

Notes on Alkaloids

By
Dr. Ganaptri Saikia
Nowgong Girls' College

Introduction

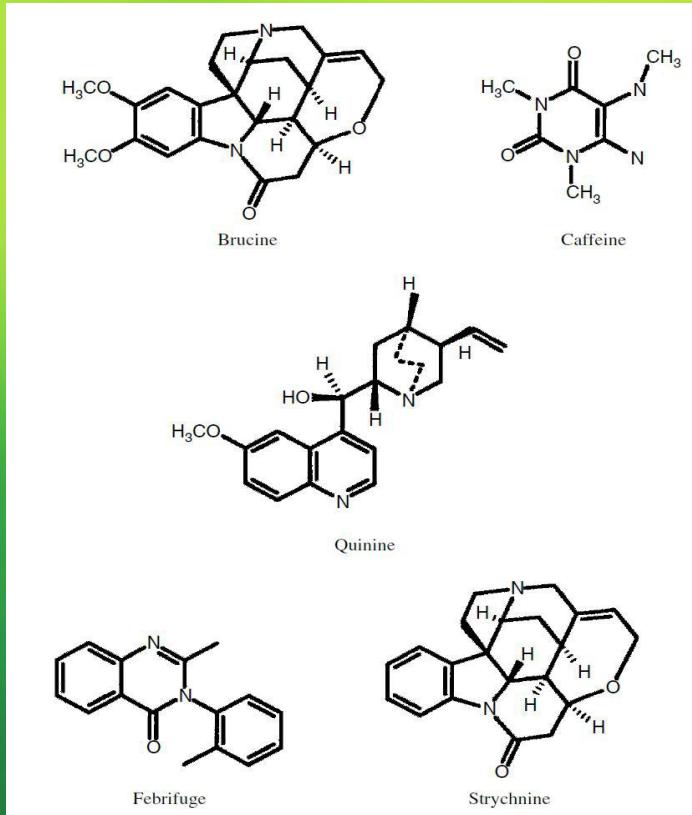
❖ The term alkaloid or alkali-like was proposed by pharmacist W. Meissner in 1819 for basic, nitrogen containing compounds of plant origin.

❖ Alkaloids are naturally occurring compounds containing carbon, hydrogen, nitrogen, and usually oxygen and are primarily found in plants, especially in certain flowering plants

❖ Generally, alkaloids are defined as physiologically active basic compounds of plant origin in which at least one nitrogen atom forms part of a cyclic system.

❖ Plant alkaloids, one of the largest groups of natural products, represent a highly diverse group of chemical entities.

❖ Many of these compounds possess potent pharmacological effects. For example, the well known plant alkaloids include the narcotic analgesics, morphine and codeine, apomorphine (a derivative of morphine) used in Parkinson's disease, the muscle relaxant papaverine, and the antimicrobial agents sanguinarine and berberine. Also several potent anti-cancer drugs have been developed from plant compounds



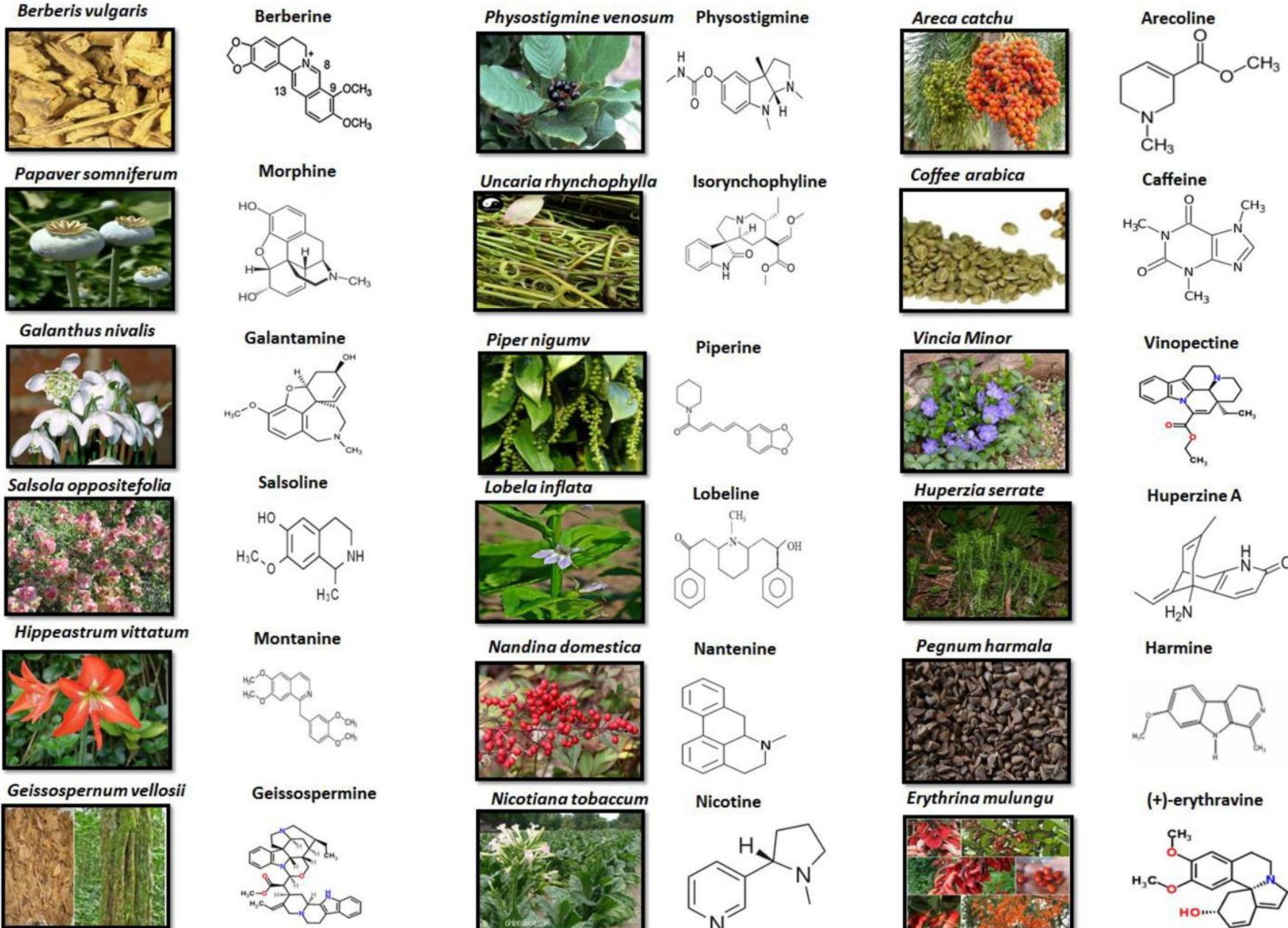
Natural occurrence

❖ Alkaloids encompass an enormous class of approximately 12,000 natural products, distributed throughout known vascular plants. They are rarely found in lower plants like algae, fungi etc. The alkaloids occur in the leaves, seeds, roots and bark of nearly 40 plant species. Alkaloid content of plants varies with the season, age and its locality. Closely related alkaloids generally occur together in the same plant, e.g. nearly 20 alkaloids have been isolated from opium. It is also generally observed that a given genus of related genera possesses the same or structurally related alkaloids, e.g. seven different genera of the family Solanaceae contain hyoscyamine. Further, simple alkaloids often occur in various different unrelated plants, while the more complicated ones such as quinine, nicotine, colchicine, etc. generally occur in one species.

