

ALKALOIDS

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Alkaloids

INTRODUCTION

- ❑ **The term alkaloids or alkali like was proposed by the pharmacist W. Meissner in 1819.**
- ❑ **According to him "Alkaloids are basic nitrogen compounds isolated from plants".**
- ❑ **As the chemistry of the various alkaloids were investigated two more characteristics were added to the definition of alkaloids. These are**

a. Complex molecular structure.

b. Significant pharmacological activity.

❑ The basic properties of the alkaloids is due to the presence of nitrogen atom inside the ring.

❑ DEFINITION

❑ So the alkaloids are defined as physiologically active basic compounds of plant origin, in which at least one nitrogen atom forms part of a

❑ However, even this definition is not fully satisfactory because some compounds although alkaloids do not confine to this definition, while other compounds which are not alkaloids confine to this definition. For example

❑ Compounds like ephedrine, horde nine, betaines do not contain there nitrogen as part of a heterocyclic system) are classed as alkaloids.

❑ Thiamine (a Vitomin) and purines (caffeine, Xanthine) which are heterocyclic Physiologically active. Nitrogenous bases but regarded as alkaloids.

OCCURRENCE OF ALKALOIDS:-

As many as more than 2,000 alkaloids are known but they are found only in 10-15% of all the Vascular plant. They are rarely found in lower plants like algae, fungi, gymnosperms or mono cotyledons. They are chiefly occur in higher plants particularly the dicotyledons.

They are mostly found in the families Apocynaceae, Papaveraceae, Ranunculaceae, Rubiaceae Rutaceae and Solanaceae.

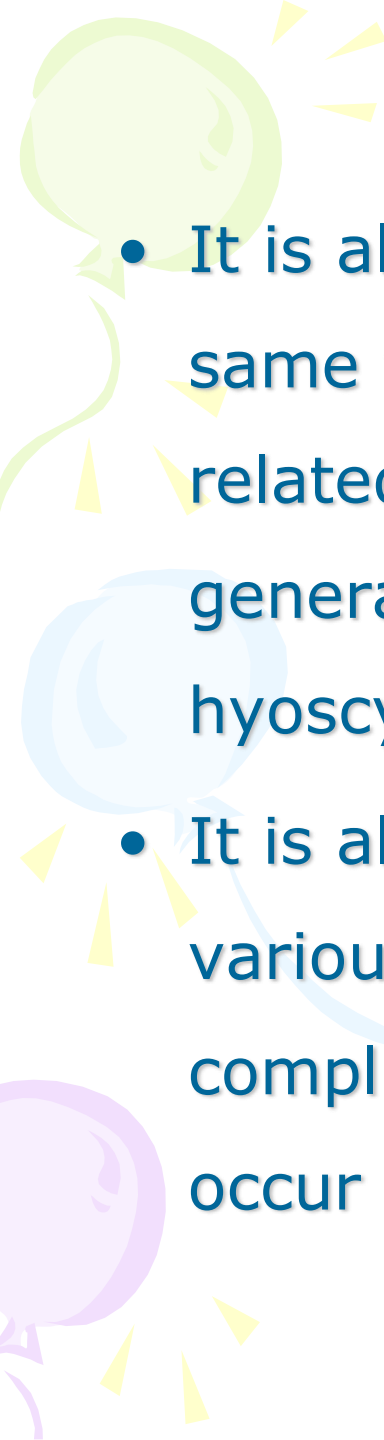
In Plants alkaloids, due to their basic nature, exist as salts of organic acids like acetic, oxalic, citric, malic, lactic, tartaric acids.



Same feeble basic alkaloids like nerceine, nicotine occur free in nature.

A few alkaloids also occur as glycosides of sugar like glucose rhamnose and galactose for example alkaloids of solanum and Veratrum groups as amides (Piperine) or as esters (tropine and cocaine) of organic acids.

Closely related alkaloids generally occur together in the same plant. nearly twenty alkaloids have been isolated from opium.


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- It is also observed that different genera of the same family may contain the same or structurally related alkaloids. For example seven different genera of the family solonaceae contain by hyoscysamine.
 - It is also found that simple alkaloids occur in various different unrelated plants while the more complicated such as quinine, nicotine colchicines occur in one species or geneus of a family.

NOMENCLATURE OF ALKALOIDS:-

Due to the complex molecular structure of alkaloids there was no systematic nomenclature of alkaloids.

A large number of alkaloids have been named according to the plants from which they are obtained for eg. papaverine from papaver somniferum and berberine from berberis vulgaris L.

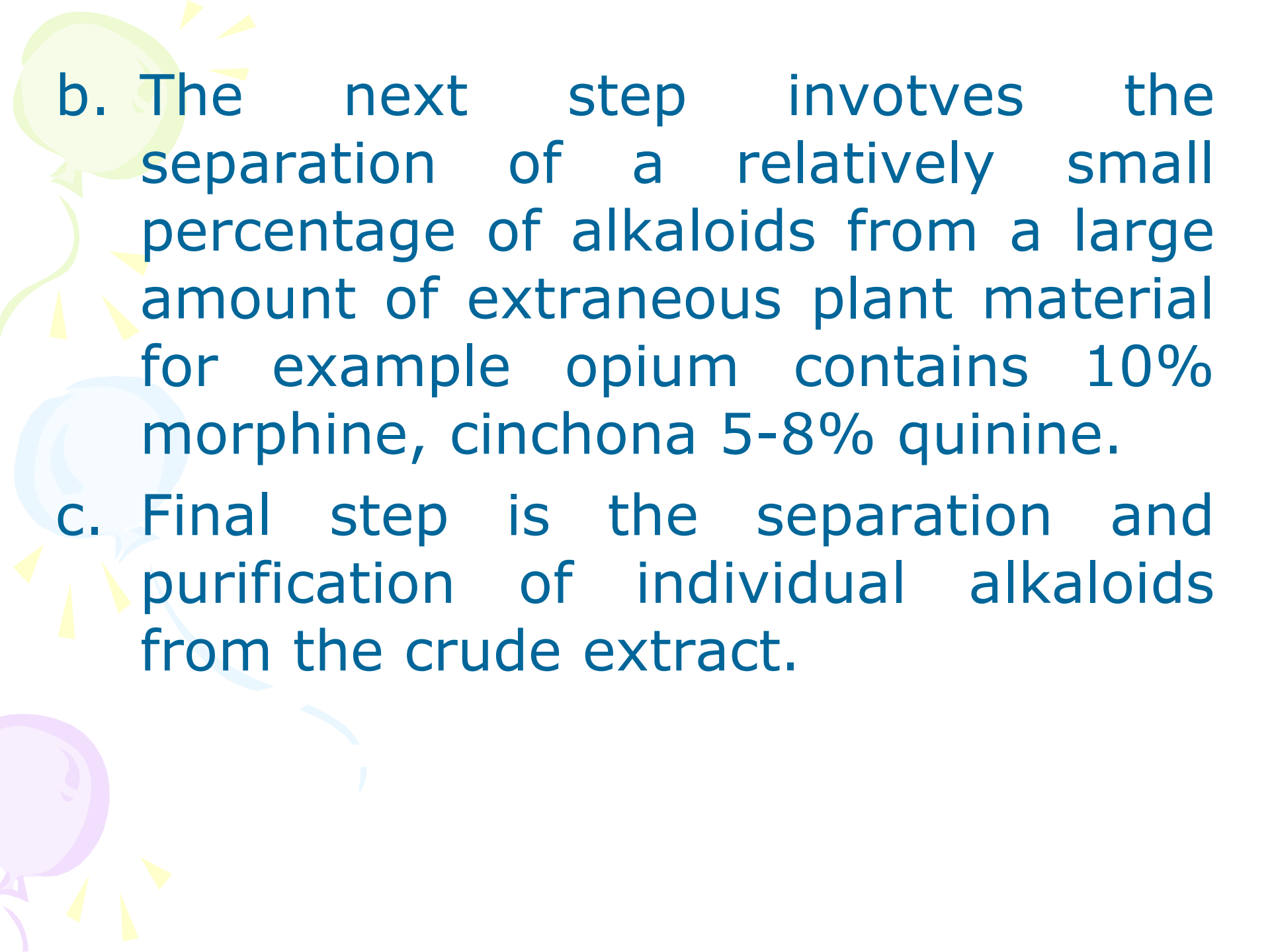
A few alkaloids are named according to their Physiological action such as morphine (Ger. morphin - God of dreams), norcotine (GK-norkoo-to benumb).

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- ❑ The names of minor alkaloids are derived by adding one prefix or suffix to the name of principal alkaloid eg. The name narcotine, cotarnine, and tarconine are derived by the name cinchonine which is the principal alkaloid of einchona series.
 - ❑ Prefixes such as epi, iso neo pseudo have been used to designate. isomesic or slightly modified structures.

ISOLATION OF ALKALOIDS:-

a. First of all, the presence of an alkaloid in plant is ascertained by employing various reagents called alkaloids reagents such as tannic acid, picric acid, perchloric acid, potassium mercuric iodide (Mayer's reagent), iodine dissolved in potassium iodide (Wegner's reagent), potassium bismuth iodide (Dragendoff's reagent), phosphomolybdic acid (Sonneuschein's reagent) with which the alkaloids either give a precipitate or turbidity.

