OH group is present at position 3 .
4. The presence of an OH group in Methyl Morphol, Morphenol indicates that the ether linkage must be present at position number 4 & 5. This is further confirmed by the

fusion with KOH when a trihydroxy compound clearly indicates that the two OH groups at 4 & 5 position are due to the ether linkage at these positions.

The position of the third O atom was found to be at 6 position in the following manner

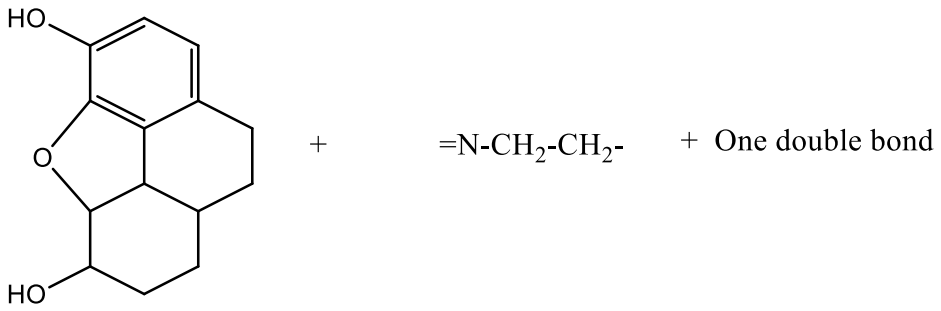
Codeine on oxidation gives Codeinone which on acetylation gives ethanol methylamine and a diacetyl derivative of 4,6-dihydroxy-3-methoxy phenanthrene.



4,6-dihydroxy-3-methoxy phenanthrene

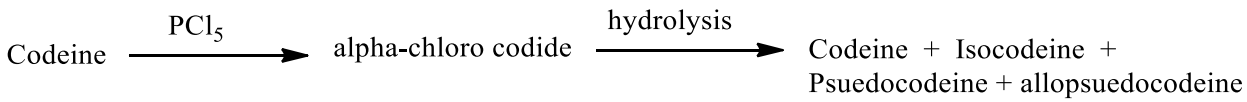
This hydroxyl group at C6 position is produced from the oxygen of the keto group in Codeinone at 6th position which in turn was obtained by the oxidation of secondary alcoholic OH group at the same position.

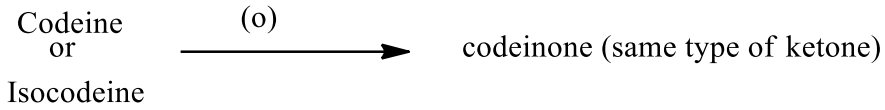
9. Partial structure of Morphine : All the above points indicate that the partial structure of Morphine is

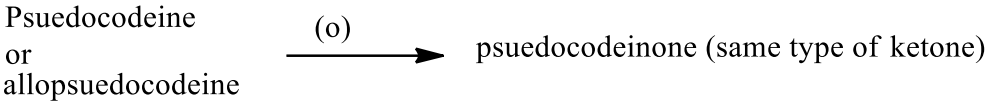


If the position of the double bond and side chain is known then all the reactions will be explained and the structure of Morphine can be explained.

10. Position of the double bond:

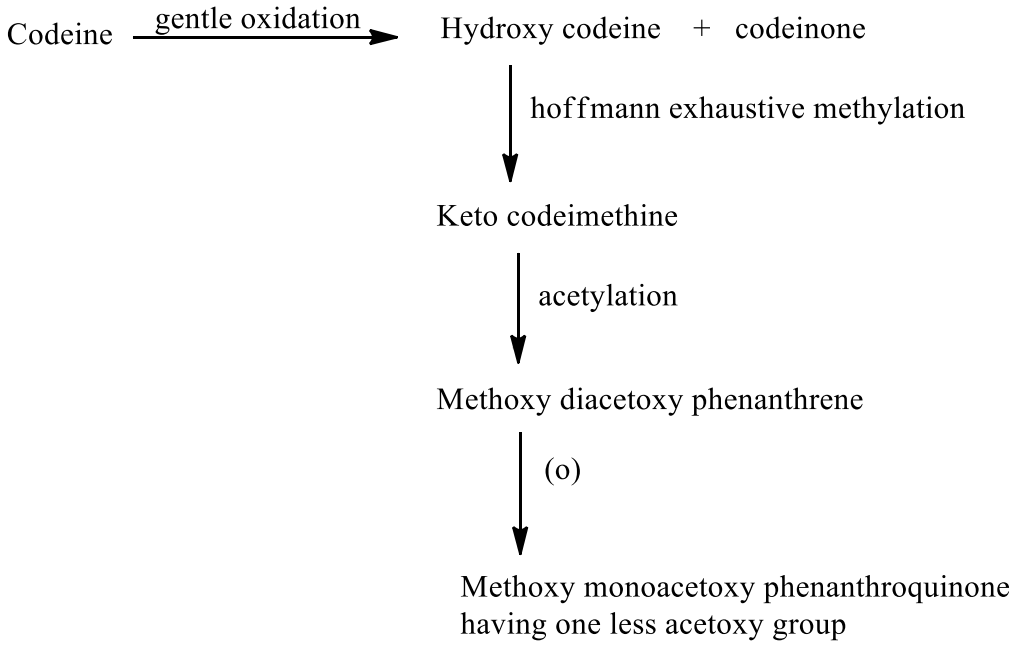






All the above compounds have identical structure but differ in the configuration of the OH group at C6 position. This is only possible if a double bond is present at position 7 & 8 and the OH group is at 6th position. (Geometrical isomers)

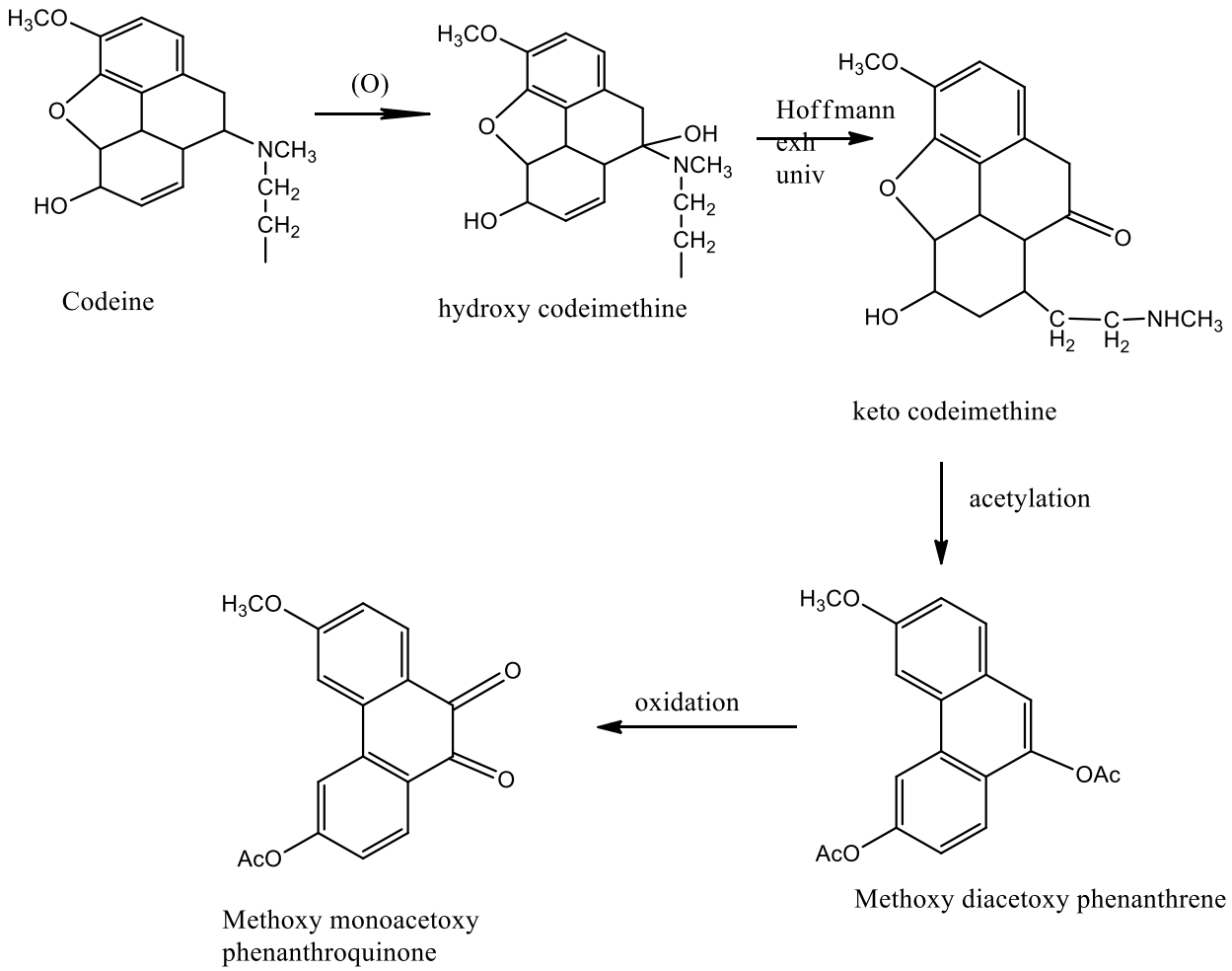
11. Point of linkage of the side chain:



Loss of one acetoxy groupduring the formation of phenanthroquinone indicates that the lost acetoxy group I the former compound is present at either C9 or C10POSITION. As this acetoxy group is introduced at this position via a ketone group during acetylation it means that the keto group in Codeimethine and hence the OH group in Hydroxy codeine must be present at C9 or C10 POSITION.

STERIC FACTORS FAVOUR C9 to be the point of attachment of the NCH3 side chain in Morphine as the new OH group of Hydroxy codeine is converted into a keto group in keto codeimethine which on Hoffmann exhaustive methylation results in the formation of a double bond at C9 & C10 during the fission of the N side chain.

Keeping all these points in consideration, following structure can be given to the reaction compounds



Codeine

hydroxy codeimethine

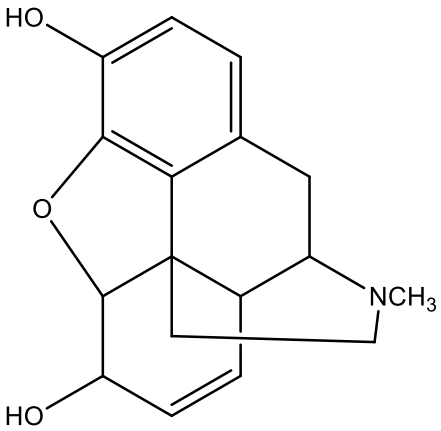
keto codeimethine

Methoxy diacetoxy phenanthrene

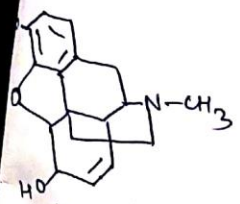
Methoxy monoacetoxy phenanthroquinone

As the N terminal of the side chain is present at C9 the C terminal should be located at an angular position of C13 OR C14 so that elimination of the side chain can take place on aromatization.

Thus, the structure of Morphine can be….this explains all the reactions.

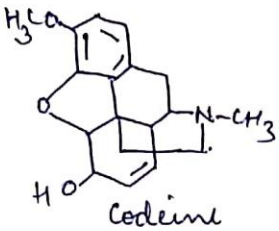

HO
O
NCH3
HO

the above reactions can therefore be explained on the basis of the following str :-



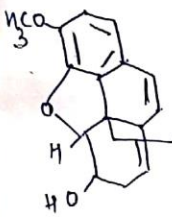
Morphine

$(CH_3)_2SO_4$
Methylation



Codeine

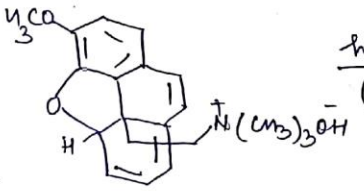
(i) CH_3I
(ii) AgOH.
Hoffmann Exhaustive Methylation



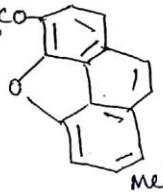
(i) CH_3I.
(ii) OH^-

$+N(CH_3)_3OH^-$

heat
$-H_2O$.



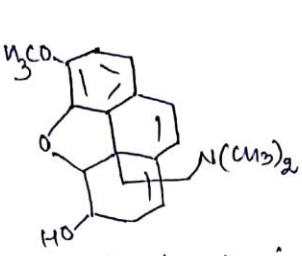
heat with $(CH_3CO)_2O$



$+ (CH_3)_3N + CH_2 \parallel CH_2$.

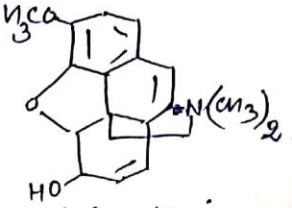
Methyl Morphenol.