Since alkaloids are basic in nature, it is expected that in plants they exist as salt of plant acids such as acetic, oxalic, citric, malic, lactic, tartaric, tannic acid etc. Some alkaloids are also found to occur free, as glycosides, as amides or as esters or organic acids.

General structural features of alkaloids

The chemical structure of alkaloids are extremely variable. Generally alkaloid contains at least one nitrogen atom in its structure which is responsible for the basicity of alkaloids. They are generally tertiary nitrogen compounds and contain one or two nitrogen atoms usually in the tertiary state in a ring system, most of the alkaloids also contain oxygen.



General properties of alkaloids

- ❖ The alkaloids are usually colourless, crystalline, non-volatile solids which are insoluble in water, but are soluble in ethanol, ether, chloroform, etc.
- ❖ Some alkaloids are liquids which are soluble in water, e.g. coniine and nicotine.
- ❖ A few are coloured, e.g. berberine is yellow.
- ❖ Most alkaloids have a bitter taste and are optically active (laevorotatory).
- ❖ The optically active alkaloids are very useful for resolving racemic acids.
- ❖ The alkaloids form insoluble precipitates with solutions of phosphotungstic acid, phosphomolybdic acid, picric acid etc. Many of these precipitates have definite crystalline shapes and so may be used to help in the identification of an alkaloid.

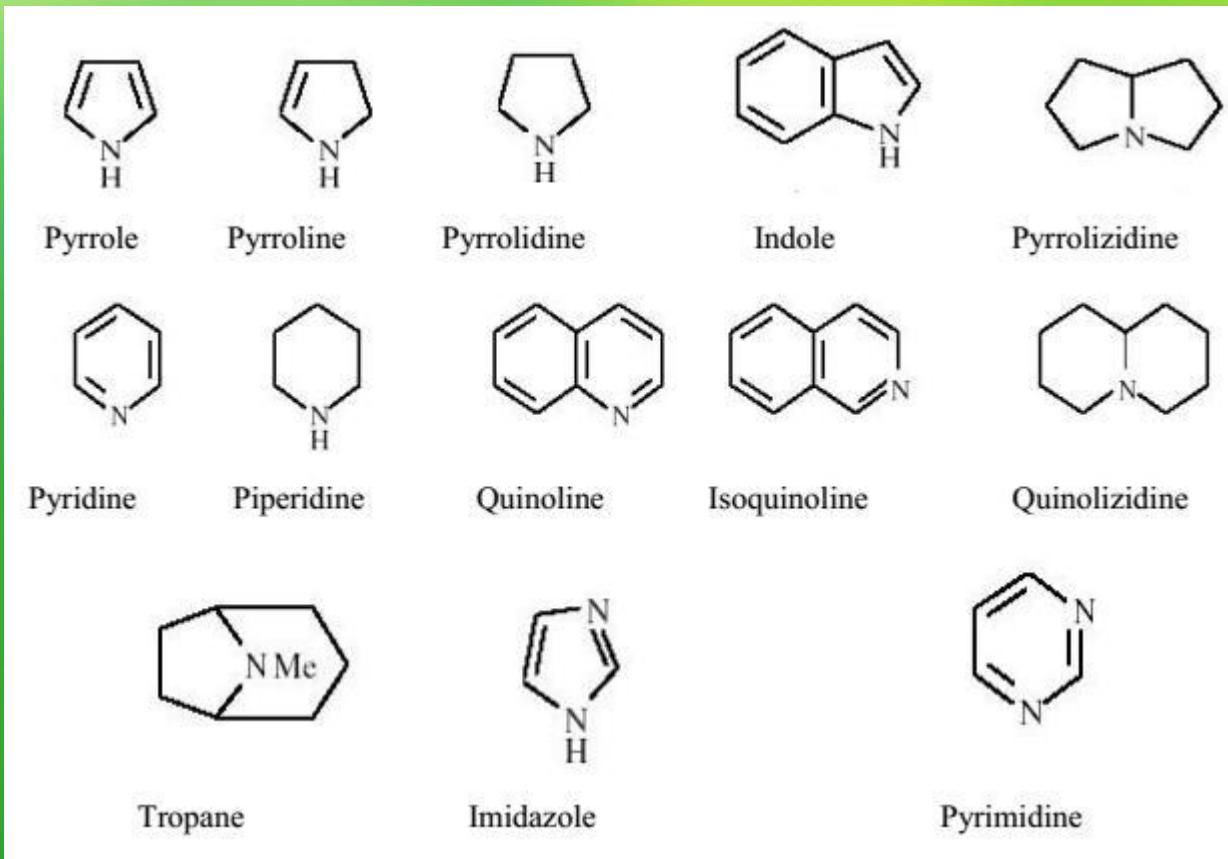
Classification of alkaloids

Alkaloids are chiefly classified according to the main ring system which is common to a group of alkaloids-

- ❖ Phenylethylamine alkaloids
- ❖ Pyrrolidone alkaloids
- ❖ Pyridine or piperidine alkaloids
- ❖ Pyridine-pyrrolidine alkaloids
- ❖ Tropane alkaloids
- ❖ Quinoline alkaloids
- ❖ Isoquinoline alkaloids
- ❖ Phenanthrene alkaloids
- ❖ Indole alkaloids
- ❖ Tropolone alkaloids