These precipitates have characteristic colours and are used for the detection of alkaloids in very small amount.

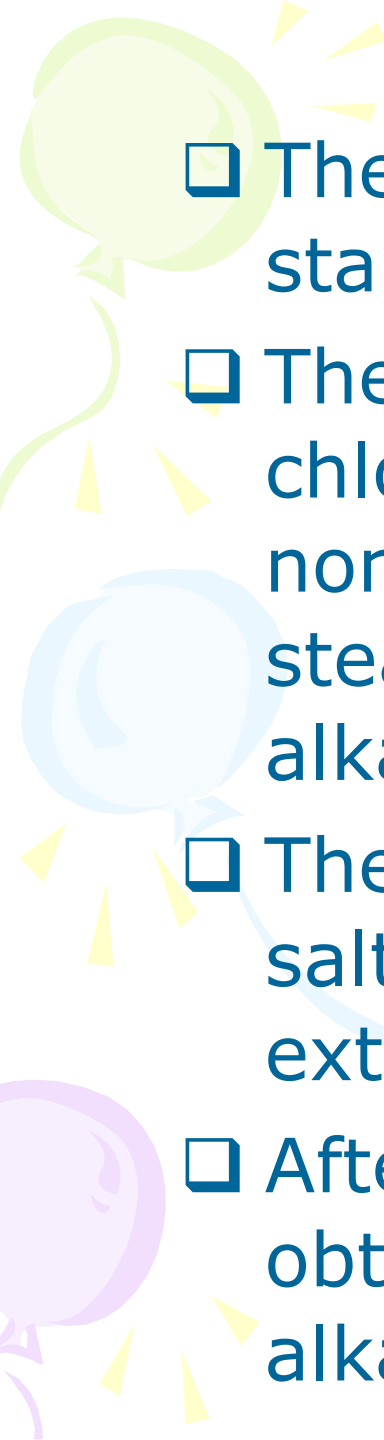


b. The next step involves the separation of a relatively small percentage of alkaloids from a large amount of extraneous plant material for example opium contains 10% morphine, cinchona 5-8% quinine.

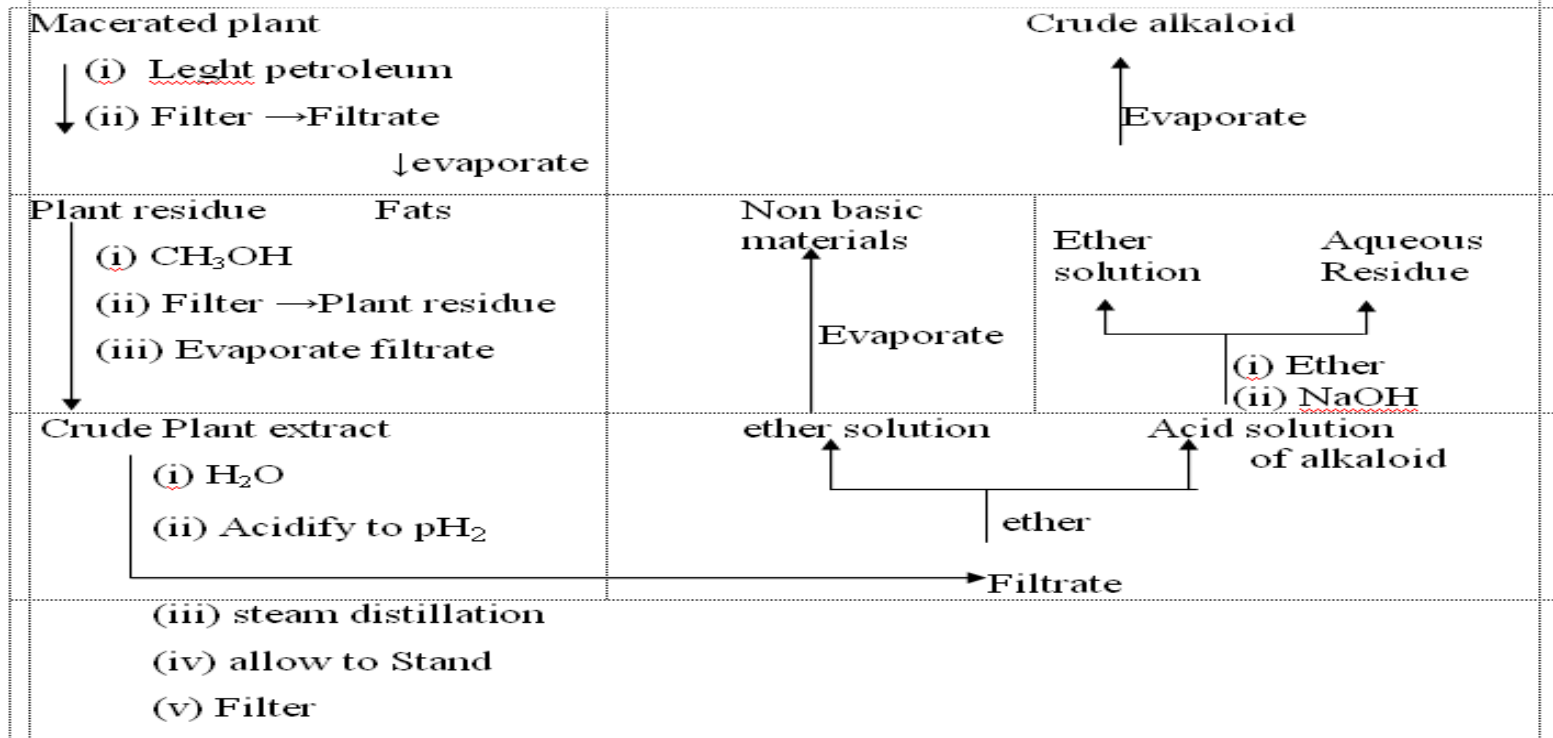
c. Final step is the separation and purification of individual alkaloids from the crude extract.

A general procedure recommended by Manske are as-

- The dried and powdered plants material is first extracted with petroleum ether (if it is rich in fat and then filtered for the removal of soluble fats.
- The residue is then extracted with CH_3OH to remove cellulosic and other insoluble material .
- The filtrate so obtained is evaporated.
- The evaporated mass is dissolved in water, acidified to $\text{pH} 2$ and steam distilled to remove methyl alcohol.

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- ❑ The residual solution is allowed to stand for several days in a refrigerator.
 - ❑ The filtrate is extracted with ether or chloroform to remove water soluble non basic organic material and then steam distilled when the steam volatile alkaloids are separated.
 - ❑ The solution of the rest of the alkaloid salts is made alkaline and again extracted with ether or chloroform.
 - ❑ After this extraction ethereal layer obtained is evaporated to give crude alkaloids.

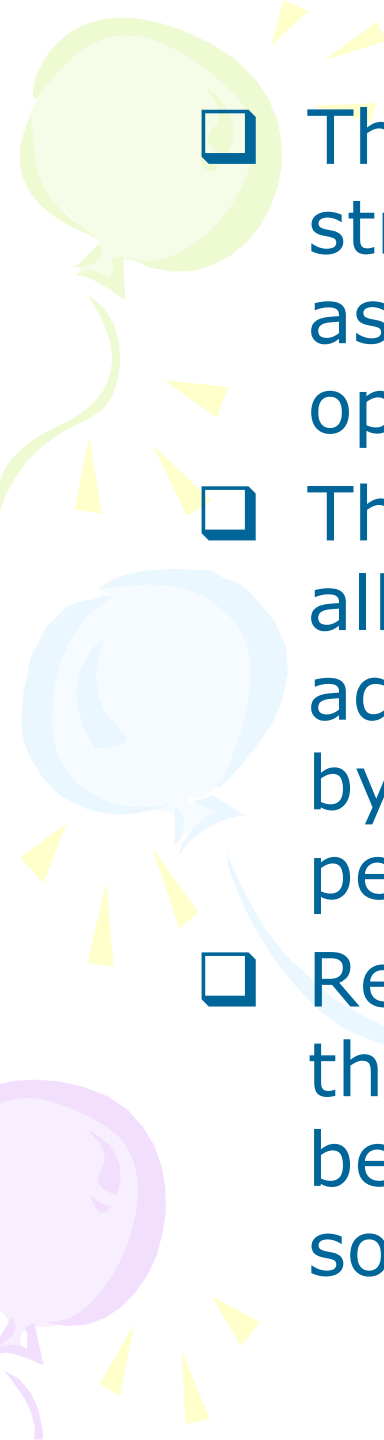
GRAPHICAL REPRESENTATION FOR ISOLATION




□ The resulting crude alkaloid mixture is separated into individual alkaloids by means of fractional crystallization, fractional precipitation, column chromatography and counter current extraction.