(i) Heat with H_2O.
(ii) Demythylation



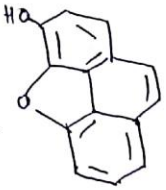
β-Codeimethine

NaOH, heat
Shifting of double bond.

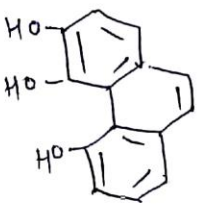


α-codeimethine
(α-Methyl Morphimethine)

Na–alcohol.



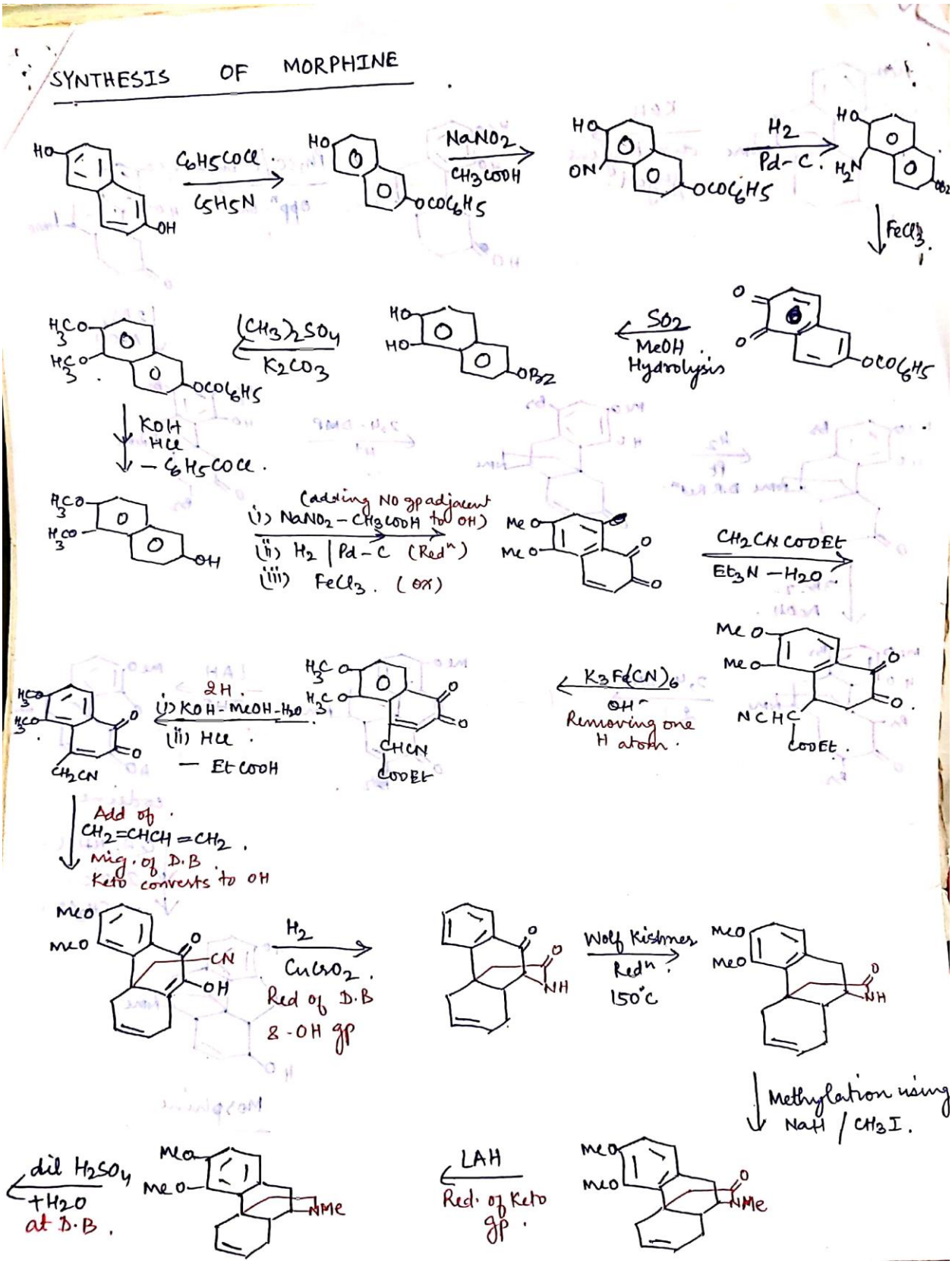
Morphenol.

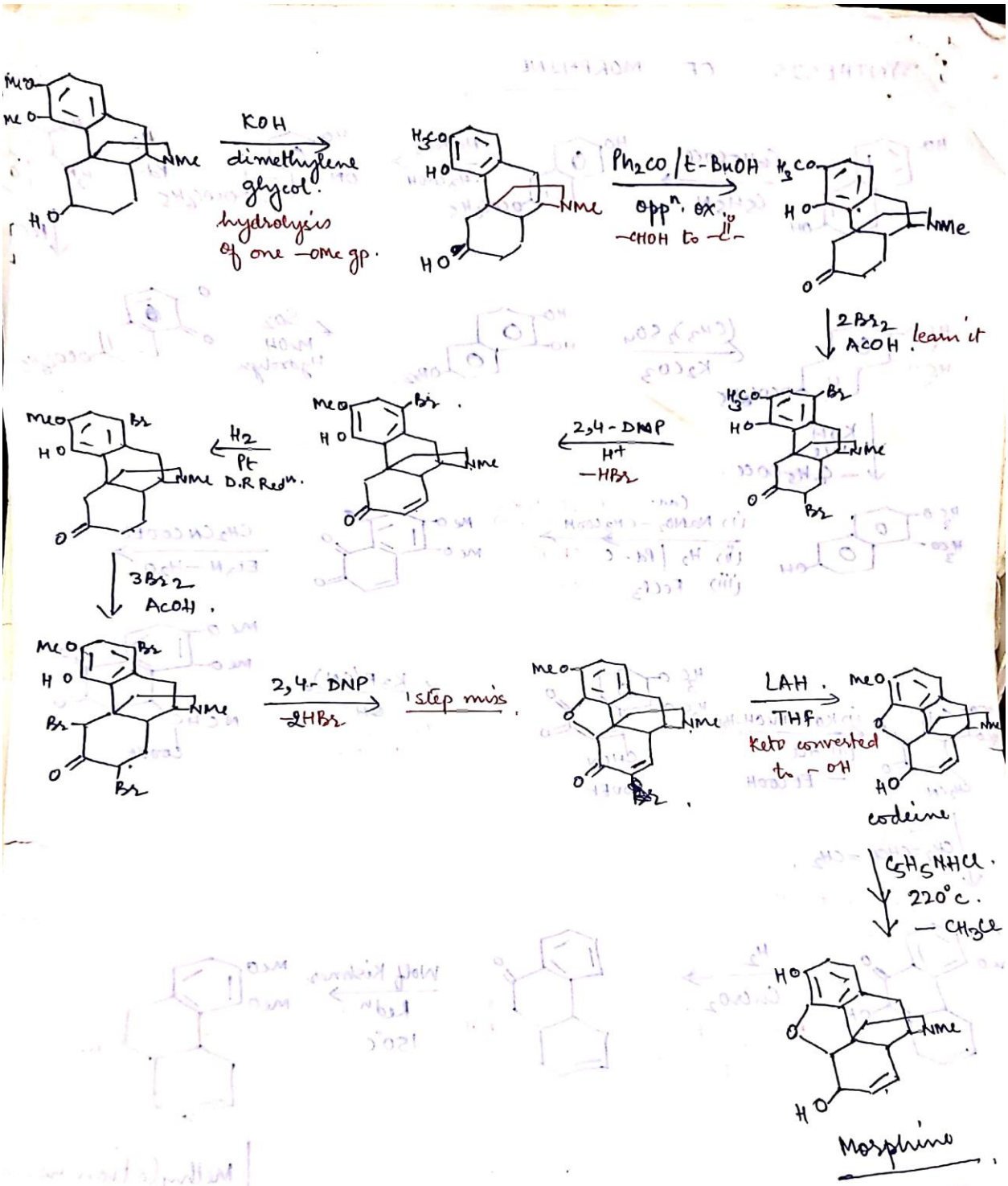


Morphol.
(3,4,5-trihydroxy phenanthrene).

12. SYNTHESIS:-
Finally, the above str. is confirmed by it's synthesis.

SYNTHESIS OF MORPHINE




KOH
dimethylene glycol.
hydrolysis of one –OMe gp.
Ph2CO / t-BuOH
oppn. ox.
–CHOH to –C–
2Br2
AcOH
learn it
H2
Pt
D.R Redn.
2,4-DNP
H+
–HBr
3Br2
AcOH
2,4-DNP
–2HBr
1 step miss
LAH.
THF
Keto converted to –OH
codeine
C5H5NHCl.
220°C.
– CH3Cl
Morphine

Unit 4

Porphyrins

1. Haemoglobin
2. Chlorophyll
3. Phthalocyanins

PORPHYRINS

Porphyrins are a group of heterocyclic macrocycle organic compounds, composed of four modified pyrrole subunits interconnected at their α carbon atoms via methine bridges. The parent of porphyrin is porphine, a rare chemical compound of exclusively theoretical interest. Substituted porphines are called porphyrins.

One result of the large conjugated system is that porphyrins typically absorb strongly in the visible region of the electromagnetic spectrum, i.e. they are deeply colored.

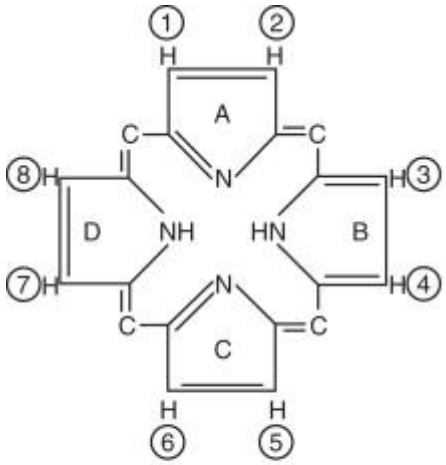
Porphyrins have the tendency to form complex metallic derivatives with Copper, iron, zinc, magnesium etc. These complex metallic derivatives have vital functions in respiratory pigments, oxidation catalyst, photosynthetic reagent.

Metal complexes derived from porphyrins occur naturally. One of the best-known families of porphyrin complexes is heme, the pigment in red blood cells, a cofactor of the protein hemoglobin.

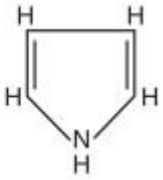
Another example is Chlorophyll found in green plants and Myoglobin found in muscles.

Porphyrins are the conjugate acids of ligands that bind metals to form complexes. The metal ion usually has a charge of 2+ or 3+.

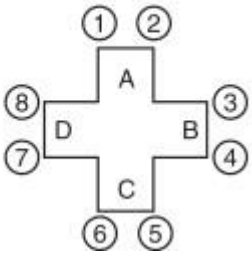
A porphyrin without a metal-ion in its cavity is a *free base*.



Porphin



Pyrrole



HAEMOGLOBIN

Haemoglobin, the red pigment in blood, consists of a protein component and the iron complex of a porphyrin derivative: haemoglobin = globin (protein) + haem (non protein Fe (II) complex). During the breathing process, oxygen attaches loosely to the iron ion, and the oxyhaemoglobin thus formed surrenders its oxygen in the body and reverts back to haemoglobin. Outside the body the iron converts to the trivalent form. Haemoglobin binds carbon monoxide more strongly than oxygen, its colour weakening to cherry red, hence the pink complexion of victims of carbon monoxide poisoning.

Chemical structure of the Fe(II)-protoporphyrin IX heme group in myoglobin and hemoglobin.