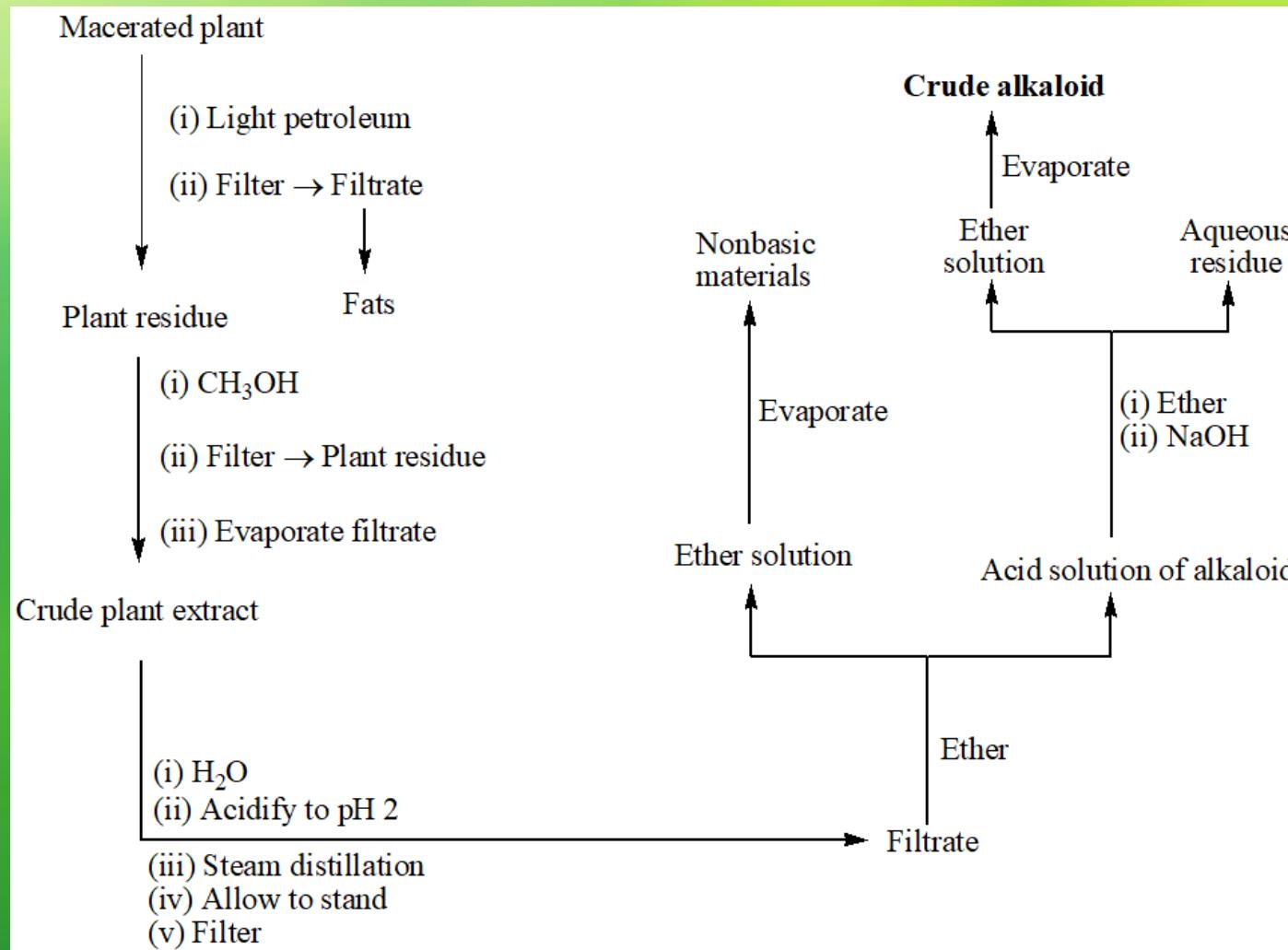
Heterocyclic structure of skeleton constituting group of alkaloids



Isolation of alkaloids

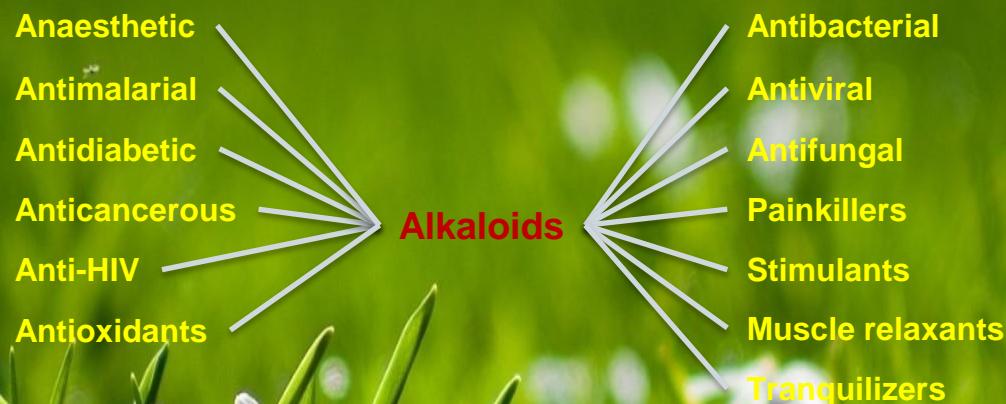
A common method of isolation of alkaloids as follows:

- ❖ First the plant is dried, and then finely powdered.
- ❖ The dried and powdered plant 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 methanol to remove cellulosic and other insoluble material and the filtrate so obtained is evaporated.
- ❖ The evaporated mass is dissolved in water, acidified to pH 2 and finally steam distilled to remove methanol.
- ❖ The dark residual solution is either allowed to stand for several days in a refrigerator or heated with molten paraffin to remove suspended impurities.
- ❖ The filtrate is extracted with ether or chloroform to remove water soluble nonbasic organic material and then steam distilled when the steam volatile alkaloids are separated.
- ❖ The solution of the rest of the alkaloid solution is made alkaline and again extracted with ether or chloroform and the ethereal layer obtained after this extraction is evaporated to give crude alkaloids.
- ❖ The resulting crude alkaloid mixture is separated into individual alkaloids by means of fractional crystallization, fractional precipitation, column chromatography, partition chromatography, gas chromatography or counter current extraction.



Physiological action of alkaloids

Alkaloids showed diverse medicinal properties. From the beginning of civilization, alkaloid containing plant extracts have been used in all cultures as medicine and poisons. Due to the physiological effects of alkaloids, they are considered as important compounds in medicine. Many alkaloids are sufficiently toxic to animals to cause death if eaten. Several alkaloids such as nicotine and anabasine are used as insecticides. Many alkaloids act on the nervous system, one of two important information systems in animals. Plants that contain protoberberine alkaloids are reported to be used as analgesics, antiseptics, and sedatives in Chinese folk medicine. In Indian and Islamic folk medicine, such plants are used for bleeding disorders and eye diseases, and antiseptics, sedatives, and uterine muscle depressants. Various physiological effects of alkaloids are listed below-

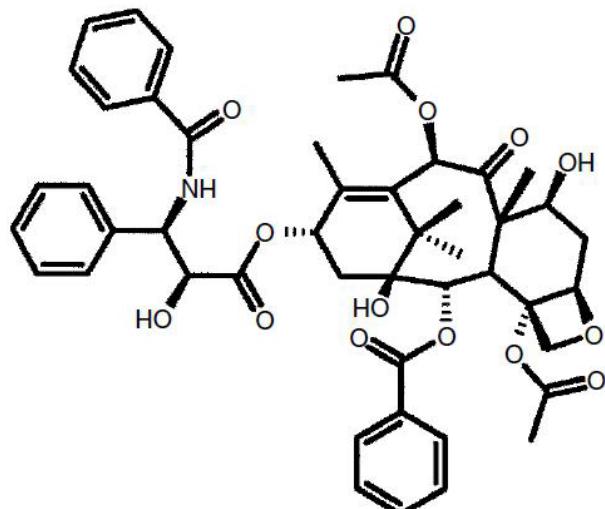


Among many thousands of drugs, about 40% of them are of plant origin. The broadest spectrum of pharmacological action is exhibited by alkaloids, especially isoquinoline ones. The first crude drug to be investigated chemically was opium, a drug that had been used for centuries for both its analgesic and narcotic properties. Morphine is one of the most known alkaloids which had been used and still is for medical purposes. This alkaloid is a powerful narcotic which is used for the relief of pain, but its usefulness is limited because of addictive properties