Determination of molecular structure of alkaloids

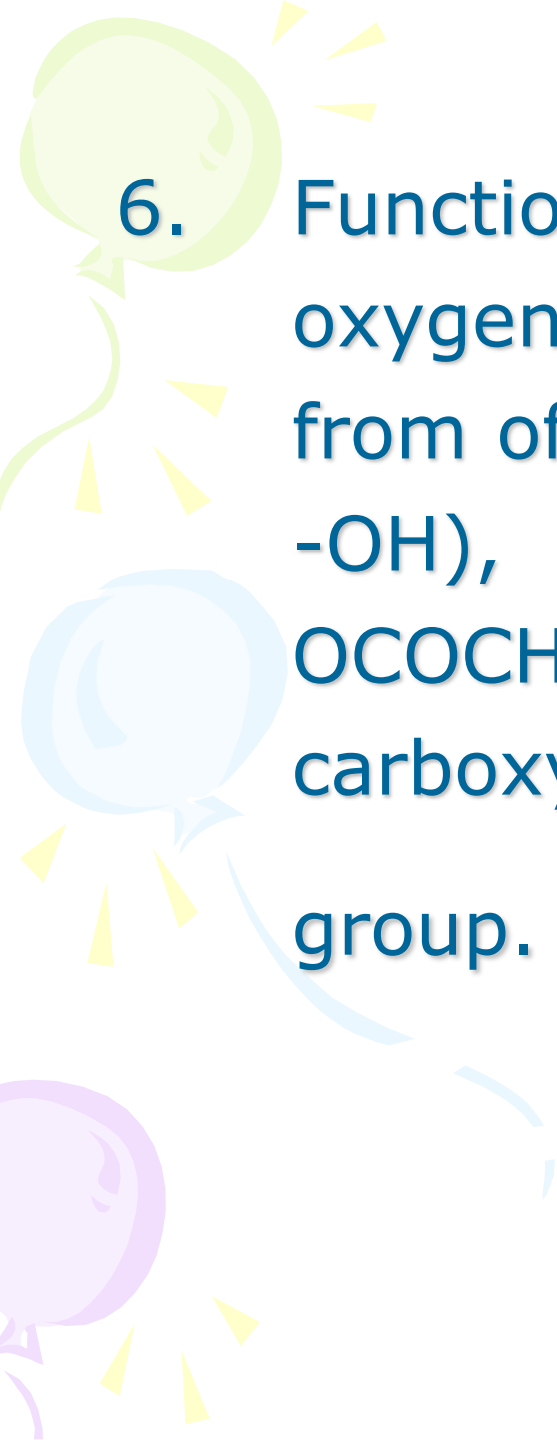
- ❑ As the molecular structure of majority of alkaloids is quite complex, very little progress was achieved in the elucidation of their structures during 19th century.
- ❑ But now the new methods for the identification of unknown substances are known.
- ❑ Therefore, it becomes possible to establish the molecular structure of all the known simple as well as complex, alkaloids.
- ❑ In general, the molecular structure of an alkaloids is elucidated according to the following steps:-

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- ❑ The first step in determining the structure of pure alkaloid consists in ascertaining its molecular formula and optical rotatory power .
 - ❑ The presence of unsaturation in an alkaloid may be ascertained by the addition of bromine or halogen acids or by hydroxylation with dilute alkaline permanganate.
 - ❑ Reduction may also be used to show the presence of unsaturation. This can be done by reagents LiAlH_4 and sodium borohydride.

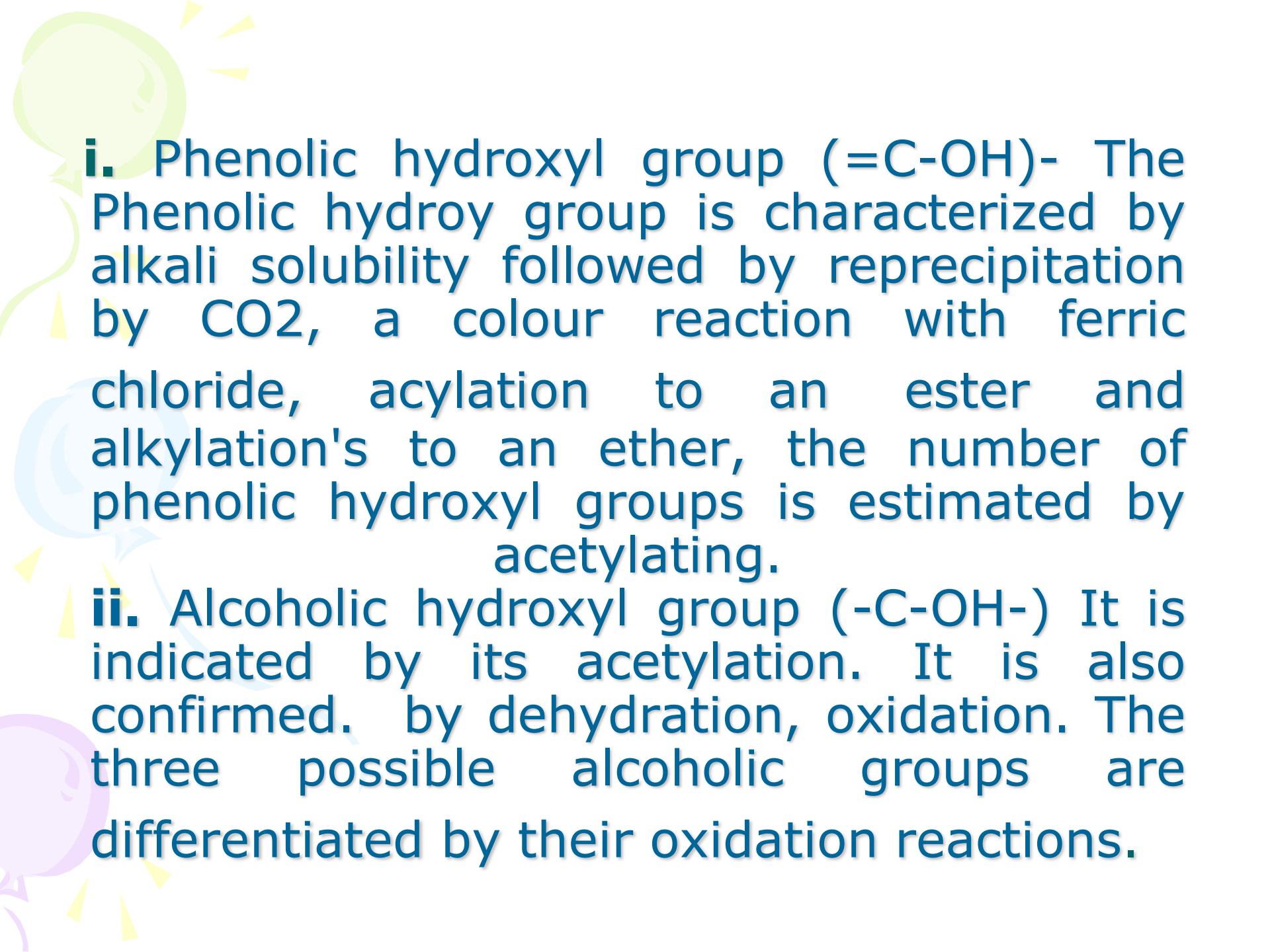


4. An alkaloid is cleaved into simple fragments by hydrolysis with water, acid or alkali. For example, piperine, on hydrolysis gives piperidine and piperic acid indicating that the two fragments are linked with each other by means of an acid amide linkage.

5. The next step involves in ascertaining the functional nature of oxygen and nitrogen atoms either in the molecule itself or in its fragments obtained by hydrolysis.



6. Functional nature of oxygen:- The oxygen atom may be present in the form of alcoholic or phenolic hydroxyl (-OH), methoxyl (-OCH₃), acetoxy (-OCOCH₃), benzyloxy (-OCOC₆H₅), carboxyl (-COOH) or carbonyl (C=O) group.



i. Phenolic hydroxyl group ($=C-OH$)- The Phenolic hydroxyl group is characterized by alkali solubility followed by reprecipitation by CO_2 , a colour reaction with ferric chloride, acylation to an ester and alkylation's to an ether, the number of phenolic hydroxyl groups is estimated by acetylating.

ii. Alcoholic hydroxyl group ($-C-OH-$) It is indicated by its acetylation. It is also confirmed by dehydration, oxidation. The three possible alcoholic groups are differentiated by their oxidation reactions.




a. Primary alcohol (-CH₂OH)-

On oxidation gives first an aldehyde and then acid both having the same number of carbon atoms as the parent alcohol.



b. Secondary alcohol (>CHOH)

On oxidation first gives ketone having same number of carbon atoms and then acid with fewer number of carbon atoms..



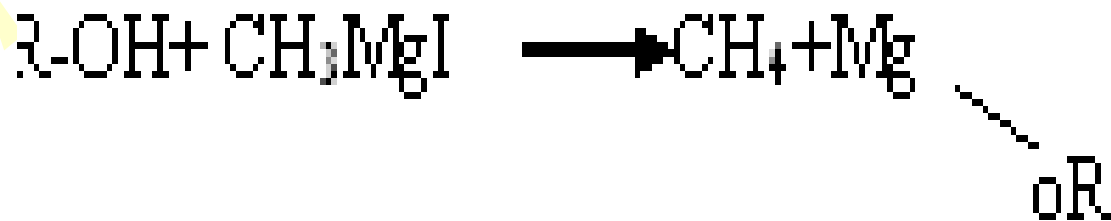


c. Tertiary alcohol: on oxidation gives ketone and acid both having fewer number of carbon atoms.