Structure Elucidation of Haem or Haemin :

1. **Molecular formula :** $C_{34}H_{32}N_4O_4ClFe$
2. **Presence of two double bonds:** On catalytic reduction it takes up two molecules of hydrogen to form a tetrahydro compound indicating the presence of two double bonds in its structure.

$$C_{34}H_{32}N_4O_4ClFe + 2H_2 \xrightarrow{Ni/Pd} \underset{\text{tetra hydro haemin}}{C_{34}H_{36}N_4O_4ClFe}$$

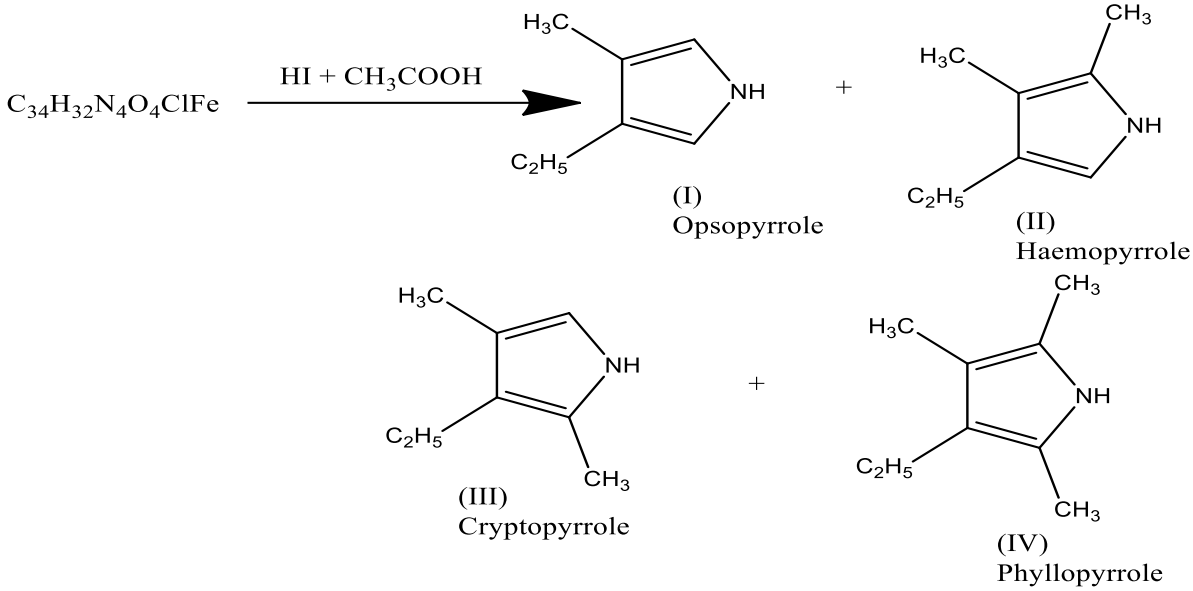
3. **Nature of oxygen atoms:** The oxygen atoms present in Haemin are present as COOH group because on reaction with $NaHCO_3$ it gives brisk effervences indicating the presence of COOH group.

$$COOH + NaHCO_3 \longrightarrow CO_2$$

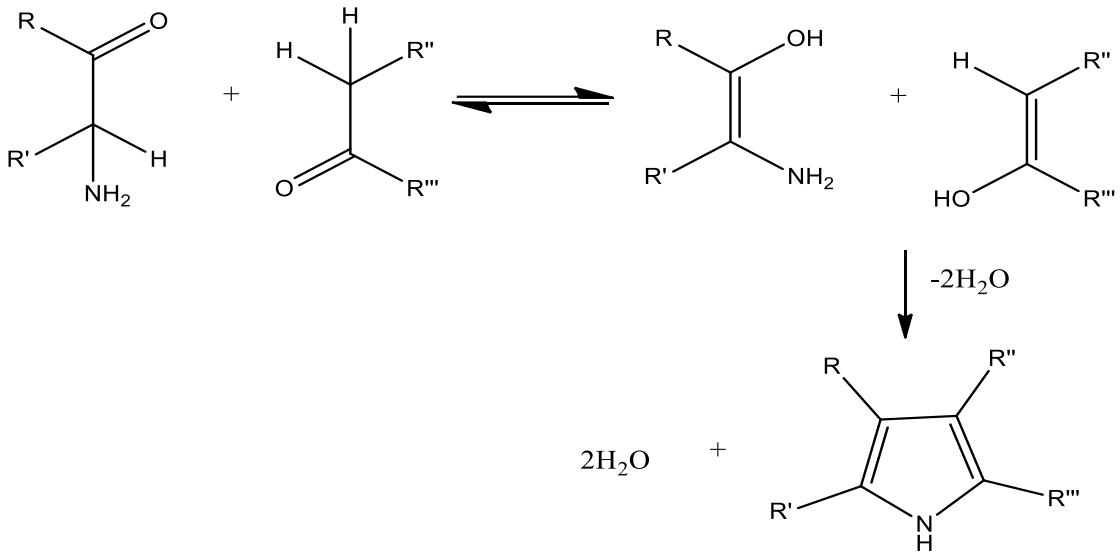
The four oxygen atoms are present as two COOH group as on reaction with Methanol it forms a diester.

$$C_{32}H_{30}N_4ClFe(COOH)_2 \xrightarrow{CH_3OH/HCl} \underset{\text{Diester}}{C_{32}H_{30}N_4ClFe(OCOCH_3)_2}$$

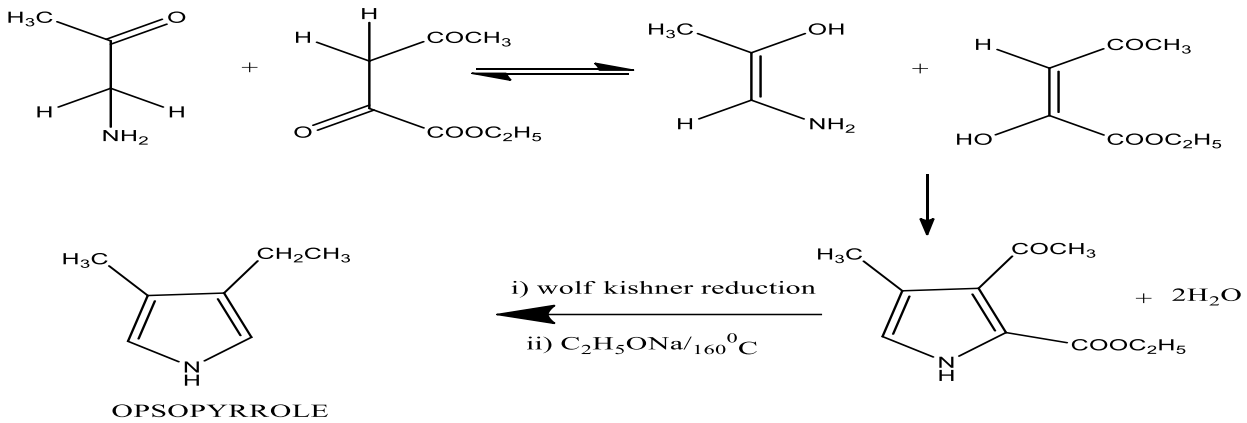
4. **Reductive degradation with HI + CH_3COOH:** When vigorous reduction of Haemin is carried out by means of HI & acetic acid, it gives four substituted pyrrole derivatives.



The structure of these four compounds is confirmed by its synthesis given by Knorr. In general the synthesis of these derivatives involves the condensation of an α-aminoketone with another ketone having an active methylene group. The general reaction is as follows

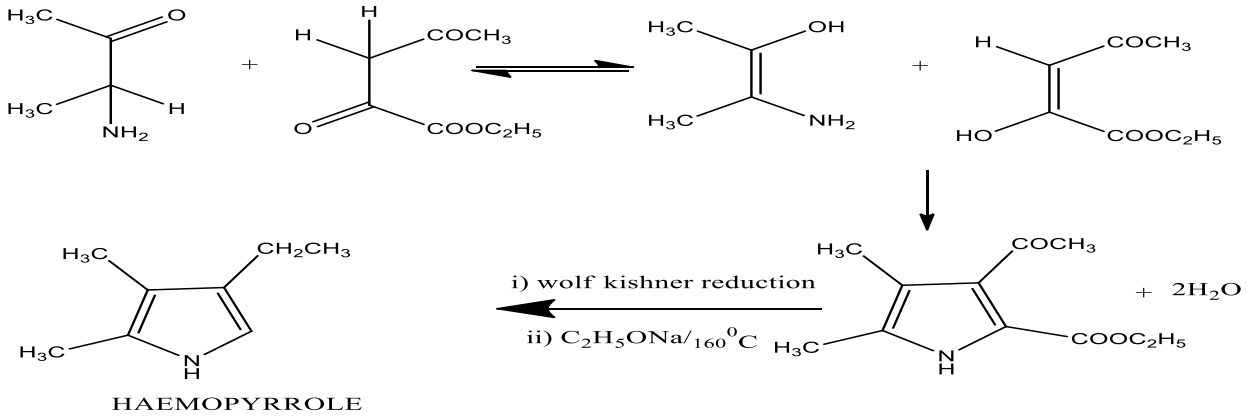


Synthesis of Opsopyrrole:



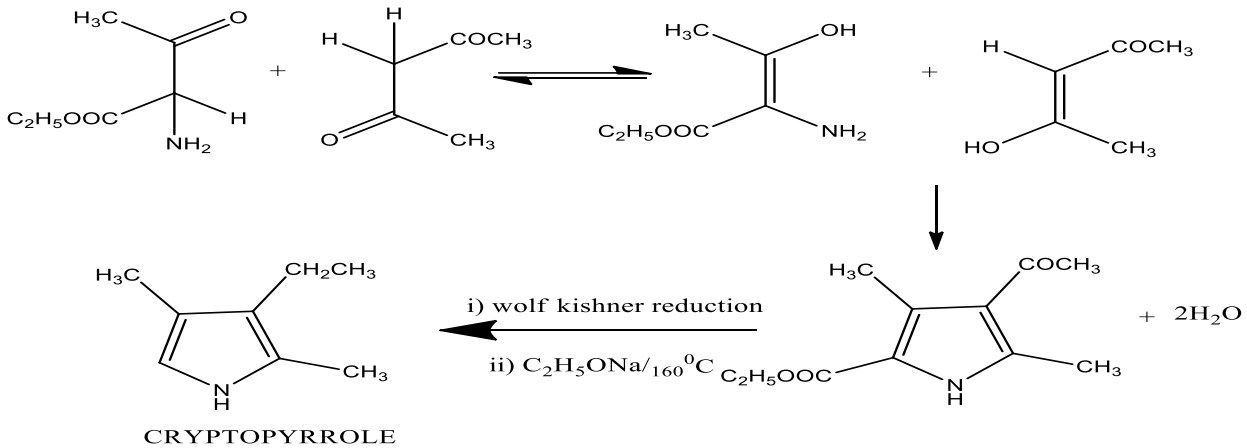
OPSOPYRROLE

Synthesis of Haemopyrrole :



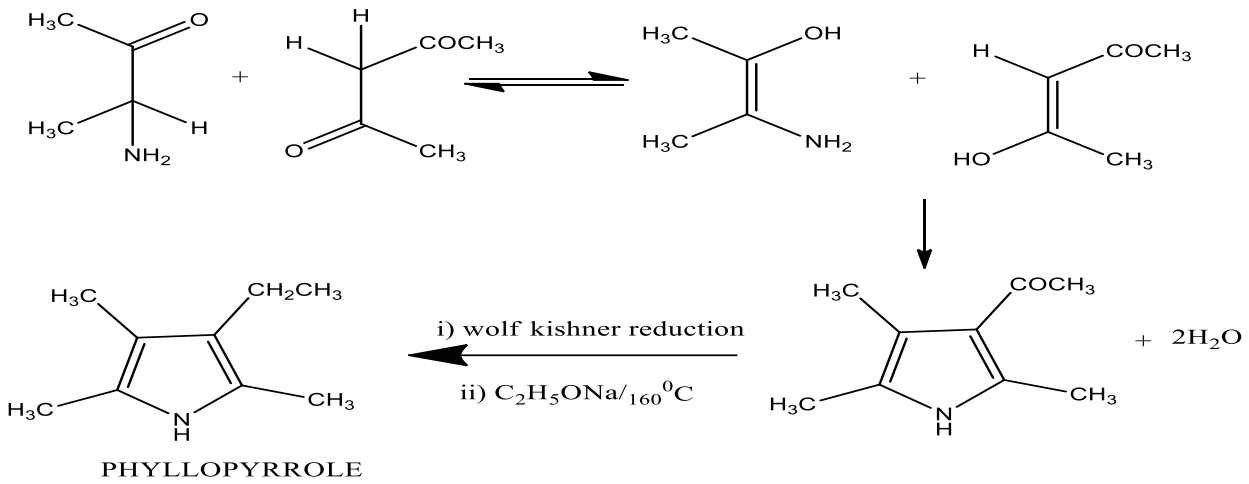
HAEMOPYRROLE

Synthesis of Cryptopyrrole:

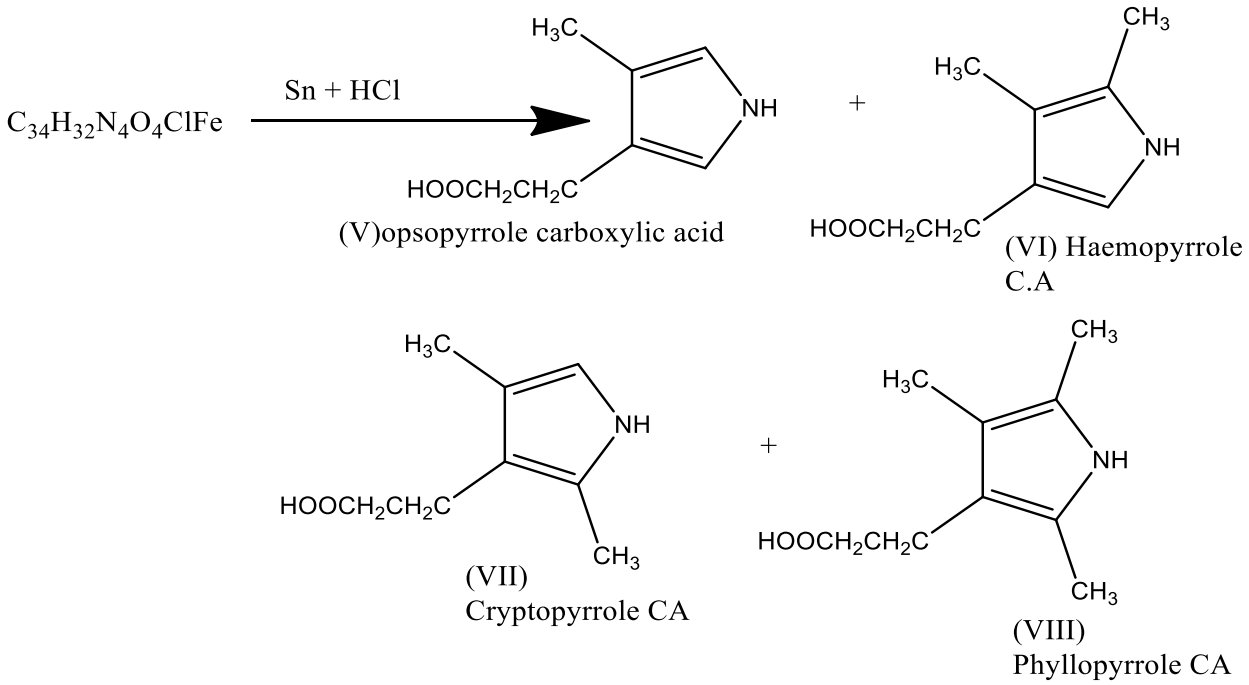


CRYPTOPYRROLE

Synthesis of Phyllopyrrole:

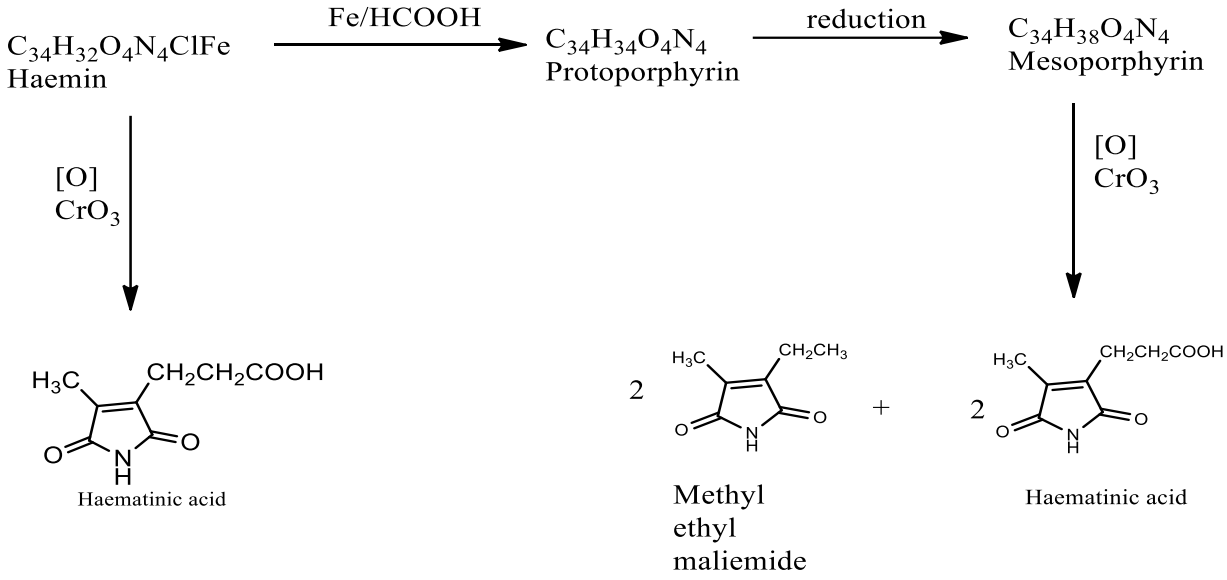


5. **Reductive degradation with Sn + HCl :** Haemin on reduction with Sn + HCl gives four substituted pyrrole carboxylic acids.



In all the structures from V-VIII, the carboxylic group is attached at the ethyl group of I-IV.

6. **Reductive degradation with iron dust and formic acid:** Haemin on reduction with iron dust and formic acid undergoes the following reaction.



CONCLUSIONS FROM REDUCTIVE DEGRADATION: From the reductive degradation following conclusions can be drawn

a) The formation of compound I-IV & V-VIII indicates that haemin contains 4 substituted pyrrole nuclei which are linked together.

b) The formation of compounds I-IV & V-VIII indicates that each pyrrole nuclei has a methyl (CH_3) group at β position.

c) The structure and formation of Haematinic acid and methyl ethyl maleimide indicaes that the four pyrrole units are linked to each other at α position (oxidation at α position). Also the presence of a methyl (CH_3) group in compounds II,III,IV,VI,VII & VIII at α position indicates that these pyrrole nuclei are joined at the α position means of one carbon atom only.

d) Formation of two molecules of Haematinic acid indicates that out of four pyrrole units, two units have a propionic acid residue at the β' position.

e) Formation of two molecules of methyl ethyl maleimide by the oxidation of Mesoporphyrin indicates that out of four pyrrole nuclei , two pyrrole nulei in haemin have 2 unsaturated groups (which can be reduced to C_2H_5) at the β' position . These unsaturated groups can be two vinyl groups (-CH=CH2) which undergo reduction to give ethyl groups.

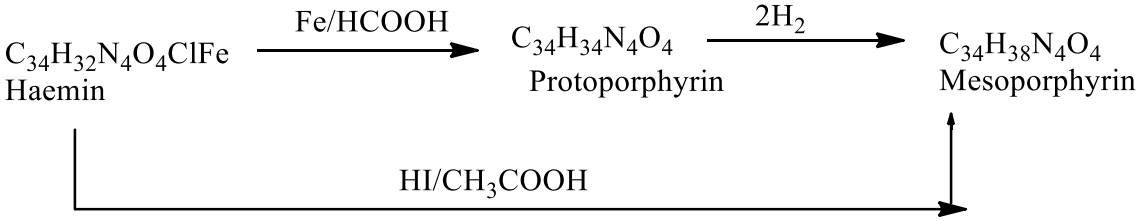
f) The presence of ethyl group in I-IV again supports the presence of two vinyl groups at β position in two pyrrole nuclei.

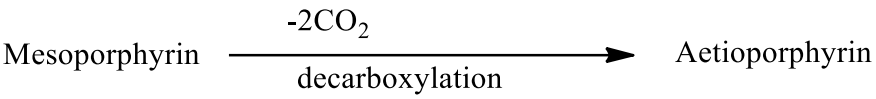
From all the above points the following ring structure can be proposed for Haemin which consisits of four pyrrole nuclei linked at α position via one c atom, with four β position occupied by methyl groups , two β' position occupied by vinyl groups and the remainingtwo β' positions occupied by propionic acid residues.

7. **Nature of the Porphyrin ring:** Depending upon the types of substituents attached on the porphyrin rings , porphyrins can be of the following types

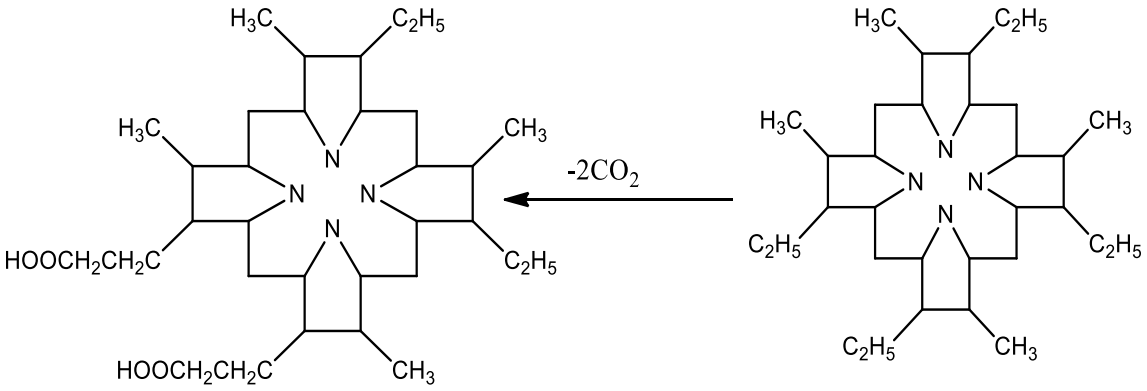
i) Aetioporphyrin
ii) Rhodoporphyrin
iii) Phylloporphyrin
iv) Mesoporphyrin
v) Pyrroporphyrin

To find out which type of Porphyrin ring is present in Haemin following experiments are done.

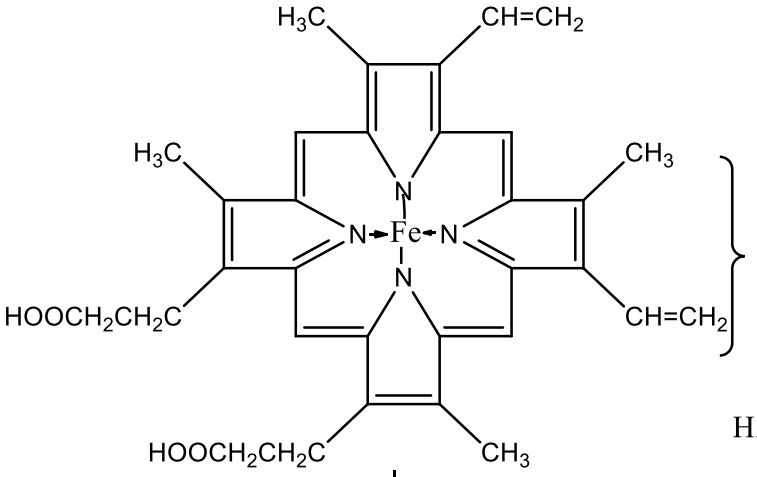




The structure of Aetioporphyrin was found to be tetra methyl tetra ethyl porphyrin. Thus, the structure of Meso and Aetioporphyrin can be

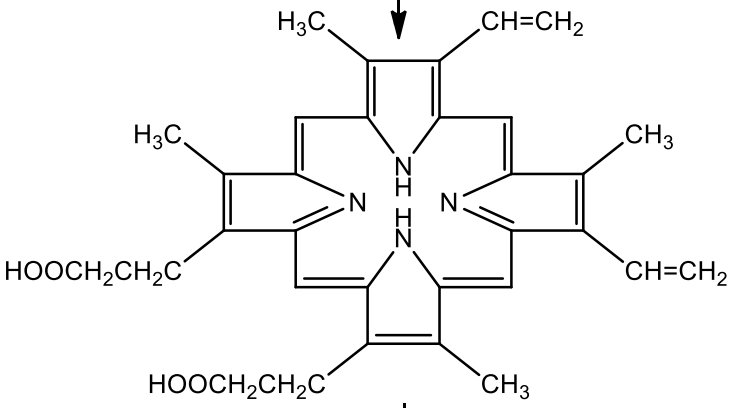


As Mesoporphyrin is obtained by the reduction of porphyrin ($-CH=CH_2 \rightarrow C_2H_5$) and the latter is obtained from Haemin by the removal of iron atom, it follows that the structure of Haemin. Protoporphyrin maybe written as



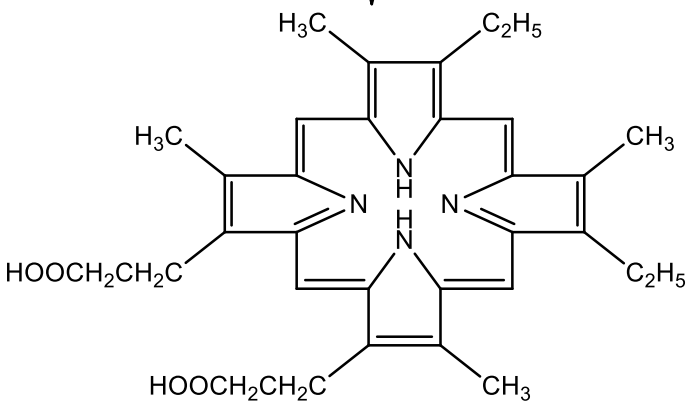
HAEMIN

Fe/HCOOH



PROTOPORPHYRIN

REDUCTION



MESOPORPHYRIN

CHLOROPHYLL

* **Chlorophyll**, any member of the most important class of pigments involved in photosynthesis, the process by which light energy is converted to chemical energy through the synthesis of organic compounds. Chlorophyll is found in virtually all photosynthetic organisms, including green plants, cyanobacteria, and algae. It absorbs energy from light; this energy is then used to convert carbon dioxide to carbohydrates.