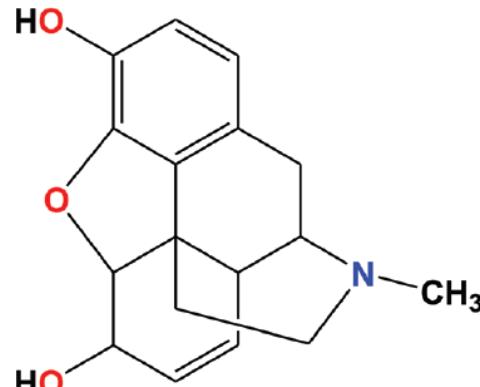
Alkaloid	Physiological action	Alkaloid	Physiological action
Palmatine, jatrorrhizine, and tetrahydropalmatine	Antimalarial activity	Tetrahydropalmatine	Analgesic, bradycardial, hypotensive and sedative activities
zephyrantine	antitumor activity	secocepharantine	antiviral effect
noscapine	anti-cough remedy	Berberine	anti-HIV, cardioprotective, immunoregulative, anti-inflammatory, cerebro-protective, anti-mutagenic, molluscicidal activity
Proaporphines and crotosparine isolated from <i>Cocculus sparciflorus</i>	hypotensive and anticancer activity	Homoerythrine derived alkaloids isolated from stem of <i>Galipea bracteata</i>	anti-fungal, anti-malarial, antioxidant, anti-inflamatory, vaso-relaxing, anxiolytic and analgesic activities
Taxol	cytostatic drug, for the treatment of lung cancer, breast cancer, neck cancer and ovarian cancer	Coniine, tropine, vendoline, morphine and tyrosine	anticancer activity

In modern times, the stimulants caffeine in coffee, tea and cacao and nicotine in cigarettes are consumed worldwide. Alkaloids with hallucinogenic, narcotic or analgesic properties have found applications in medicine e.g. morphine, atropine and quinine. Some alkaloids served as model compounds for modern synthetic drugs whereas several are abused as illegal drugs e.g. cocaine. A number of alkaloids are too toxic for any therapeutic use e.g. coniine and strychnine. Moreover the plant constituents are still screened for new biologically active compounds.

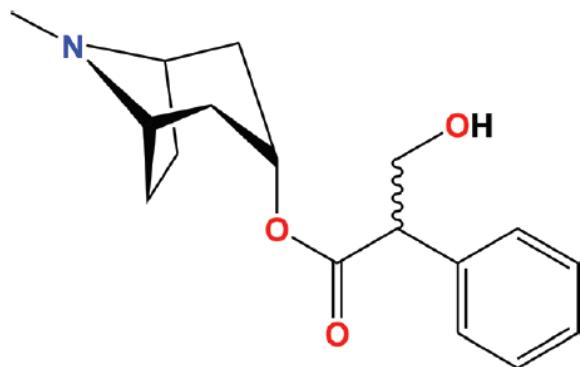
- Nicotine isolated from *Nicotiana tabacum* of family Solanaceae is a highly addictive stimulant of the nervous system in small doses, such as those obtained by smoking tobacco in cigarettes, whereas higher doses can be extremely toxic.
- Nicotine is also used as an insecticide in the form of nicotine sulfate.
- Various alkaloids like codeine, heroin, morphine and opium, derived from the sap of *Papaver somniferum* are widely used as medicines or highly addictive and recreational drugs.
- An addictive narcotic drug cocaine, derived from the foliage of *Erythroxylon coca* used as a stimulant and local anaesthetic.
- Quinine, a bitter tasting alkaloid extracted from *Cinchona ledgeriana* is well known for its antimalarial activity.
- Morphine is a powerful painkiller, often given to terminally ill patients.
- An addictive narcotic drug cocaine, derived from the foliage of *Erythroxylon coca* used as a stimulant and local anaesthetic
- Reserpine has useful tranquilizing properties and is used in the treatment of mental disorders and for the reduction of hypertension.



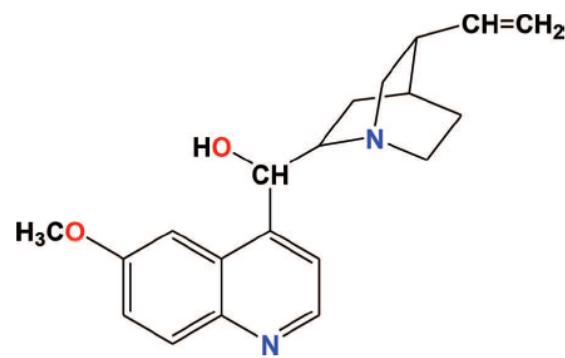
Taxol



Morphine



Atropine



Quinine from cinchona species

Determination of molecular structure of alkaloids

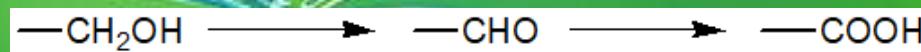
In general, molecular structure of an alkaloid is elucidated according to the following steps:

1. The first step in determining the structure of a pure alkaloid consists in ascertaining its molecular formula and optical rotatory power.
2. 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, preferably by using lithium aluminium borohydride and sodium borohydride as reagent.
3. Frequently , an alkaloid is cleaved into simple fragments by hydrolysis with water, acid or alkali and the fragments so obtained are examined separately since the structure of the fragment may easily be established than that of the whole molecule.
4. 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 as in step 3.
5. **Functional nature of oxygen:** The oxygen atom may be present in the form of alcoholic or phenolic hydroxyl (-OH), methoxy (-OCH₃), acetoxy (-COCH₃), benzoxy (-OCOC₆H₅), carboxyl (-COOH) or carbonyl (-C=O) group. Various functional groups can be characterized according to the following characteristics.

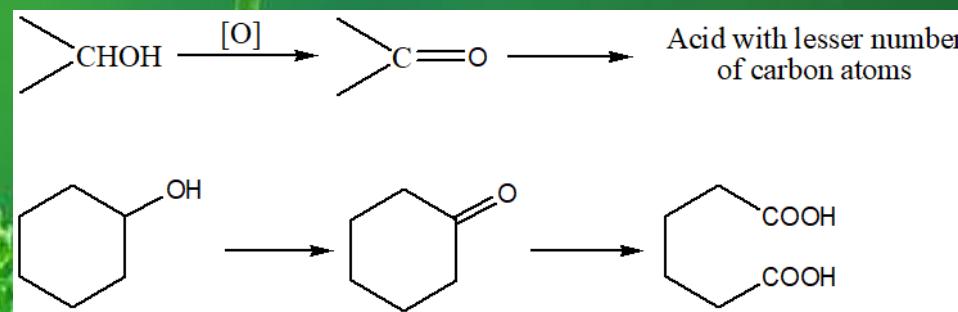
(i) Phenolic hydroxyl group (=C-OH): The phenolic hydroxyl group is characterised by alkali solubility followed by reprecipitation by carbon dioxide, a colour reaction with ferric chloride, acylation to an ester and alkylation to an ether. The number of phenolic hydroxyl group is estimated by acetylation.

(ii) Alcoholic hydroxyl group (-C-OH): The alcoholic hydroxyl group is generally indicated by its acylation reaction along with the negative tests for phenolic group. It is further confirmed by characteristics like dehydration, oxidation etc.

(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.