- The number of alcoholic hydroxyl groups can be determined by Zerewitinoff active hydrogen determination.

□ It consists in heating the alcohol with methyl magnesium iodide and measuring the methane so formed.

the methane so formed.



$CH_4 = 22.4$ letters of alcohol at N.T.P

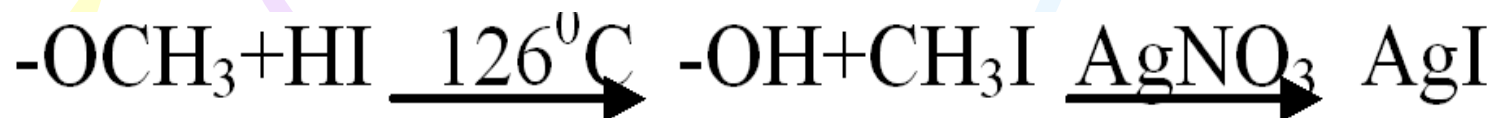
A decorative graphic on the left side of the slide features a light green balloon at the top, a light blue balloon in the middle, and a light purple balloon at the bottom. Yellow streamers and triangular shapes are scattered around the balloons.


Carboxyl Group) (-COOH)

- ❑ The carboxylic group is indicated by its solubility weak bases, like NaHCO_3 , NH_3 etc. esterification with alcohols and specific absorption in the infrared.
- ❑ The acidic groups are generally estimated quantitatively either by acid-alkali titration or by silver salt method.

Alkoxy group (-OR)

- ❑ The alkoxy group generally methoxy (-OCH₃) and - OGH₅ occur in the alkaloids
- ❑ It is detected by zeisel method, which involves boiling of the alkaloid with concentrated hydriodic acid at its boiling point (1260C)where the alkoxy groups are converted into alkyl halides which is estimated as silver iodide by treatment with ethenolic silver nitrate.



A decorative vertical strip on the left side of the slide features three balloons: a light green one at the top, a light blue one in the middle, and a light purple one at the bottom. Each balloon is attached to a thin, wavy string and has several small, yellow, triangular shapes radiating from its base, resembling sunbeams or streamers.

□ The number of moles of silver iodide indicate the number of alcoholic groups in the alkaloid.

Carbonyl group ($>C=O$)

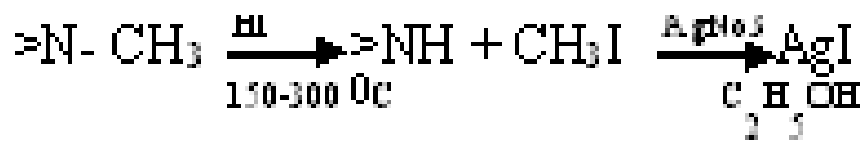
- ❑ Carbonyl groups such as aldehyde or ketones are detected by the carbonyl reagent, such as hydroxylamine, phenyl hydrazine, 2,4-dinitrophenyl hydrazine.
- ❑ Distinction between an aldehydic and a ketone group can be made on the basis of reduction and oxidation reactions.
- ❑ The presence of a carboxyl group and distinction between an aldehyde and a ketone may be further confirmed by spectroscopic means like infrared, ultraviolet and nuclear magnetic resonance.

Ester group (-OCOR)-

- Esters such as $-OCOCH_3$, $-OCOC_6H_5$ and related groups like amides, lactone, lactam are detected by their hydrolysis with water, dilute acids, alkali to the hydroxyl and acidic compounds.
- The nature is established by knowing the nature of the acid
- $-CONH_2 + NaOH \xrightarrow{\text{Heat}} -COONa + NH_3$
- $-COOR_1 + NaOH \xrightarrow{\text{Heat}} -COONa + R_1OH$


Functional nature of nitrogen

- ❑ In most of the alkaloids the nitrogen atom is involved in a ring structure.
- ❑ Nitrogen may be secondary (>NH) or tertiary (>N-CH₃ or >N-)
- ❑ The N- alkyl groups estimated by Herzog Meyer method in which the alkaloid is heated with hydriodic acid at about 1500-3000C under pressure. Whereby the alkyl groups are converted into alkyl iodides which are estimated as silver iodide by means of alcoholic silver nitrate.






□ NMR Spectroscopy may also be utilized for the rapid detection of N-methyl and N-ethyl groups in alkaloids.

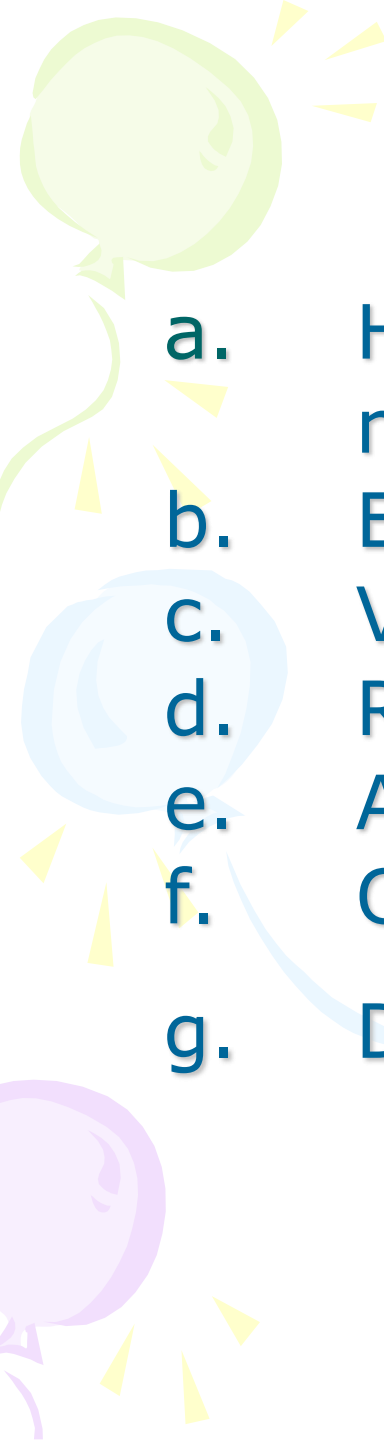


□ An alkaloid on distillation with aqueous potassium hydroxide gives methylamine, demethylamine or triethylamine indicating that one two or three alkyl groups are attached to the nitrogen atom, while if ammonia is formed it indicates the presence of a free amino group



Degradation of alkaloids.

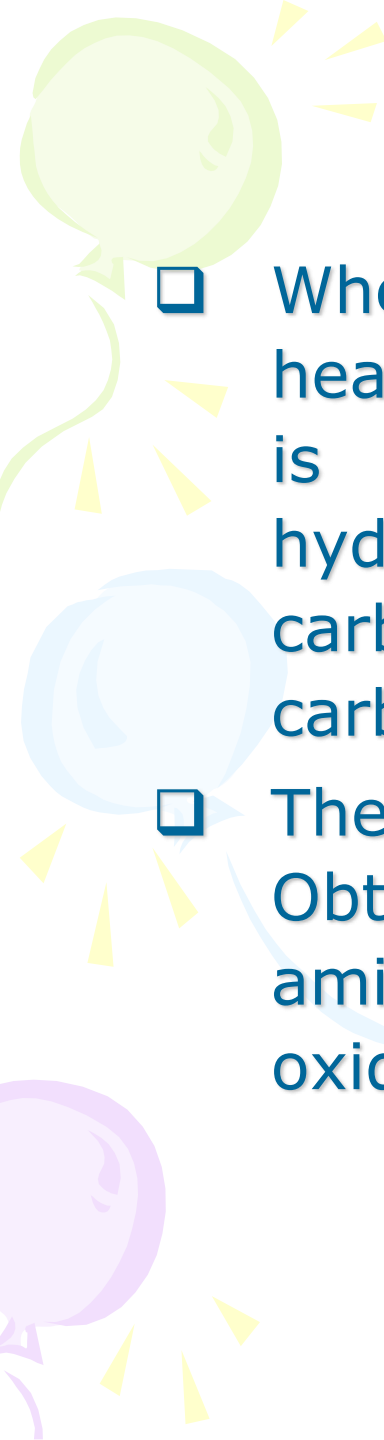
- ❑ This is the most important step in elucidating the structure of a compound
- ❑ It gives rise to certain identifiable products of well known structure and hence by knowing the changes during the degradation and the structure of the degraded products it is easy to know the structure of the original molecule.
- ❑ The various degradative reactions used in elucidating the structure of alkaloids are

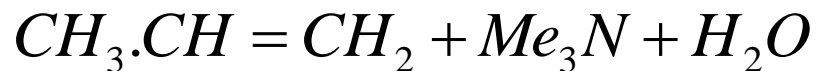
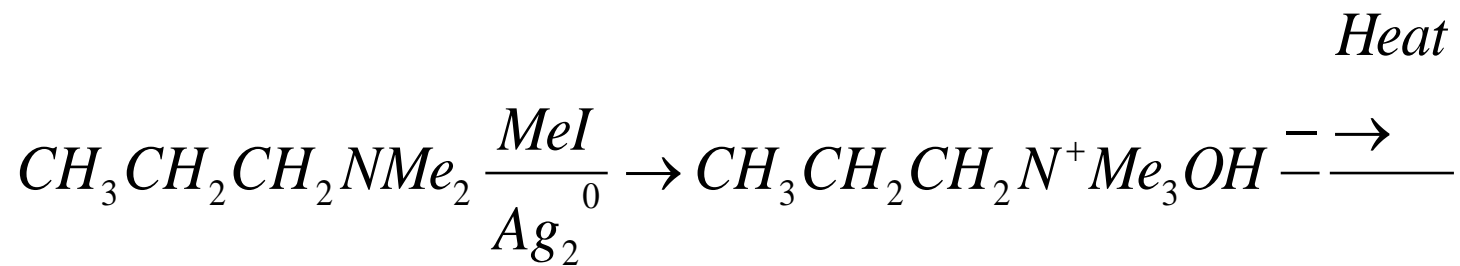
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- a. Hofmann exhaustive methylation method
 - b. Emde's degradation
 - c. Von Braun's method
 - d. Reductive degradation
 - e. Alkali fusion
 - f. Oxidation
 - g. Dehydrogenation

Hafmann exhaustive methylation method:-


This method is used for opening the heterocyclic rings with elimination nitrogen to give aliphatic compounds.