* Chlorophyll is a naturally-occurring pigment found in plants and especially in green leafy vegetables. Chlorophyll has many health benefits due to its high level of antioxidants, vitamins, and minerals. Taking liquid chlorophyll can help to detoxify your body, lose weight, build red blood cells, and is good for your skin.

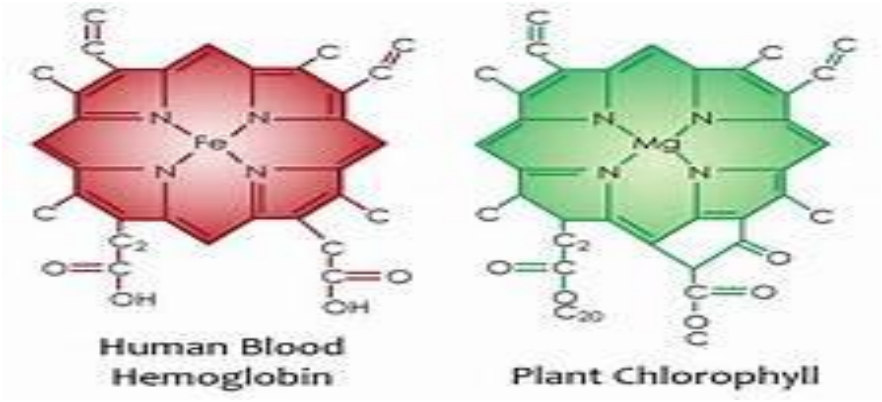
* Chlorophyll was first isolated and named by Joseph Bienaimé Caventou and Pierre Joseph Pelletier in 1817.

* The presence of magnesium in chlorophyll was discovered in 1906, and was the first time that magnesium had been detected in living tissue.

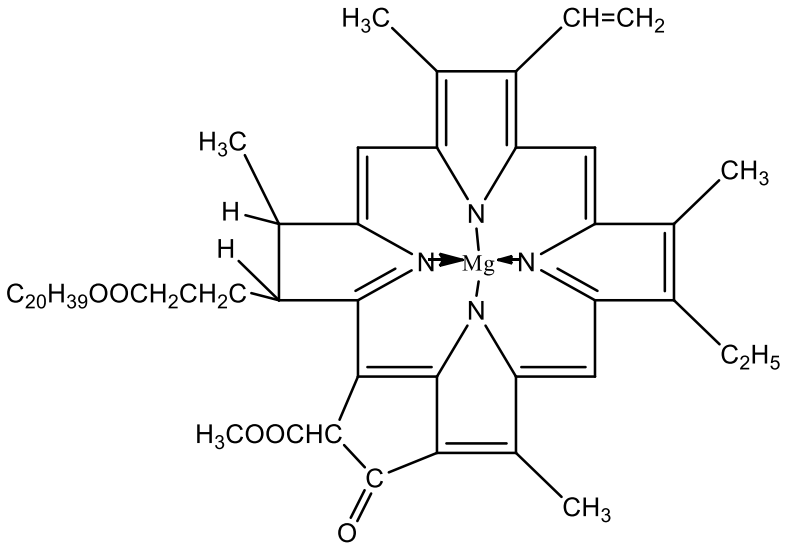
Chlorophyll a Molecular Formula is $C_{55}H_{72}O_5N_4Mg$
It has a ($-CH_3$) gp at position number 3

Chlorophyll b Molecular Formula is $C_{55}H_{70}O_6N_4Mg$
It has a ($-CHO$) gp at position number 3

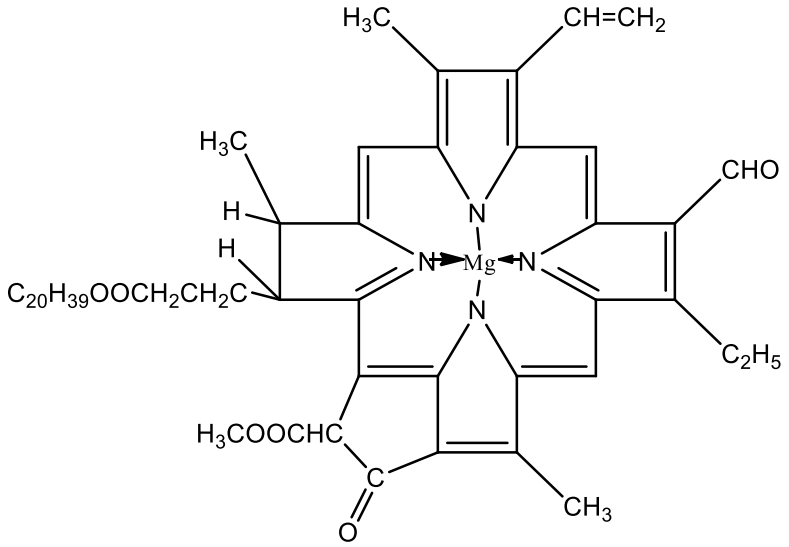
Porphyrins: Both Chlorophyll & Haemoglobin have porphyrin rings



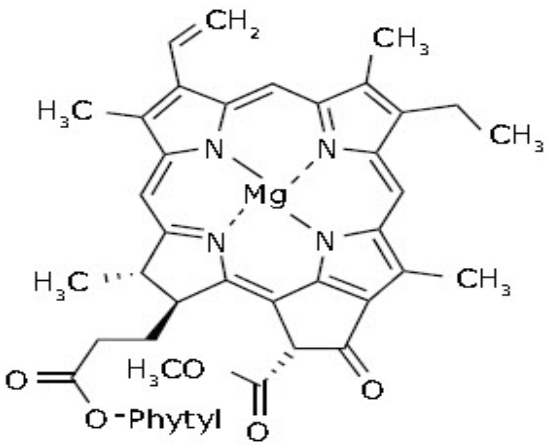
Structure Elucidation of Chlorophyll-a



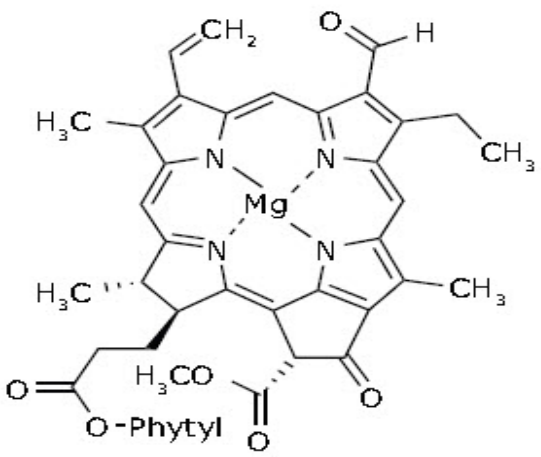
Chlorophyll-a $C_{55}H_{72}N_4O_5Mg$



Chlorophyll-b $C_{55}H_{70}N_4O_6Mg$



Chlorophyll a 00538



Chlorophyll b 00538

1. Molecular Formula: $C_{55}H_{72}N_4O_5Mg$

2. No. of Double bonds: On catalytic reduction it takes up one molecule of H2 to give a dihydro compound indicating that it has one double bond in its structure.

$$C_{55}H_{72}N_4O_5Mg + H_2 \xrightarrow{Ni} C_{55}H_{74}N_4O_5Mg$$

3. Nature of Oxygen atom : Out of five oxygen atoms four are present as ester group as on hydrolysis it gives 2 alcohols Methanol and Phytol and a dicarboxylic acid Chlorophyllide a.

$$\begin{matrix} C_{55}H_{72}N_4O_5Mg \\ \text{or} \\ C_{32}H_{30}N_4OMg \end{matrix} \begin{matrix} COOCH_3 \\ \\ COOC_{20}H_{39} \end{matrix} \xrightarrow[\text{hydrolysis}]{KOH} C_{32}H_{30}N_4OMg \begin{matrix} COOH \\ \\ COOH \end{matrix}$$

Chlorophyllide a

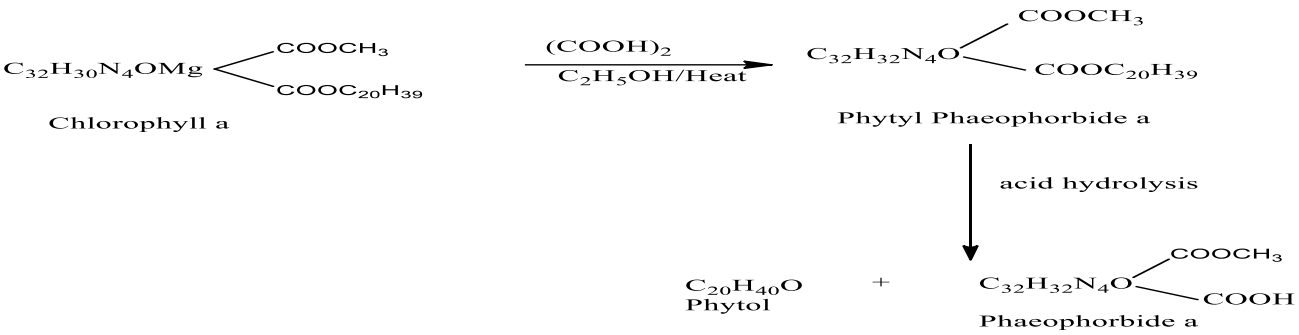
$$CH_3OH + C_{20}H_{39}OH$$

Methanol Phytol

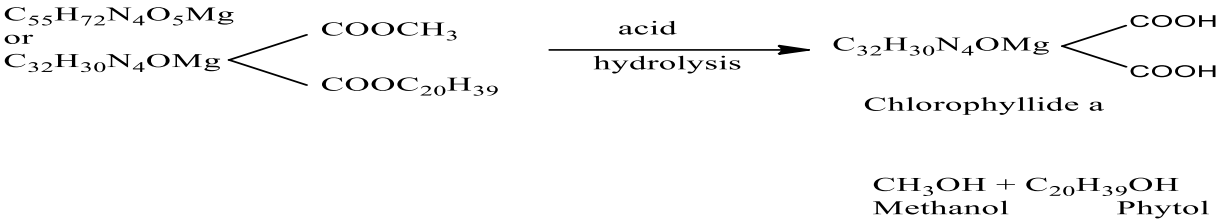
One of the oxygen atoms is present as a cyclic ketone as on reaction with hydroxl amine it gives a mono oxime.

$$\begin{matrix} C_{55}H_{72}N_4O_5Mg \\ \text{or} \\ C_{54}H_{72}N_4O_4Mg(CO) \end{matrix} \xrightarrow{NH_2OH} \begin{matrix} C_{54}H_{72}N_4O_4Mg(C{=}NOH) \\ \text{Mono oxime} \end{matrix}$$

4. Presence of a Phytyl Group : When chlorophyll a is heated with an ethanolic solution of hydrated oxalic acid, the Mg atom is replaced by two hydrogen atoms to give phytyl phaeophorbide a which on acid hydrolysis gives an alcohol Phytol and Phaeophorbide a.

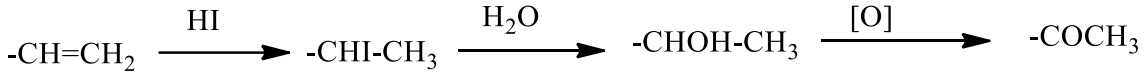


When Chlorophyll a is directly hydrolysed with an acid, it gives Chlorophyllide a, methanol and phytol.



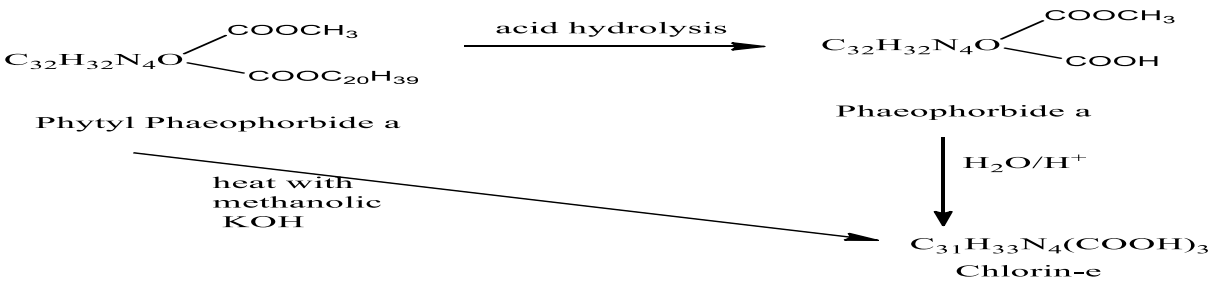
All these three hydrolytic reactions indicate the presence of a phytyl group in Chlorophyll a.