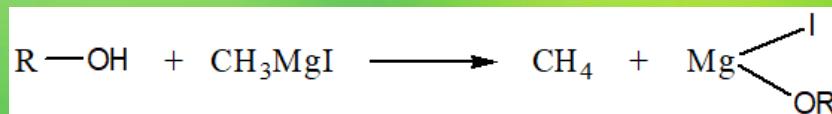


(b) Secondary alcohol ($\text{C}_2\text{H}_5\text{OH}$) on oxidation first gives ketone having same number of carbon atoms and then acid with fewer number of carbon atoms. However, if the secondary alcoholic group is constituted by cyclic carbon atom, the compound is oxidised to open chain dicarboxylic acid, although with the same 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 heating the alcohol with methyl magnesium iodide and measuring the methane so formed.



(iii) Carboxyl group (-COOH): The carboxylic group is indicated by its solubility in 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.

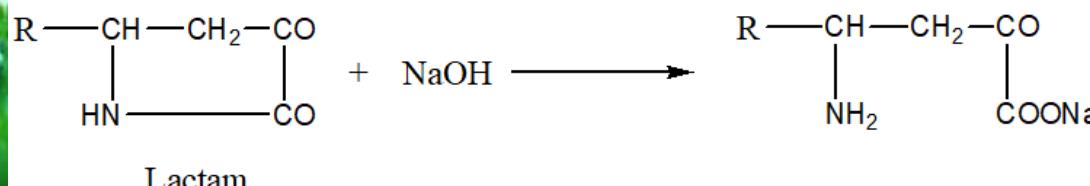
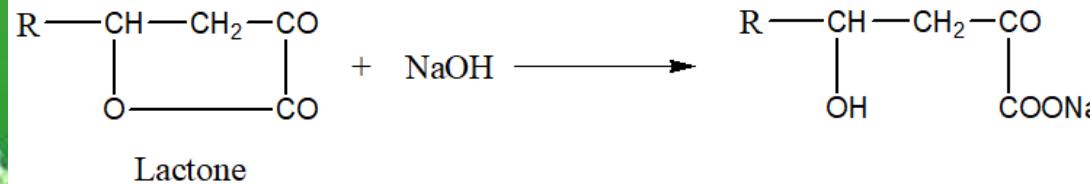
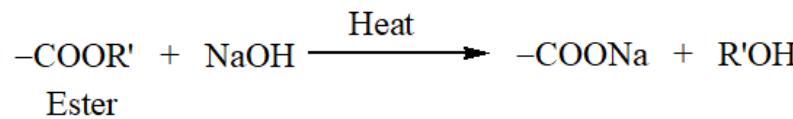
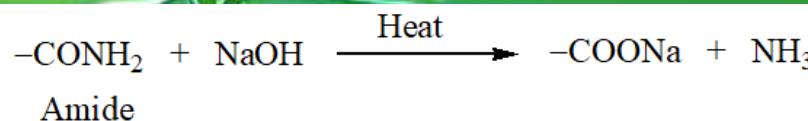
(iv) Alkoxy group (-OR): The alkoxy groups, generally methoxy ($-\text{OCH}_3$) and sometimes $-\text{OC}_2\text{H}_5$, occur frequently in the alkaloids. It is detected as well as estimated by zeigel method which involves boiling of the alkaloid with concentrated hydriodic acid at its boiling point (126°C) when alkoxy groups are converted into alkyl halides which can be easily estimated as silver iodide by treatment with ethanolic silver nitrate.



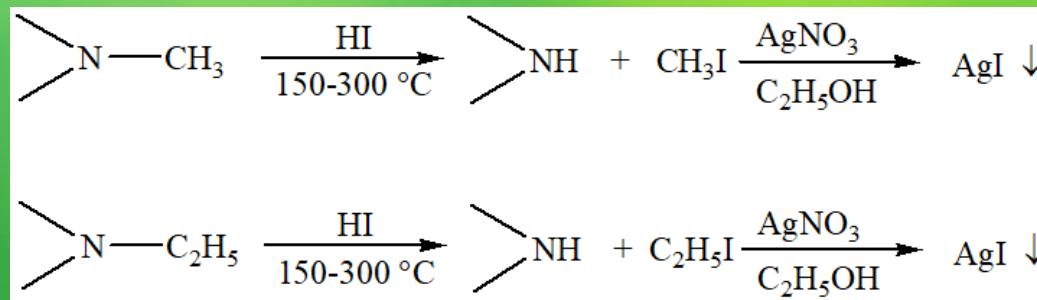
(v) **Carbonyl group ($\text{C}=\text{O}$):** Carbonyl groups such as aldehydes or ketones are detected by the usual carbonyl reagents, *viz.* hydroxylamine, phenylhydrazine, 2,4-dinitrophenylhydrazine, etc. Distinction between aldehyde and ketonic group can be made on the basis of reduction and oxidation 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.

(vi) **Ester group (-OCOR):** Esters (such as $-\text{OCOCH}_3$, $-\text{OCOC}_6\text{H}_5$) and related groups like amides, lactone, lactam and betaines 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.



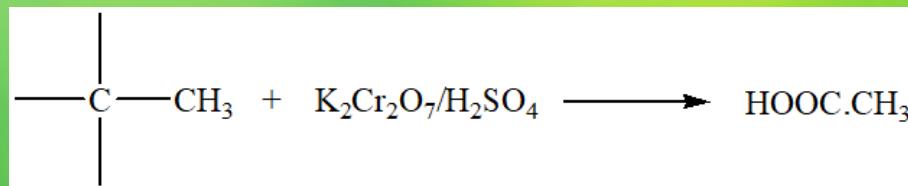
6. Functional nature of nitrogen: Since in majority of the alkaloids, the nitrogen atom is involved in a ring structure, it must be a secondary or tertiary. The N-alkyl groups are frequently estimated by HERZIG-Meyer method where the alkaloid is heated with hydriodic acid at about 150-300 °C under pressure whereby the alkyl groups are converted into alkyl iodides which are estimated as silver iodide by means of alcoholic silver nitrate.



The secondary and tertiary amino groups can be distinguished on the basis of the following reactions-

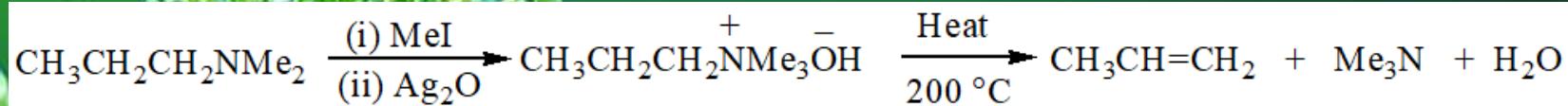
- (i) Only secondary amines are acetylated, benzoylated and give Libermann's nitroso reaction. Alkylation to quaternary salt formation may also be used for distinguishing the two types of amines since secondary amines take two moles of alkyl halides while tertiary amines only one to form quaternary salt.
- (ii) Tertiary amines are converted into amine oxide on treatment with 30% hydrogen peroxide.

7. **Estimation of C-methyl groups:** C-methyl groups are quantitatively estimated by the Kuhn-Roth oxidation. It consists in heating the compound with acidified potassium dichromate to form acetic acid which is distilled and then estimated against a standard base.