- ❑ This method was first applied to the structure of naturally occurring alkaloids by wills taller in in 1870.
- ❑ Later on it was developed by by Hafmann known as Hofmann's Exhaustive methylation.

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- ❑ When quaternary ammonium hydroxide are heated they decomposed and water molecule is evolved. (hydroxide group from the hydroxide and hydrogen atom from the β -carbon with respect to nitrogen) and nitrogen-carbon linkage broke down to give an olefin.
 - ❑ The quaternary ammonium hydroxide is Obtained by the complete methylation of the amine followed by hydrolysis with silver oxide.



Quaternary ammonium hydroxide.

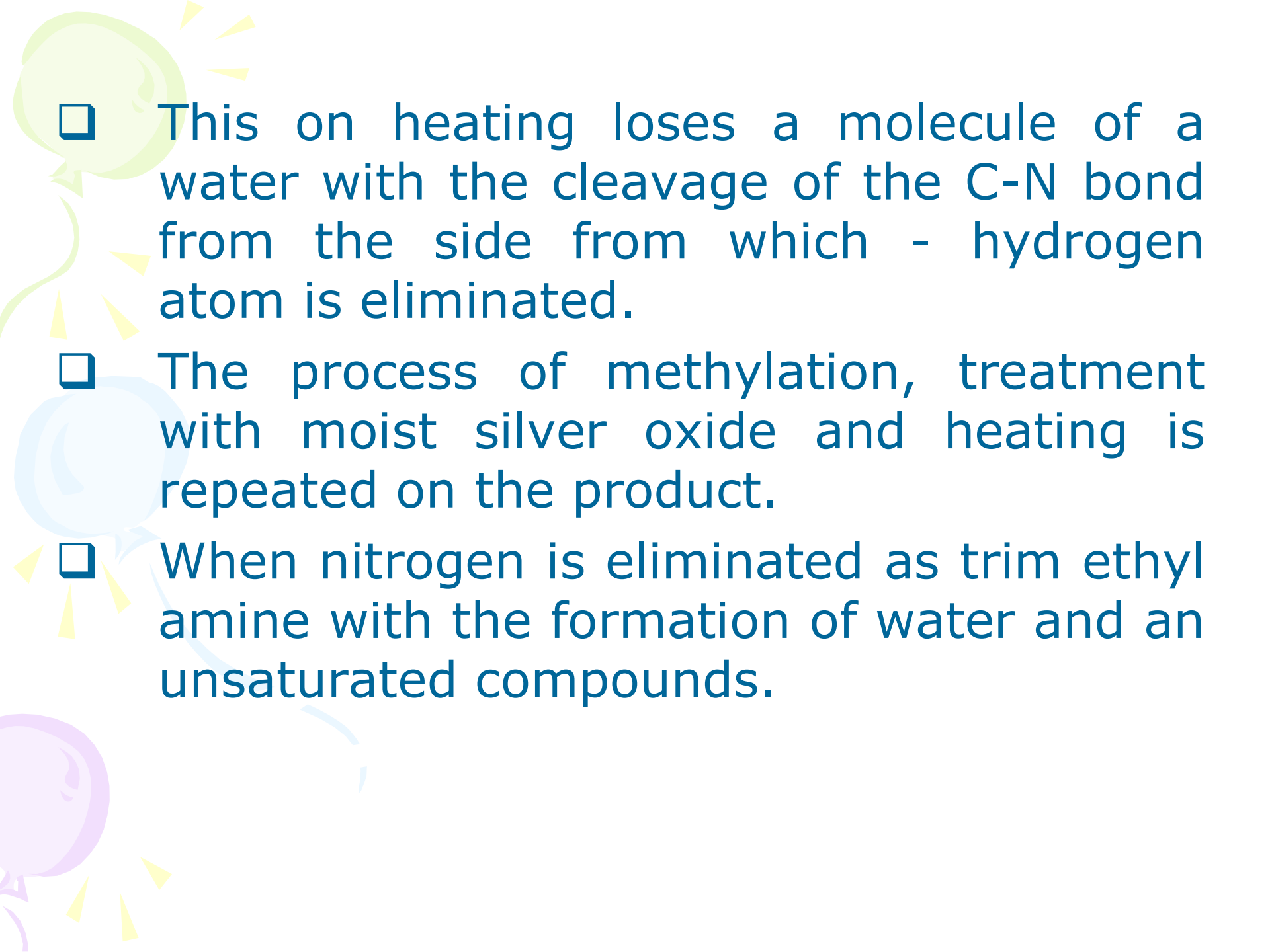
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- ❑ This method is applicable to reduced ring systems such as piperidene.
 - ❑ It fails with unsaturated compounds like pyridine hence the pyridine should first be converted into piperidene.
 - ❑ The process of Hofmann Exhaustive methylation can be explained with the degradation of pyridine.



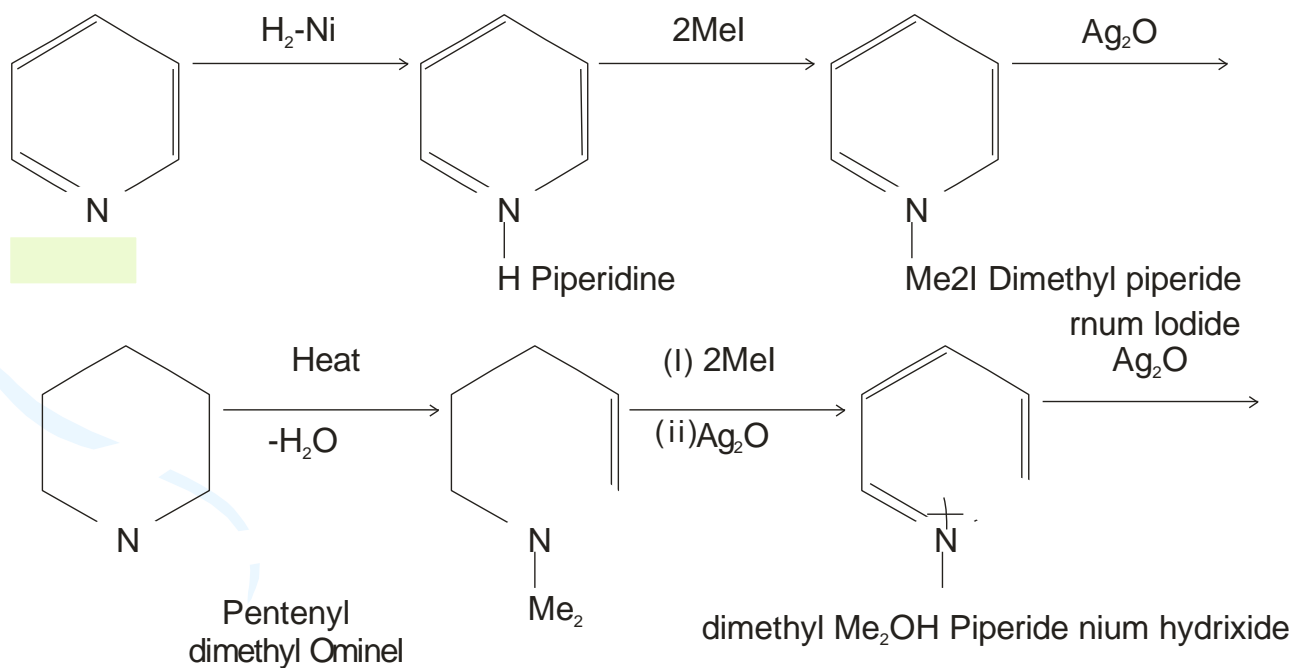
Pyridine is first reduced by catalytic hydrogenation to piperidine

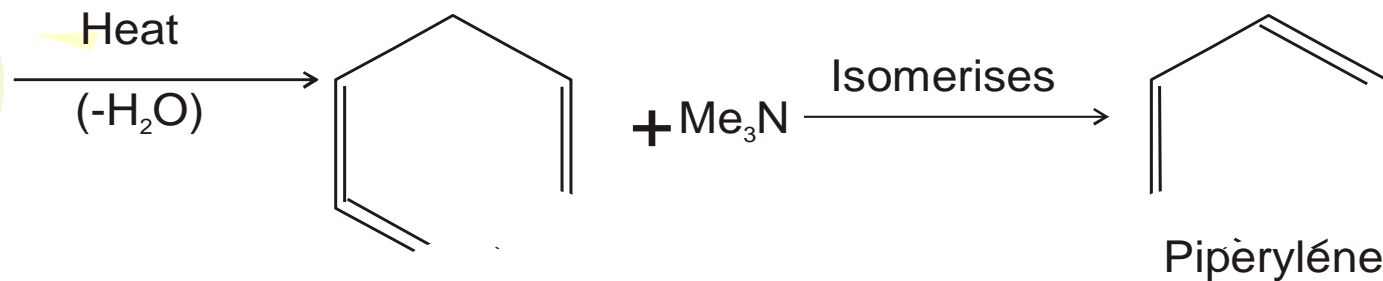
Which on treatment with excess of methyl iodide to give quaternary ammonium iodide.