5. Presence of a Vinyl Group : Chlorophyll a has one double bond in its structure as it takes up one molecule of hydrogen on catalytic reduction. This double bond is found to be present as a vinyl group by the following oxo reaction:



Phaeophorbide a is converted into Acetylporphyrin by using oxo reaction which indicates that Phaeophorbide a and hence Chlorophyll a has a vinyl group.

6. Nature of the Porphyrin ring: When Phytyl Phaeophorbide a is boiled with methanolic KOH, it undergoes hydrolysis to give Chlorin-e. This compound was found to be a tricarboxylic acid as it forms a trimethyl ether.



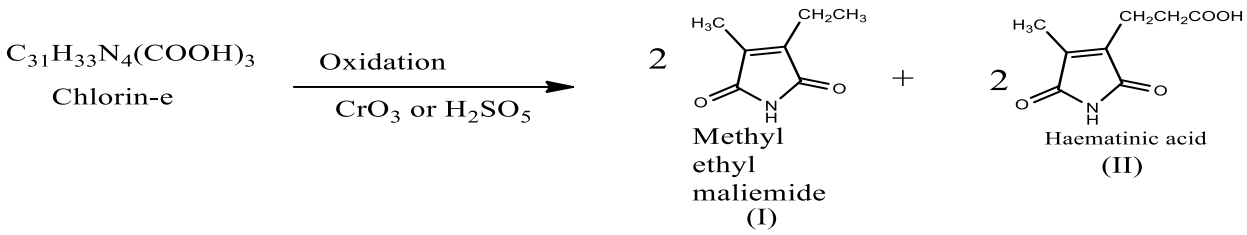
Chlorin-e is also formed by the hydrolysis of Phaeophorbide –a(having 2 COOH gp). This shows that Phaeophorbide-a must posess some group which gives rise to the third COOH gp.

Such a group can be either a lactone or a cyclic ketone as no carbon atom is lost during hydrolysis.

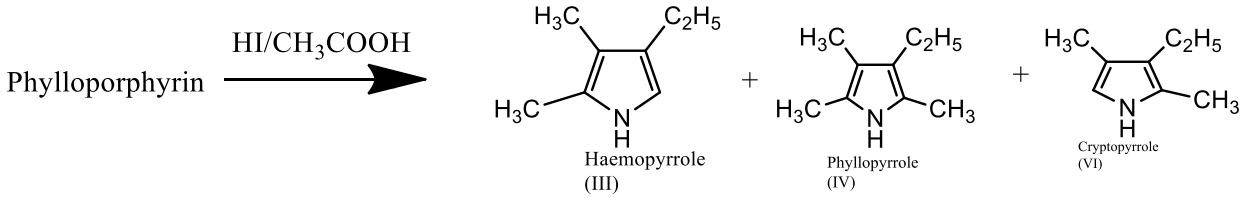
To understand the structure of Chlorophyll, we should first know the structure of Chlorin-e

7. Chlorin-e structure

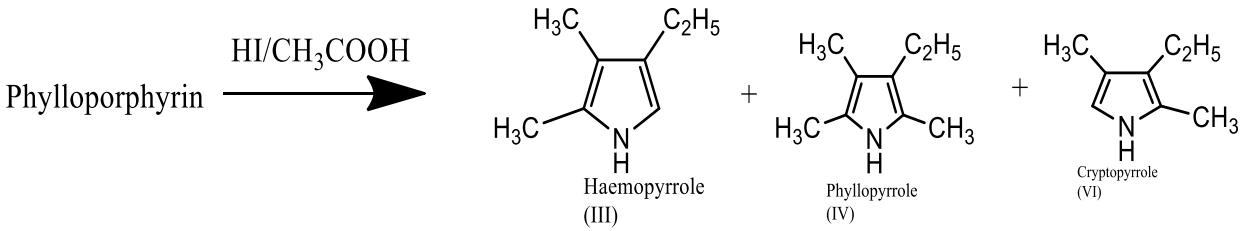
a) When Chlorin-e is oxidised with chromic acid or with Caro's acid (H2SO5), it yields Haematinic acid(I) & Methyl Ethyl Methyl Maleimide(II).



b) When Chlorin-e is reduced with HI in Acetic acid , it gives haemopyrrole (III) & Phyllopyrrole(IV).



c) When Chlorin-e is reduced with HI/CH3COOH, it gives Haemopyrrole(V), Phyllopyrrole(IV) & Cryptopyrrole(VI)



CONCLUSIONS ….

1. Formation of compounds I-VI indicates that in Chlorophyll, four substituted pyrrole nuclei are present having a –CH3 gp at β-position. Haematinic acid indicates atleast one propionic acid residue.

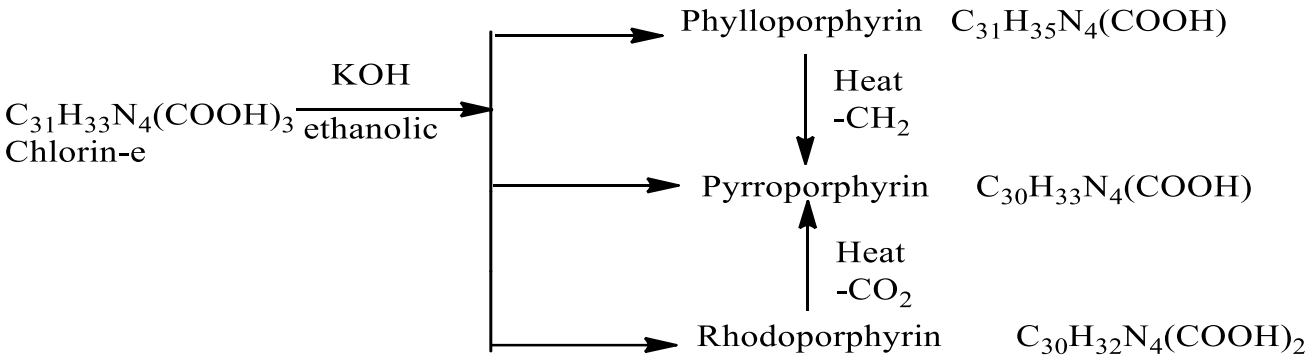
2. Formation of Haemo & Phyllo pyrrole indicates that atleast on two pyrrole rings either two C2H5 group or 2 unsaturated groups (vinyl gp) maybe present.

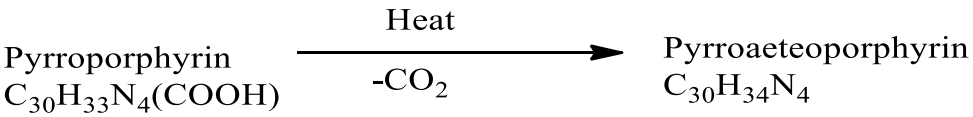
3. The formation of compounds I & II indicates that all the four pyrrole nuclei are linked to each other at α- position via one carbon atom(from the formation of haemo, phyllo & cryptopyrrole)

4. As Chlorin-e which is a tricarboxyllic acid is obtained from Chlorophyllide-a which is a dicarboxyllic acid, without any loss of carbon atoms it means Chlorophyll a must possess such group which on hydrolysis gives an acid without the loss of the carbon atom. Such a group can either be a lactone or a cyclic ketone.

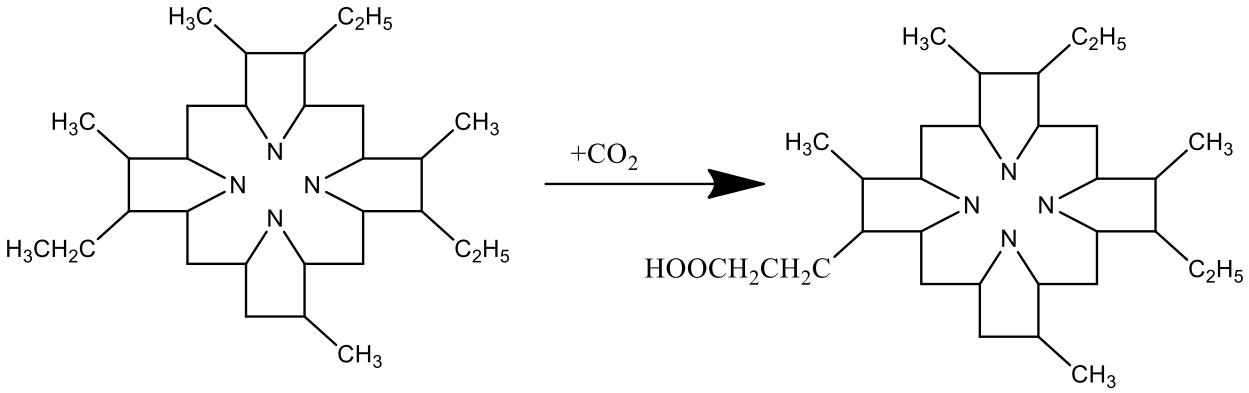
Degradation of Chlorin-e

The structure of Chlorophyll can be explained from the structure of Chlorin-e by the degradation of Chlorin-e.





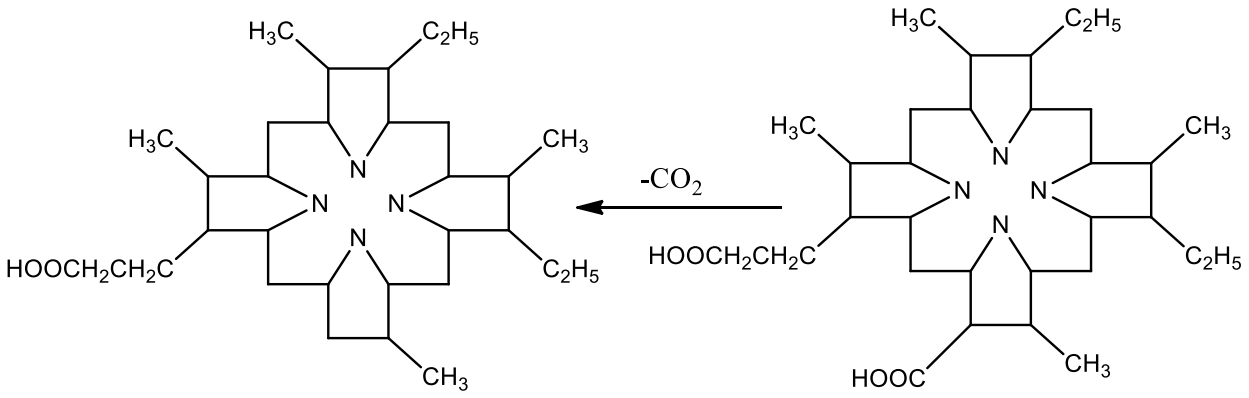
The structure of Pyrroaeteoporphyrin and hence Pyrroporphyrin was found to be