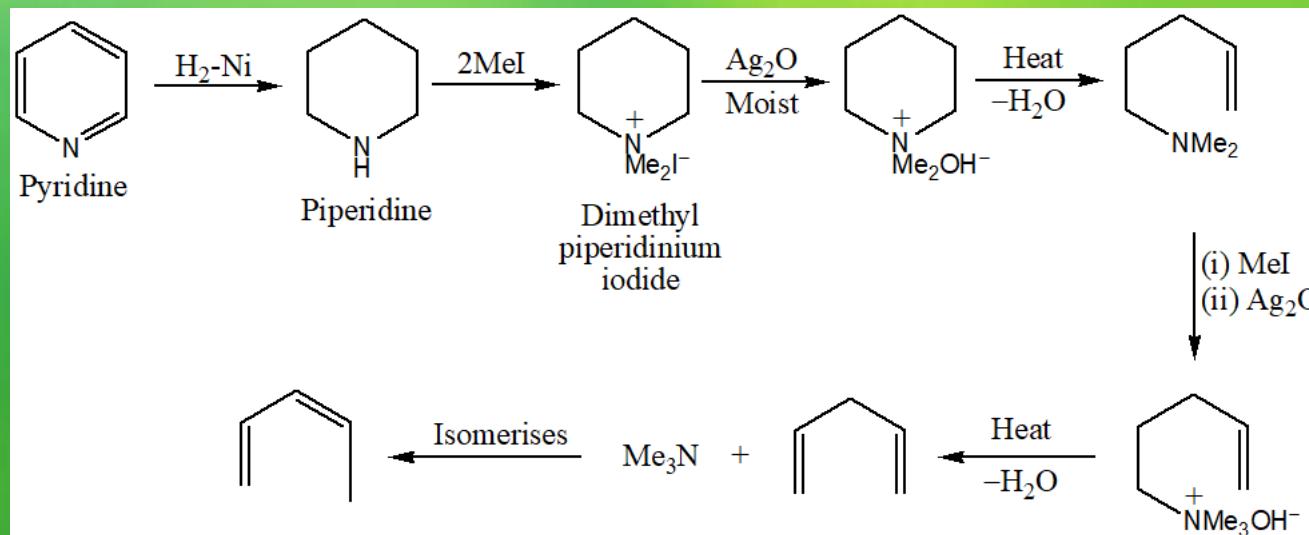


8. **Degradation of alkaloids:** This is the most important step in elucidating the structure of a compound since it gives rise to certain identifiable products of well known structure and hence by knowing the changes during the degradation and the structure of the degraded products, it will be very easy to know the structure of the original molecule. The various degradative reactions used in elucidating the structure of alkaloids are discussed below-

(A) **Hofmann exhaustive methylation method:** This is the most important method for opening the heterocyclic rings and ultimately eliminating the nitrogen to give aliphatic compounds. This method was first applied to the structures of naturally occurring alkaloids by Willstatter in 1870, it was further developed by Hofmann and hence now-a-days known as Hofmann exhaustive methylation. This method is based on the fact that when quaternary ammonium hydroxides are heated, they decompose with the loss of water and cleavage of a carbon-nitrogen linkage to give an olefin.

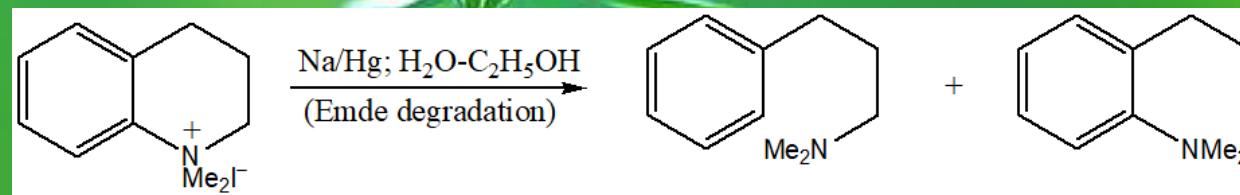
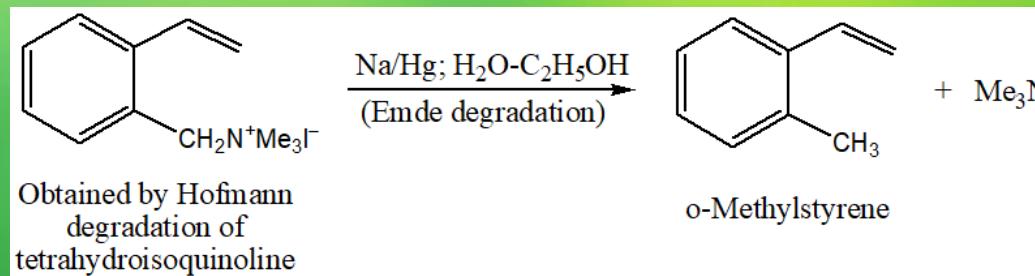


If the nitrogen atom is present in a cyclic structure, two or three such cycles are necessary to liberate the nitrogen and expose the carbon skeleton. The method is only applicable to reduced ring systems like piperidine and actually fails with the analogous unsaturated compounds like pyridine and hence the latter should be first converted to the former.



Since in the elimination of a molecule of water from quaternary ammonium hydroxide, hydrogen atom always eliminates from β position, in case it is not available the reaction fails. However, Hofmann's method suffers from the defect that some compounds even though containing β -hydrogen atom are not degraded by exhaustive methylation viz., tetrahydroquinone.

(B) Emde method: The above two types of compounds which are not degraded by Hofmann's method are successfully degraded by Emde method which consists in reducing an aqueous or alcoholic solution of the quaternary ammonium halide with sodium amalgam in aqueous ethanol, sodium in liquid ammonia or catalytically.



Thus with the help of degradation of the alkaloids, the nature of the nucleus, the various fragments constituting the alkaloids and also some type of linkages are established.

9. Physical methods: The important physical techniques used for elucidation of structure of these complex alkaloids are-

- (i) Infrared spectroscopy
- (ii) Ultraviolet spectroscopy
- (iii) X-ray analysis
- (iv) NMR spectroscopy
- (v) Mass spectrometry
- (vi) Optical rotatory dispersion and circular dichroism.

10. Finally, the structure proposed by degradative methods is confirmed by the unambiguous synthesis.

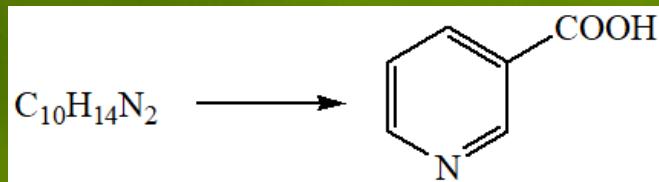
Pyridine-Pyrrolidine alkaloids: Nicotine

- ❖ Nicotine is the most important and widely distributed of the tobacco.
- ❖ It is one of the most toxic alkaloids known, a fatal dose for men being 40 mg.
- ❖ Dry tobacco leaves contain about 5 percent nicotine combined with citric or malic acid. The stems and leaves containing nicotine are powdered and extracted with water. The product is extracted with alkali when the alkaloids are liberated. The free nicotine is obtained by steam distillation and then purified through oxalate.
 - ❖ Nicotine is a colourless leavorotatory liquid (b.p. 246 °C)
 - ❖ It becomes darkened on exposure to air due to auto-oxidation
 - ❖ Nicotine is miscible with water in all proportions at temperatures below 60 °C.
- ❖ It is a deadly poison; 30-50 mg dose of nicotine when taken orally kills a man within a few seconds owing to paralysis of the nervous system, including the respiratory control centres.
- ❖ Nicotine in large amount is used as an insecticide.