Quaternary ammonium iodide on treatment with moist silver oxide or KOH give quaternary ammonium hydroxide.

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- ❑ This on heating loses a molecule of a water with the cleavage of the C-N bond from the side from which - hydrogen atom is eliminated.
 - ❑ The process of methylation, treatment with moist silver oxide and heating is repeated on the product.
 - ❑ When nitrogen is eliminated as trimethylamine with the formation of water and an unsaturated compounds.

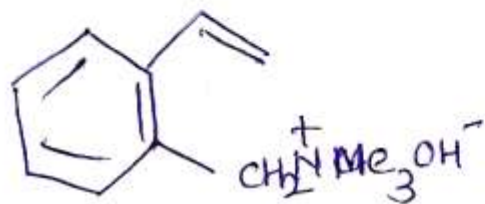
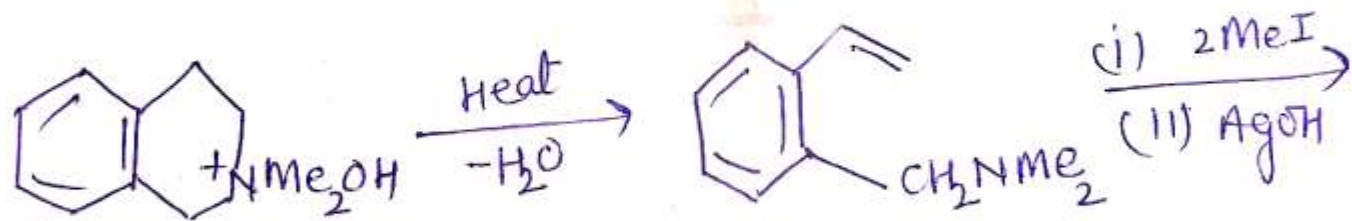
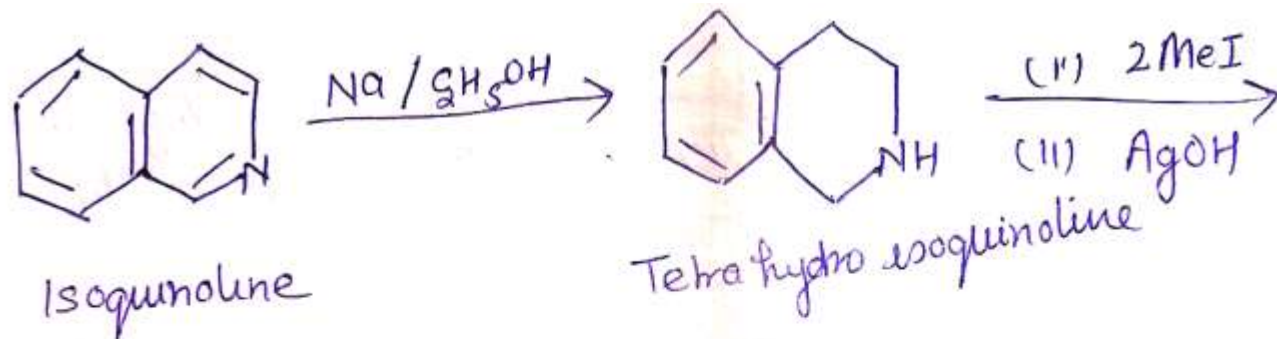
- The compounds then isomerises to the more stable conjugated diene.

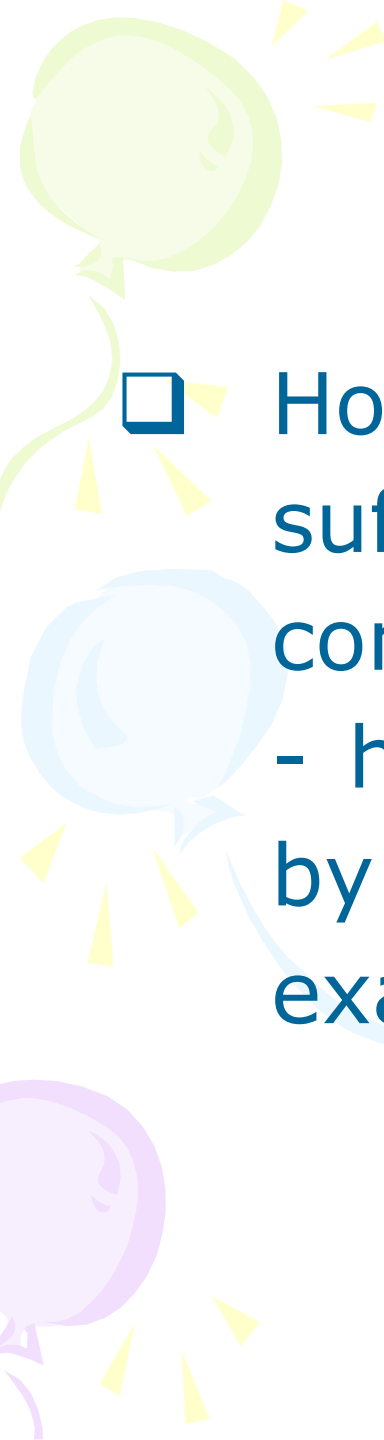




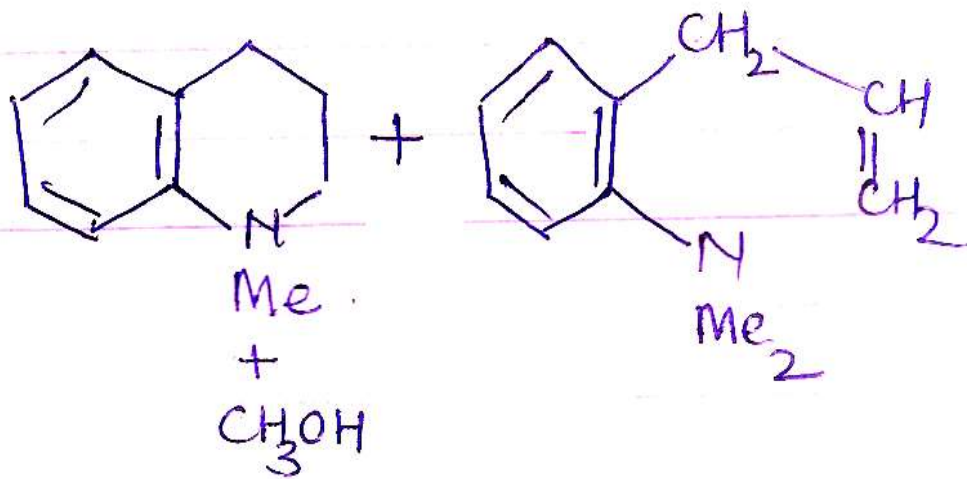
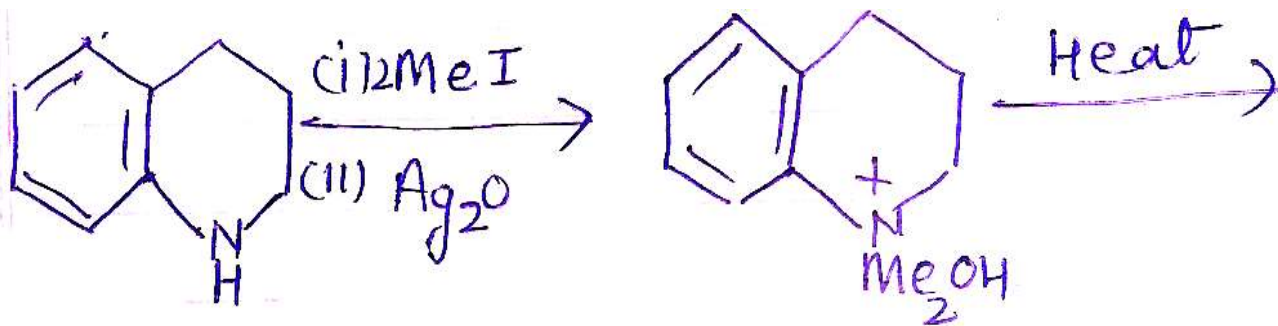
□ In the elimination of a molecule of water from quaternary ammonium hydroxide hydrogen atom always eliminates from the β -Position. If it is not available the reaction fails.