Pyrroaeteoporphyrin

Pyrroporphyrin

The structure of Pyrroporphyrin and hence Rhodoporphyrin was found to be



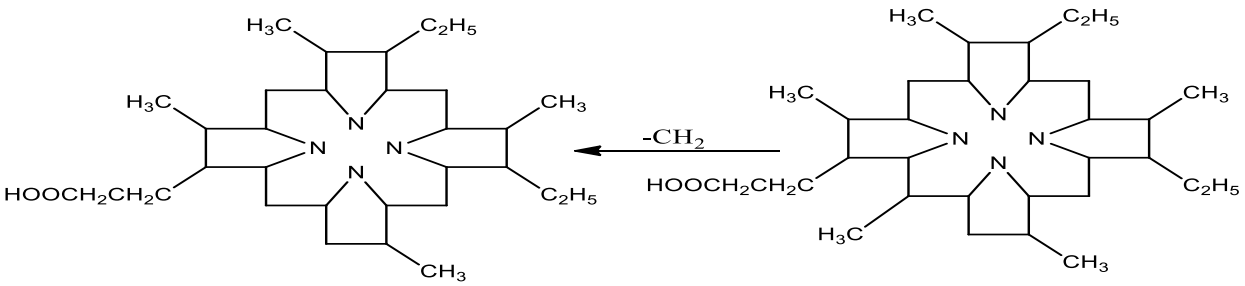
Pyrroporphyrin

Rhodoporphyrin

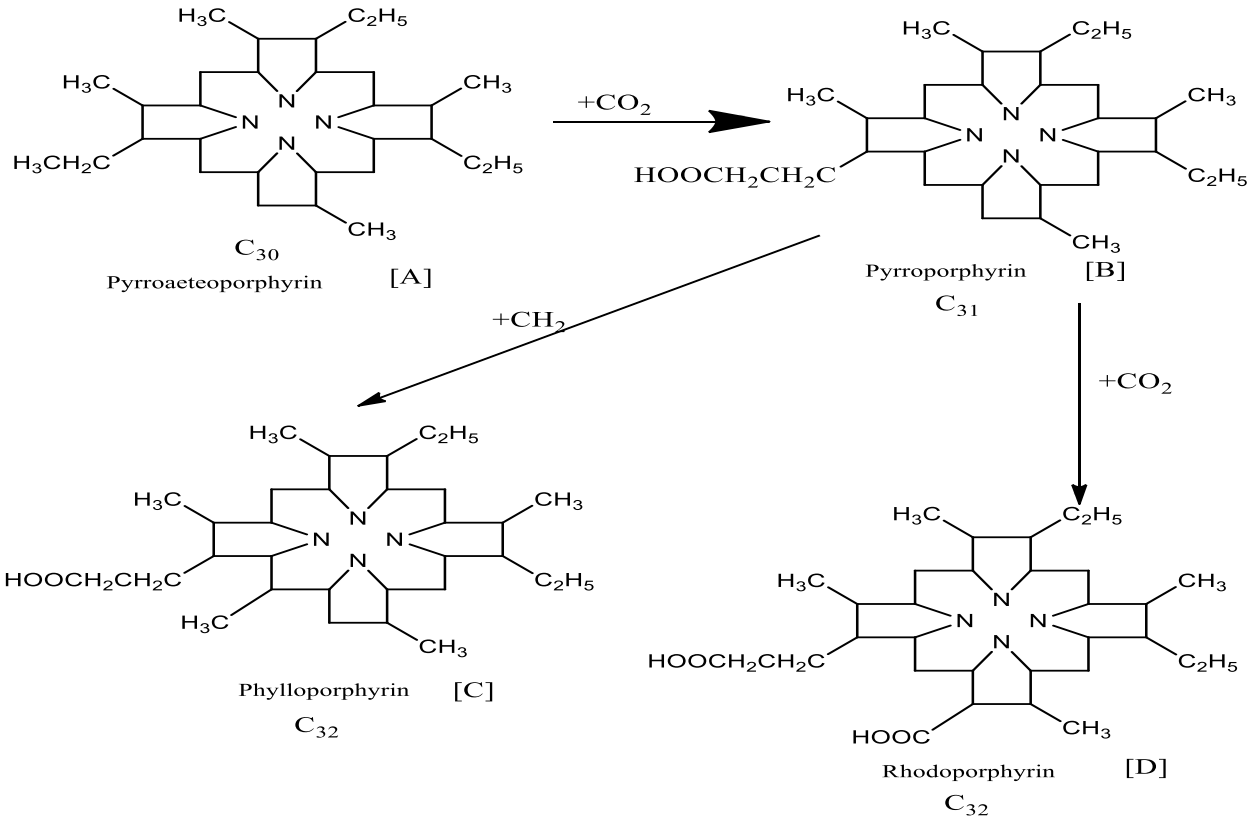
Rhodoporphyrin has two COOH groups and it loses one COOH group to get converted into Pyrroporphyrin indicating that one of the COOH gp is attached in the side chain of the Pyrrole nucleus(propionicacid residue) which is difficult to remove and the other one which is lost is directly attached to the pyrrole nucleus at 6 position. Spectroscopic data also confirmed the presence of two COOH groups at position number 6 & 7.

Phylloporphyrin has one CH2 gp more tha Pyrroporphyrin and by synthesis work it was shown that a CH3 Group is present to the γ-methine Carbon atom.

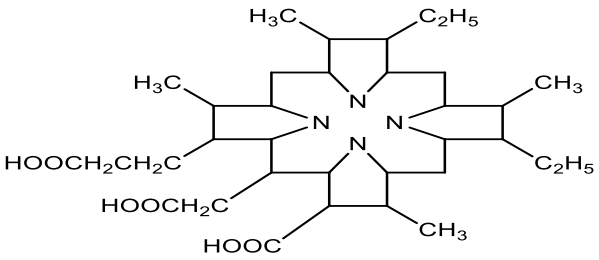
The structure of Pyrroporphyrin and hence Phylloporphyrin was found to be



From all these structures, finally the structure of Chlorin-e can be

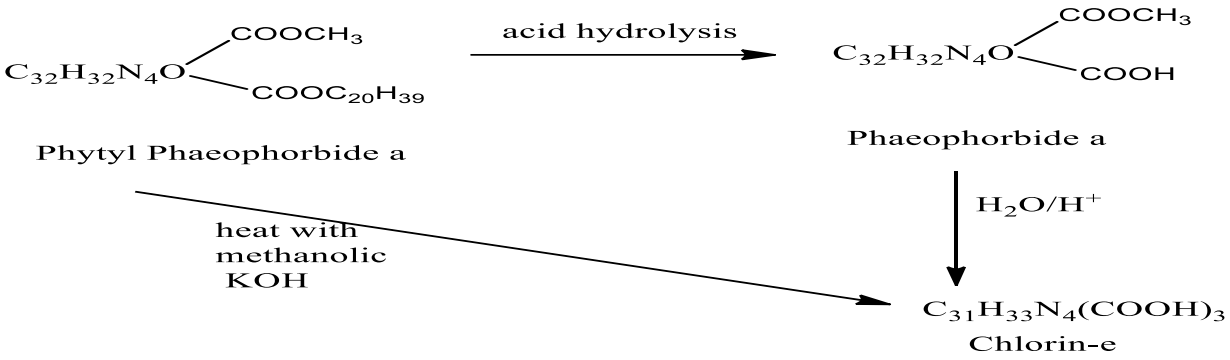


Combining structures B+C+D and adding one COOH group we get the structure of Chlorin-e



Chlorin-e tricarboxyllic acid $C_{31}H_{33}N_4(COOH)_3$

Structure of Phytyl Phaeophorbide a



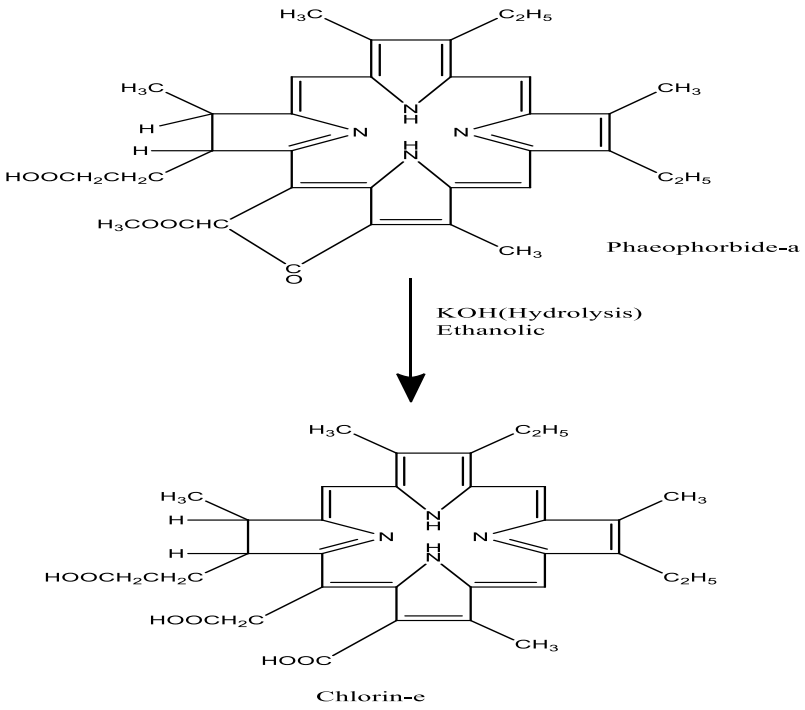
During this reaction following changes takes place:

1. A third COOH gp is introduced without the loss of carbon atom.

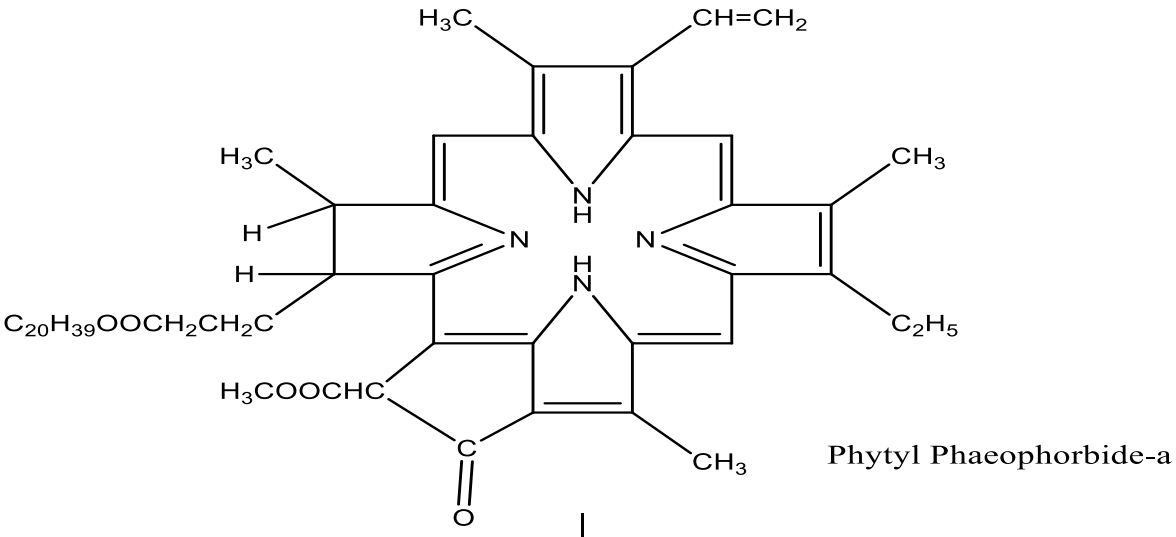
2. The hydrolysis of carbomethoxyl group takes place.

3. The keto group is lost.

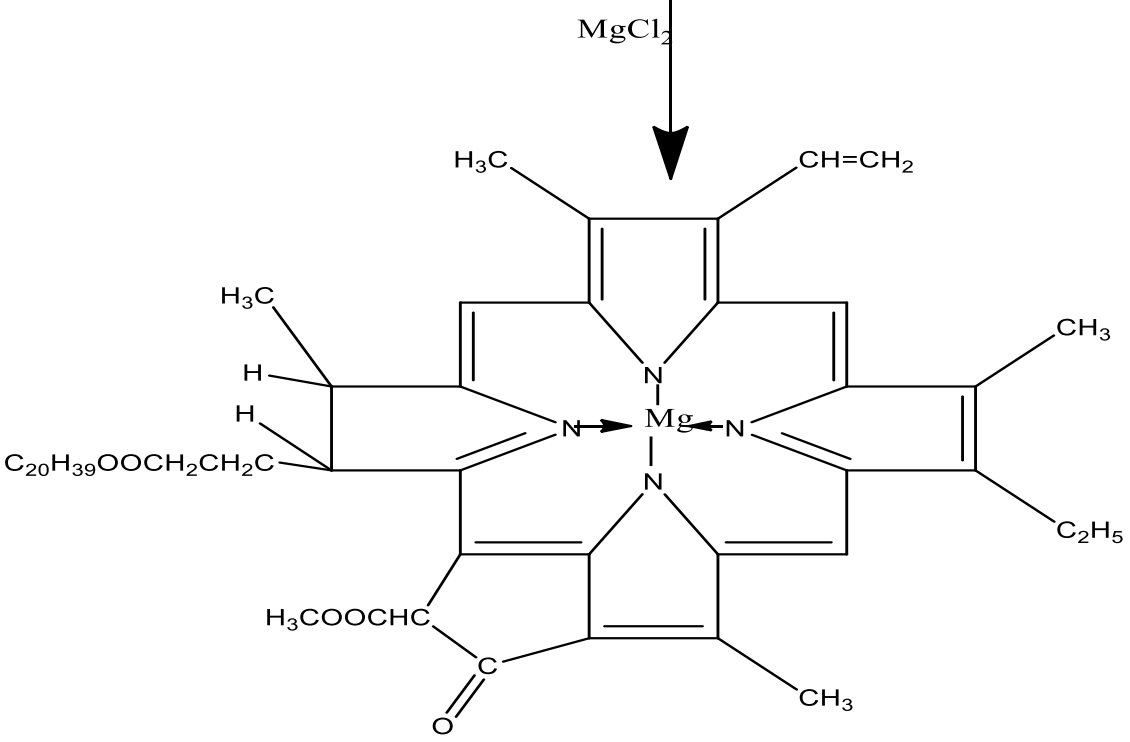
All these above points in the Chlorin e structure can only be explained if we consider that the third carboxyl group in Chlorin e is produced by the fission of a cyclic ketone and not a lactone . Looking into all the above reactions the possible structure for Phaeophorbide-a can be



Thus, the structure of Phytyl Phaeophorbide a and chlorophyll a can be



Phytyl Phaeophorbide-a



Chlorophyll-a

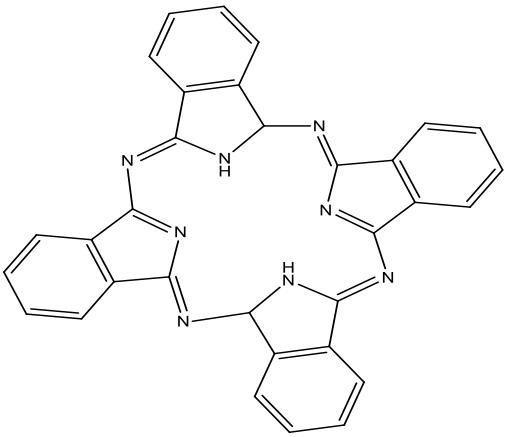
PHTHALOCYANINS

Phthalocyanine (**H_2Pc**) is a large, aromatic, macrocyclic, organic compound with the formula $(C_8H_4N_2)_4H_2$ and is of theoretical or specialized interest. It is composed of four isoindole units linked by nitrogen atoms. H_2Pc has a two-dimensional geometry and a ring system consisting of 18 π-electrons. The extensive delocalization of the π-electrons affords the molecule useful properties, lending itself to applications in dyes and pigments. Metal complexes derived from Pc^{2-}, the conjugate base of H_2Pc, are valuable in catalysis, organic solar cells, and photodynamic therapy.