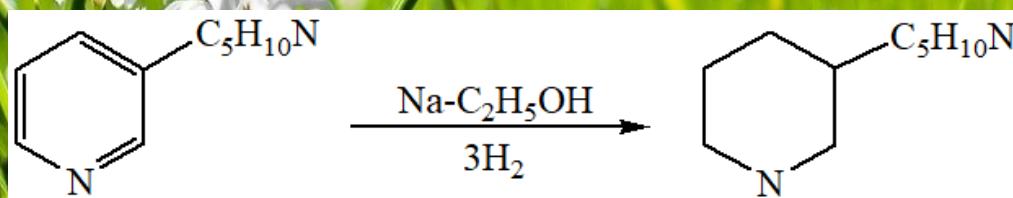
Structure Elucidation

1. Its molecular formula is $C_{10}H_{14}N_2$.
2. Both of the nitrogen atoms are found to be present as tertiary because nicotine takes up two molecules of methyl iodide to form dimethiodide. Under suitable conditions, it also forms two isomeric monomethiodides, one of the tertiary nitrogen atoms is found to be N-methyl groups.
3. Nicotine on oxidation gives nicotinic acid (pyridine-3-carboxylic acid) indicating that nicotine is 3-substituted pyridine.



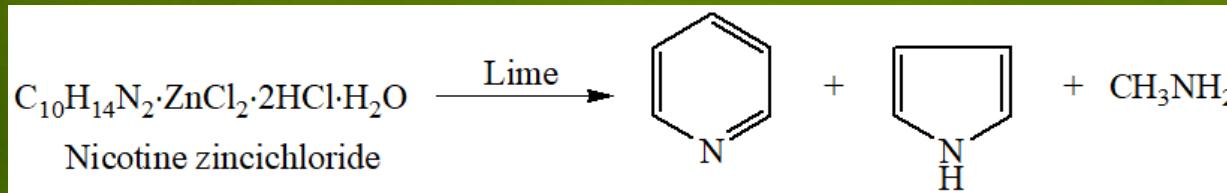
By subtracting the molecular formula of a substituted pyridine (C_5H_4N) from the molecular formula of nicotine ($C_{10}H_{14}N_2$), it is obvious that side-chain at position 3 is $C_5H_{10}N$.

4. Position and nature of the side chain: (i) Nicotine absorbs only 3 moles of hydrogen to form hexahydro derivative suggesting that the side chain is saturated since 3 moles of hydrogen are required by pyridine nucleus of the nicotine.



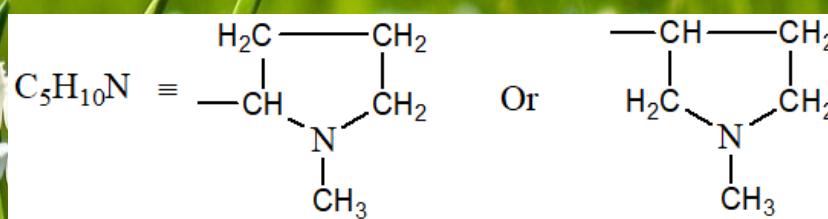
(ii) Since nitrogen atom of the pyridine moiety is present as >N . The nitrogen atom of the side chain must possess the methyl group. This is confirmed by the fact that when nicotine is heated with concentrated hydriodic acid at 150 °c (Herzig-Meyer method), methyl iodide is formed. Thus, now the side-chain having the N-methyl group can be extended as $\text{C}_4\text{H}_7\text{NCH}_3$

(iii) Nicotine forms an addition product zincichloride with zinc chloride. The zincichloride on heating with lime give pyridine, pyrrole and methylamine.

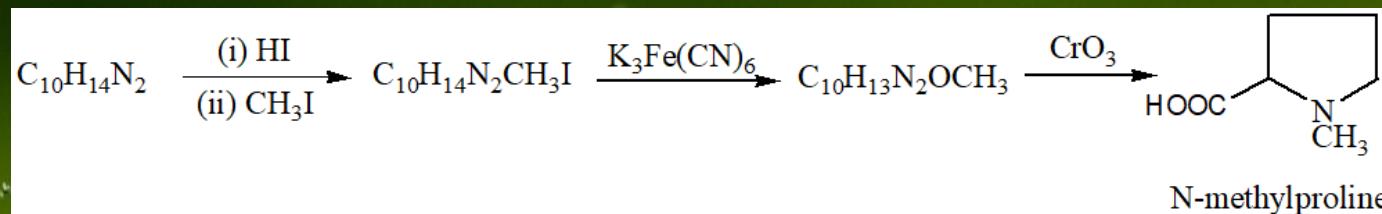


This step clearly indicated that the side-chain is pyrrole derivative. But as it already has been pointed out that the side chain is reduced and has one N-CH_3 group, it is N-methylpyrrolidine.

The point of attachment of the side chain (N-methylpyrrolidine) to the 3-position of the pyridine nucleus could be either 2 or 3. Thus, the side chain of the nicotine may be represented as below-