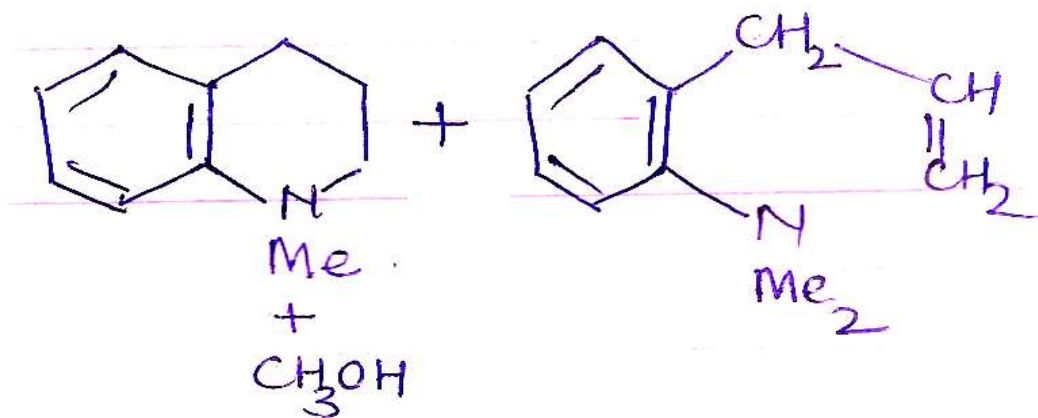
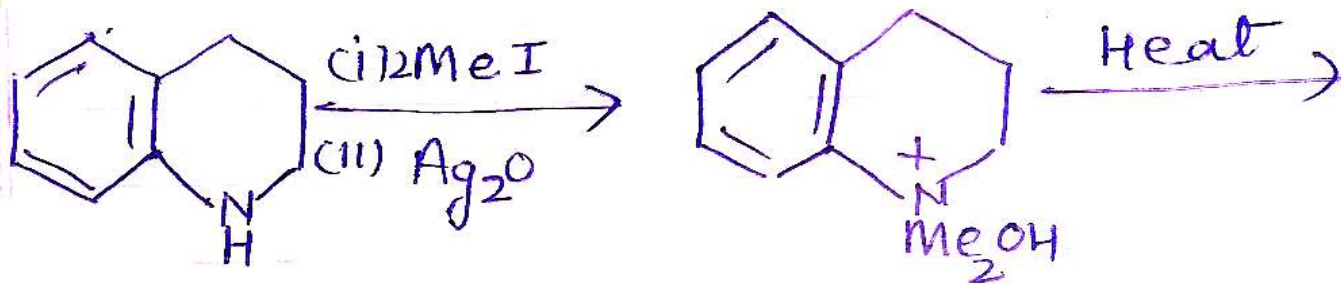
□ For example, is oquinoline is degraded only one time by H.E.M method and it is not possible to remove nitrogen from the product by this method.





❑ However, the Hofmann's method suffers from the defect that some compounds even though containing - hydrogen atom are not degraded by exhaustive methylation . for example tetra hydro quinolines.

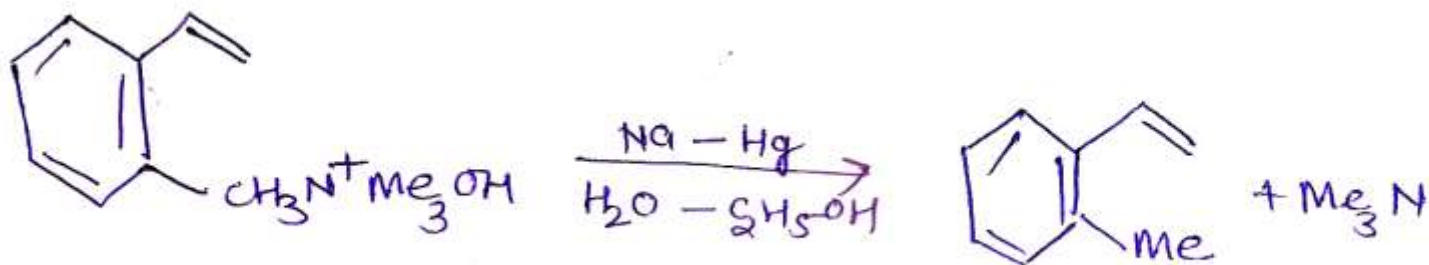
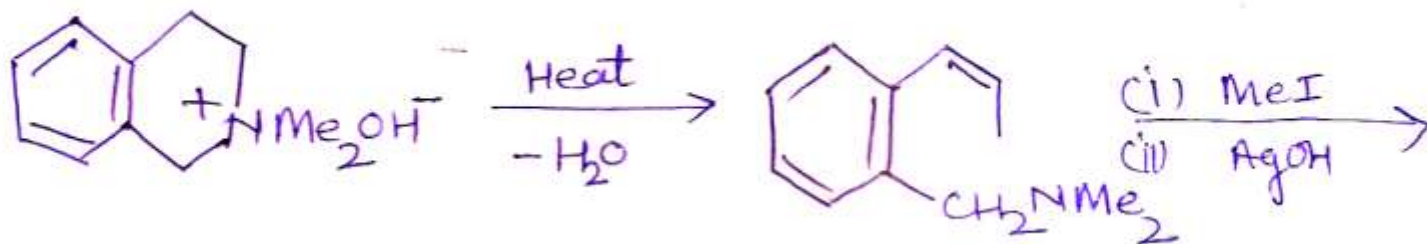
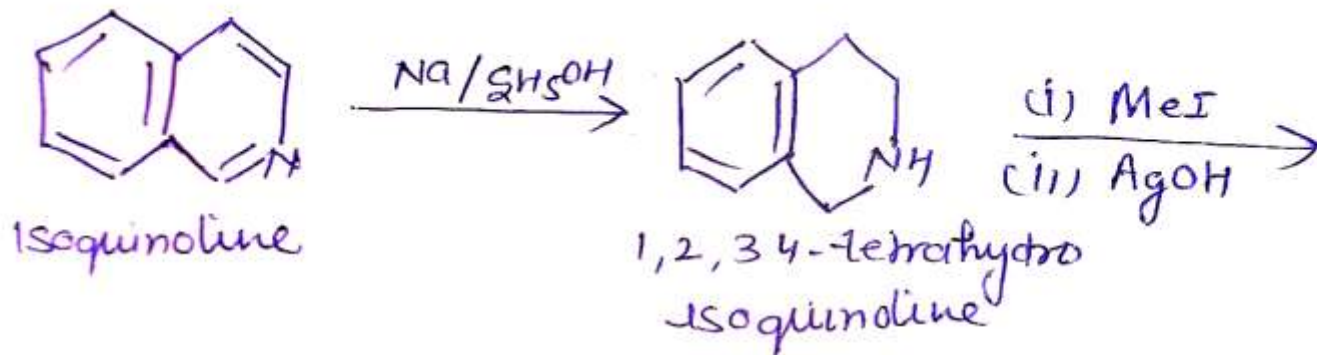




Emde method :-

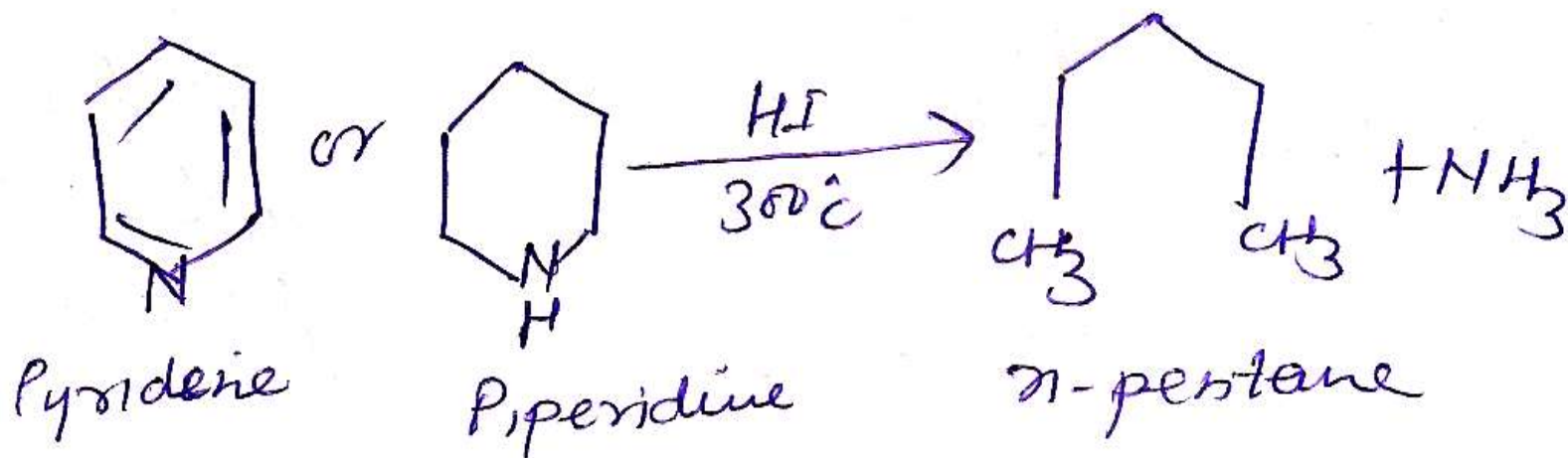
If the alkaloid does not contain β -hydrogen atom, the Hofmann exhaustive methylation method fails.