Phthalocyanins are an important class of organic dyes and pigments which are coloured blue to green. They were discovered accidentally in 1928 at Scottish dyes limited.

The Phthalocyanins forms metal complexes with many metals and the colour depends upon the nature of the metals like Cu, Mg, Fe etc, greener shades are obtained by direct chlorination of bromination.

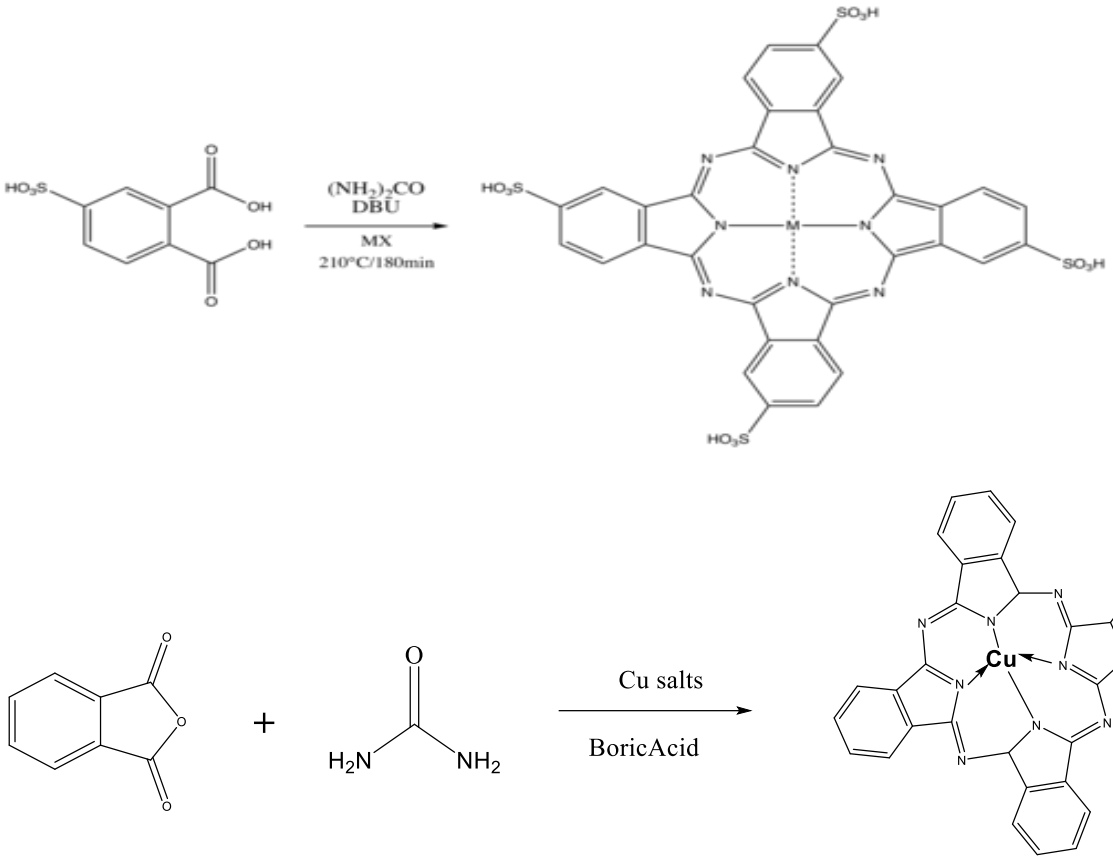
Metal Phthalocyanins are insoluble in water and are used as pigments. They are made water soluble by sulphonation and these soluble salts are used as dyes.



PREPARATION

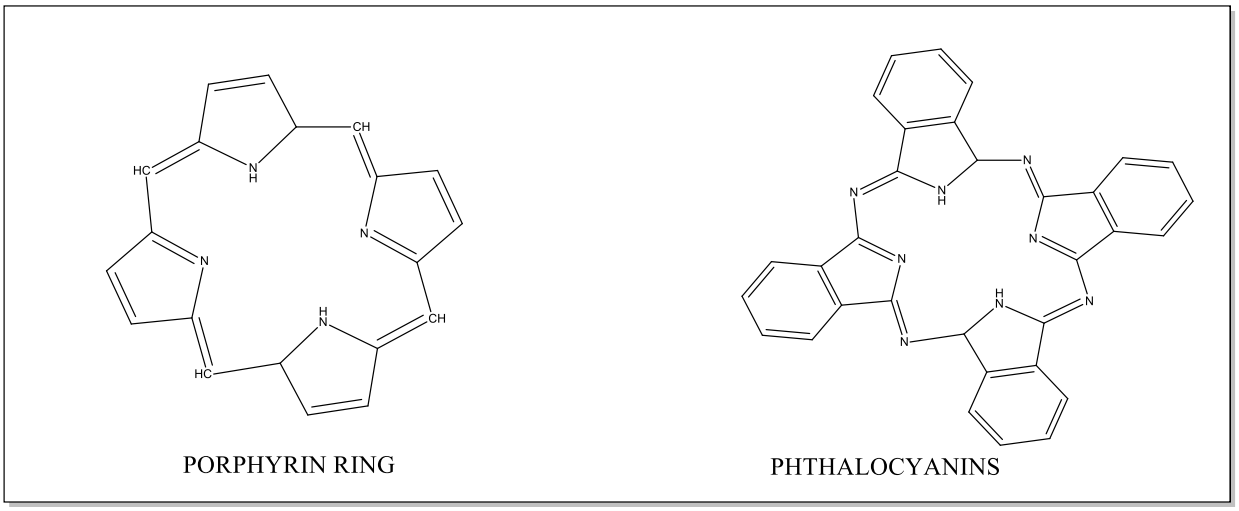
Metal Phthalocyanins can be prepared in the following ways---

1. By passing NH_3 into molten phthalic anhydride or phthalimide with urea and a metal salt.
2. By heating phthalimide or phthalic anhydride with urea and a metallic salt in the presence of a catalyst like boric acid.



Structure and its similarity with the porphyrin ring

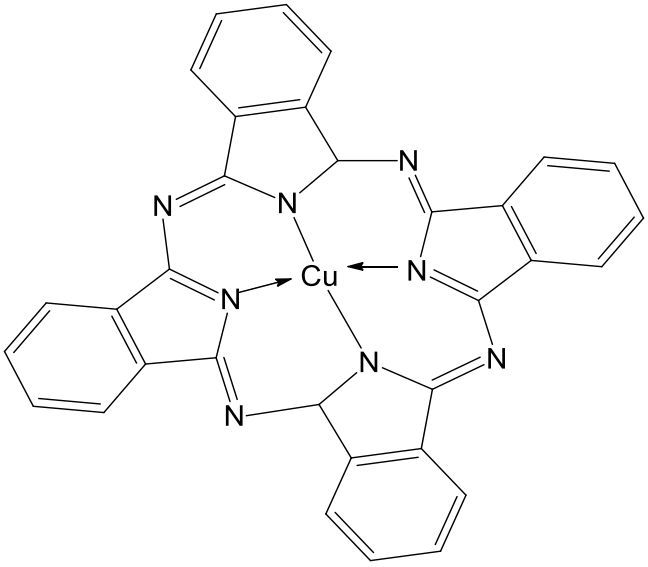
1. Phthalocyanins contains four isoindole units joined in a ring by means of nitrogen atoms. If we ignore the benzene rings, then we have four pyrrole nuclei which are linked by nitrogen atoms, a structure identical to porphyrins in which the four pyrrole rings are linked by methine groups.
2. Both porphyrins and Phthalocyanins are coloured and both contain two imino hydrogen atoms which can be replaced to form metal complexes. Because of these similarities, the Phthalocyanins are often known as Tetra-azoporphyrins.



PORPHYRIN RING

PHTHALOCYANINS

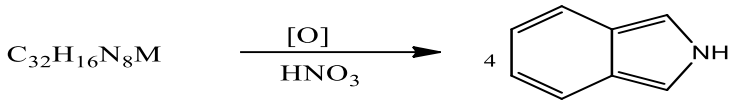
The first commercial Phthalocyanin pigment was Monastral Fast Blue BS: Copper Phthalocyanin



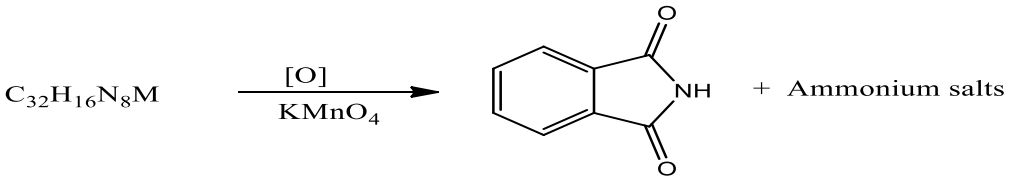
MONASTRAL FAST BLUE BS

STRUCTURE CONSTITUTION

1. **Molecular Formula**: $C_{32}H_{16}N_8M$ where M is a bivalent metal like Cu^{2+}, Mg^{2+}, Fe^{2+}
2. **Presence of Four Isoindole Units:**



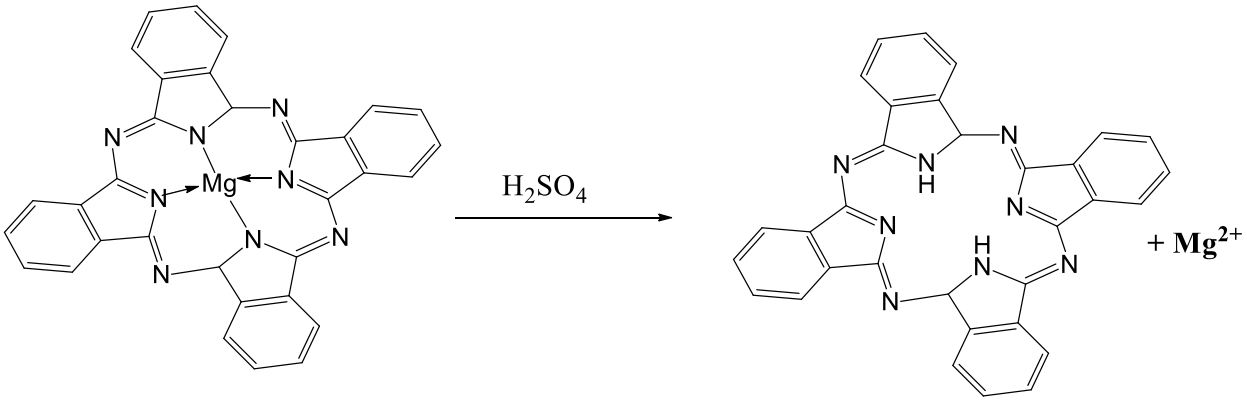
4 ISOINDOLE UNITS



PHTHALIMIDE

The amount of Phthalimide indicates the presence of four isoindole units.

3. **Point of linkage of four Isoindole units:** The four Isoindole units in magnesium Phthalocyanins are linked to each other by nitrogen atoms with a bivalent metal atom in the centre and treatment of Magnesium Phthalocyanin with H_2SO4 replaces the magnesium atom by two hydrogen atoms suggesting that the metal atom has replaced two imino hydrogen atoms.



Question Bank

SHORT QUESTIONS

1. Define Porphyrins.
2. Name the metal atoms found in Haemoglobin, Chlorophyll and Phthalocyanins.
3. What is the molecular formula of Chlorophyll a and Chlorophyll b?
4. How many pyrrole rings are present in one molecule of Chlorophyll?
5. Name the protein and non-protein part found in Haemoglobin molecule. Also mention its percentage.

LONG QUESTIONS

1. Draw the structure of Haemin.
2. Draw the structure of Chlorophyll a & b.
3. Draw the structure of Phthalocyanins.
4. Give the constitution of Haemin.
5. Give the constitution of Chlorophyll.
6. Short note on Phthalocyanins.