- ❑ In such cases Emde's method may be employed.
- ❑ In this an aqueous or alcoholic solution of the quaternary ammonium halide is reduced with sodium amalgam in aqueous ethanol, sodium in liquid ammonia or by catalytic hydrogenation.
- ❑ For example, Emde's method explains the degradation of isoquinoline.



Reductive degradation:-

- The pyridene or piperidine nuclei in some cases may be eliminated as ammonia and n-pentane by heating with hydriodic acid at -300°C .




Zinc dust distillation :-

Distillation of an alkaloid or its product over hot zinc dust degrades it to a stable aromatic derivative.


- ❑ For example, morphine gives phenanthrene on distillation with Zinc dust.
- ❑ Conine gives 2 propyl pyridine.
- ❑ Cinchonine gives quinoline with alkali.
- ❑ Thus these products indicate that morphine and cinchonine has phenanthrene and quinoline nuclei in their structures.

Alkali fusion:-

- Fusion of certain alkaloids with solid potassium hydroxide produces relatively simple fragments, the nature of which will give information of the type of nuclei present in the molecule.

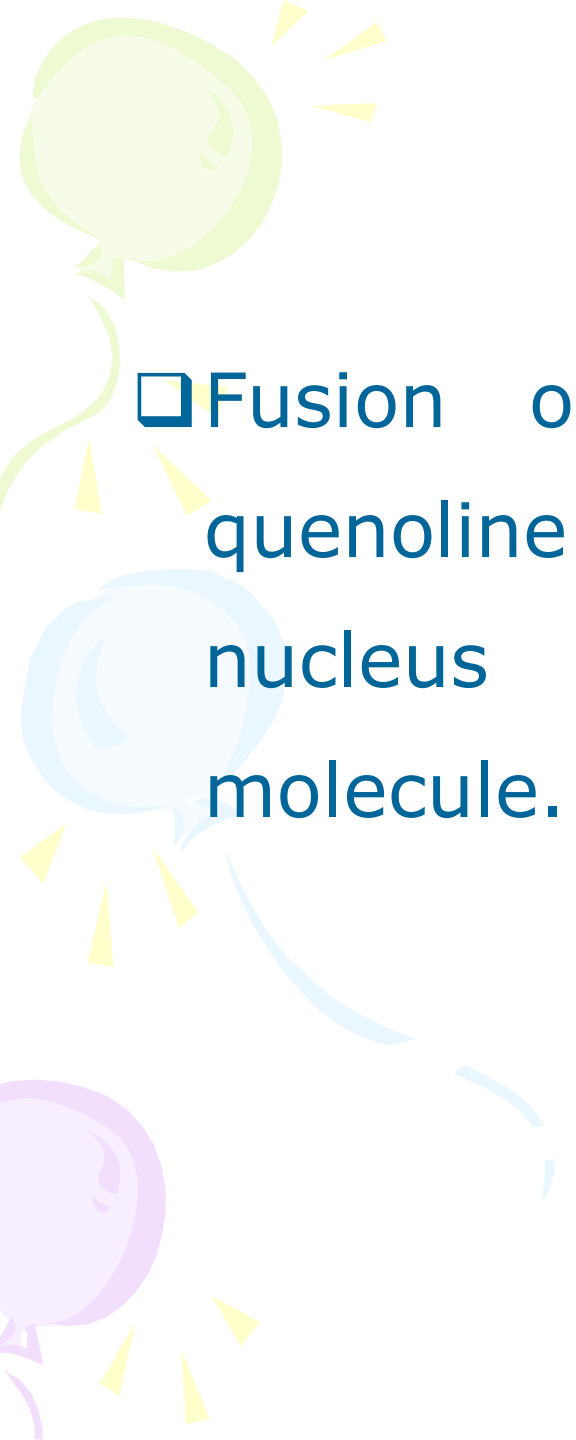


□ For example, adrenaline on fusion with solid KOH yields protocatechuic acid which indicates the latter nucleus in its structure.



□ Fusion of papaverine with KOH to give isoquinoline indicates the latter nucleus in the former molecule.

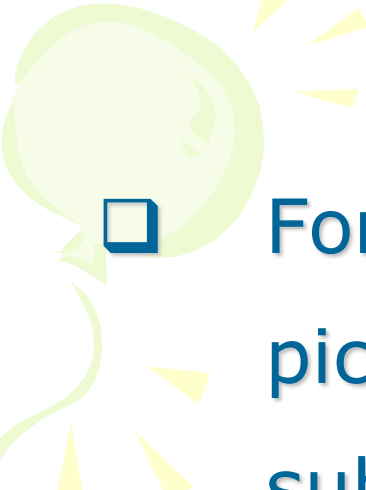


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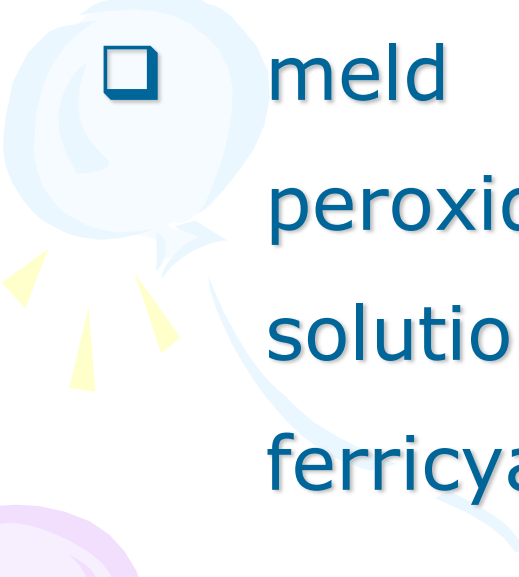
☐ Fusion of colchicine with alkali yield quinoline again shows that quinoline nucleus is present in the colchicine molecule.

Oxidation :-

Oxidation gives valuable information about the fundamental structure of alkaloids and the position and nature of some of the fundamental group or side chain such $C=C$, $-CHOH$.



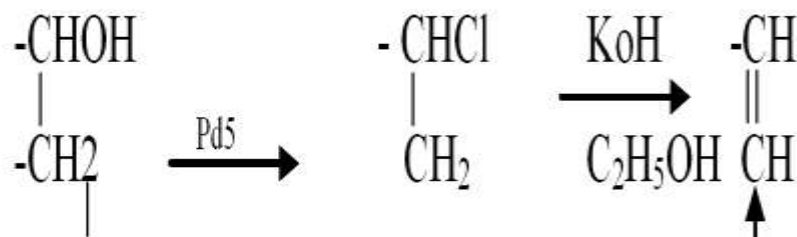
□ For example oxidation of conine to picolinic acid, indicates that conine is -substituted derivative.

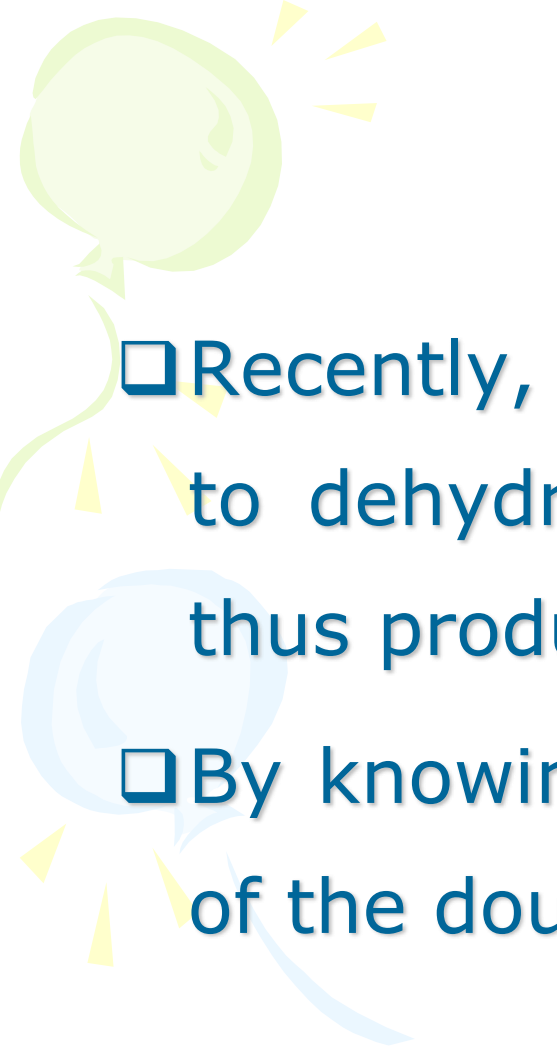


□ mild oxidation done by hydrogen peroxide, ozone, iodine in ethanolic solution or alkaline potassium ferricyanide.


□ Moderate oxidation by means of and or alkaline potassium permanganate or chromium trioxide in acetic acid

□ In cases, where possible, the compound should first be converted into an unsaturated compound which is then oxidized at the double bond





□ Recently, mercuric acetate has been used to dehydrogenate certain alkaloids which thus produces double bond.



□ By knowing the oxidation products, position of the double bond is easily established.