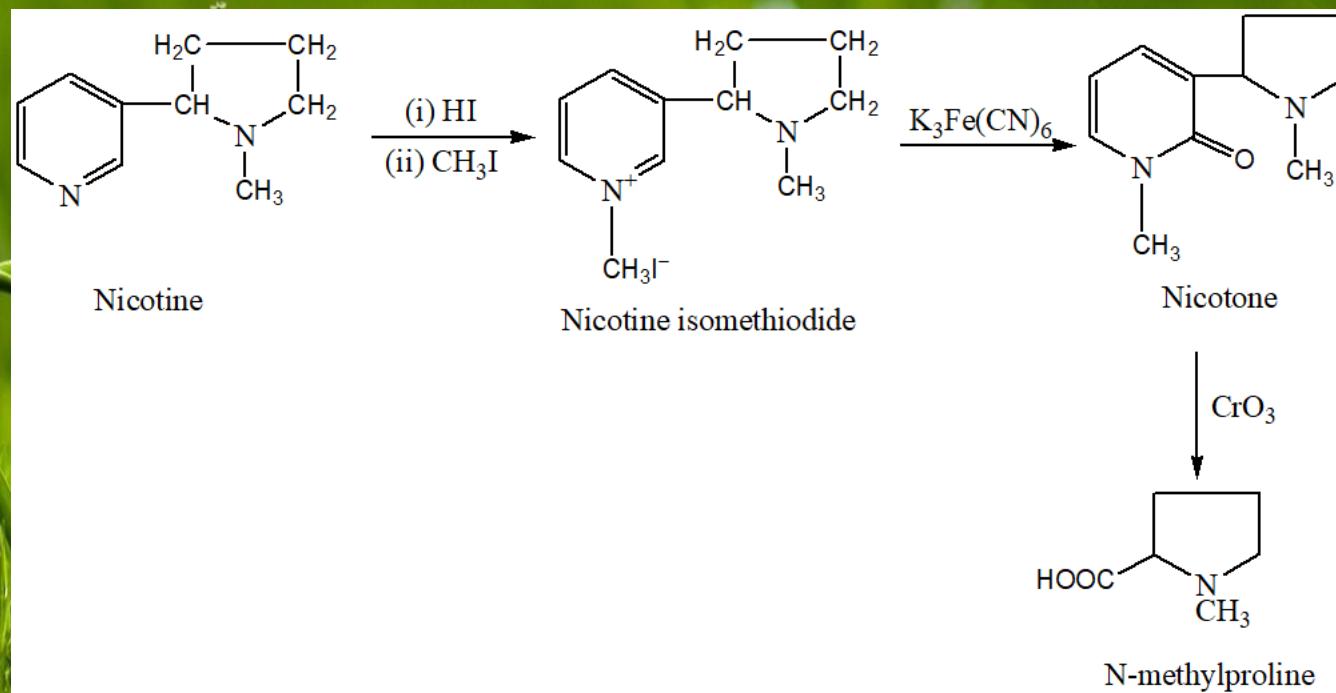


(iv) On treatment with CH_3I nicotine hydriodide give nicotine isomethiodide which on oxidation with potassium ferricyanide followed by dichromate oxidation gives N-methylproline



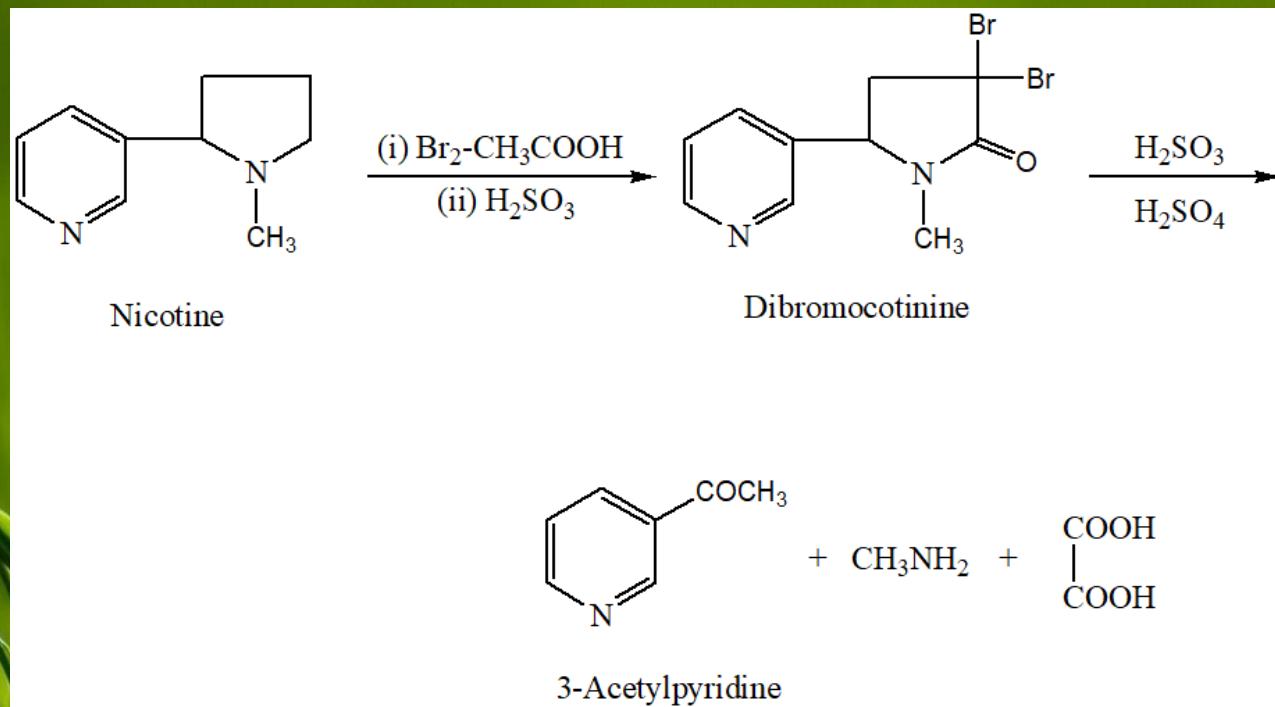
The formation of N-methylproline suggests beyond doubt that the pyrrolidine unit is attached to position 3 of the pyridine nucleus by means of α -position.

5. On the basis of the above points nicotine may be written as below which explains all the reactions-

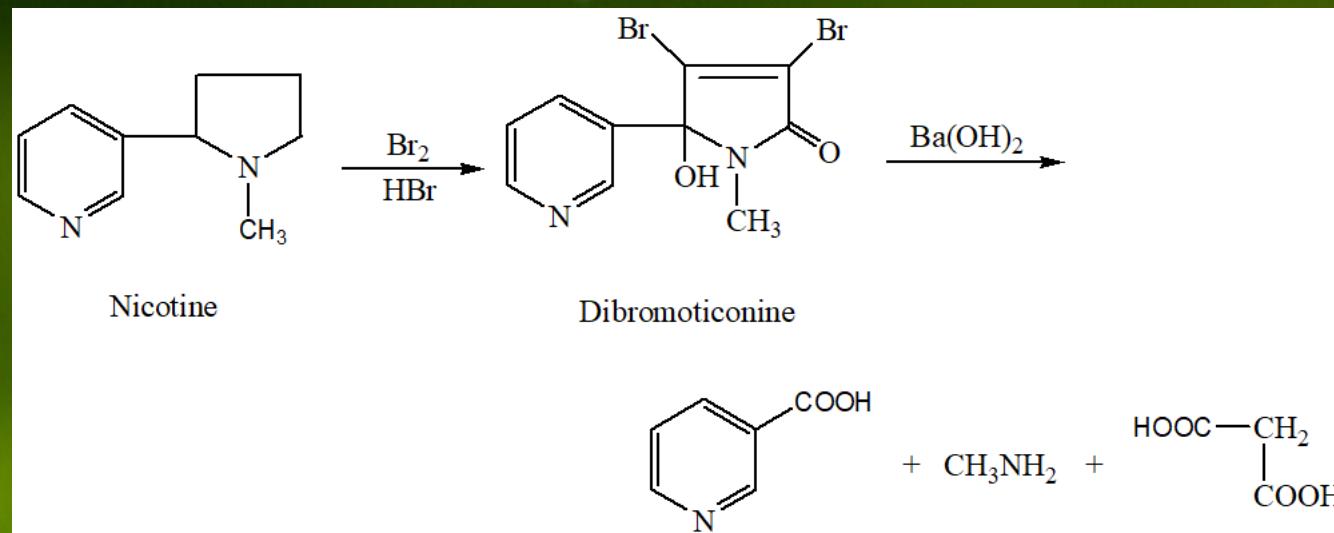


6. The proposed structure also explains the following two Pinner's observations, actually the above structure was proposed on the following two observations of Pinner.

(i) Nicotine on treatment with bromine in acetic acid affords hydrobromide perbromide along with other products on treatment with H_2SO_3 . The hydrobromide perbromide is converted to dibromocotinine which gives 3-acetylpyridine, oxalic acid and methylamine on heating with a mixture of sulphurous and sulphuric acids at 130-140°C.



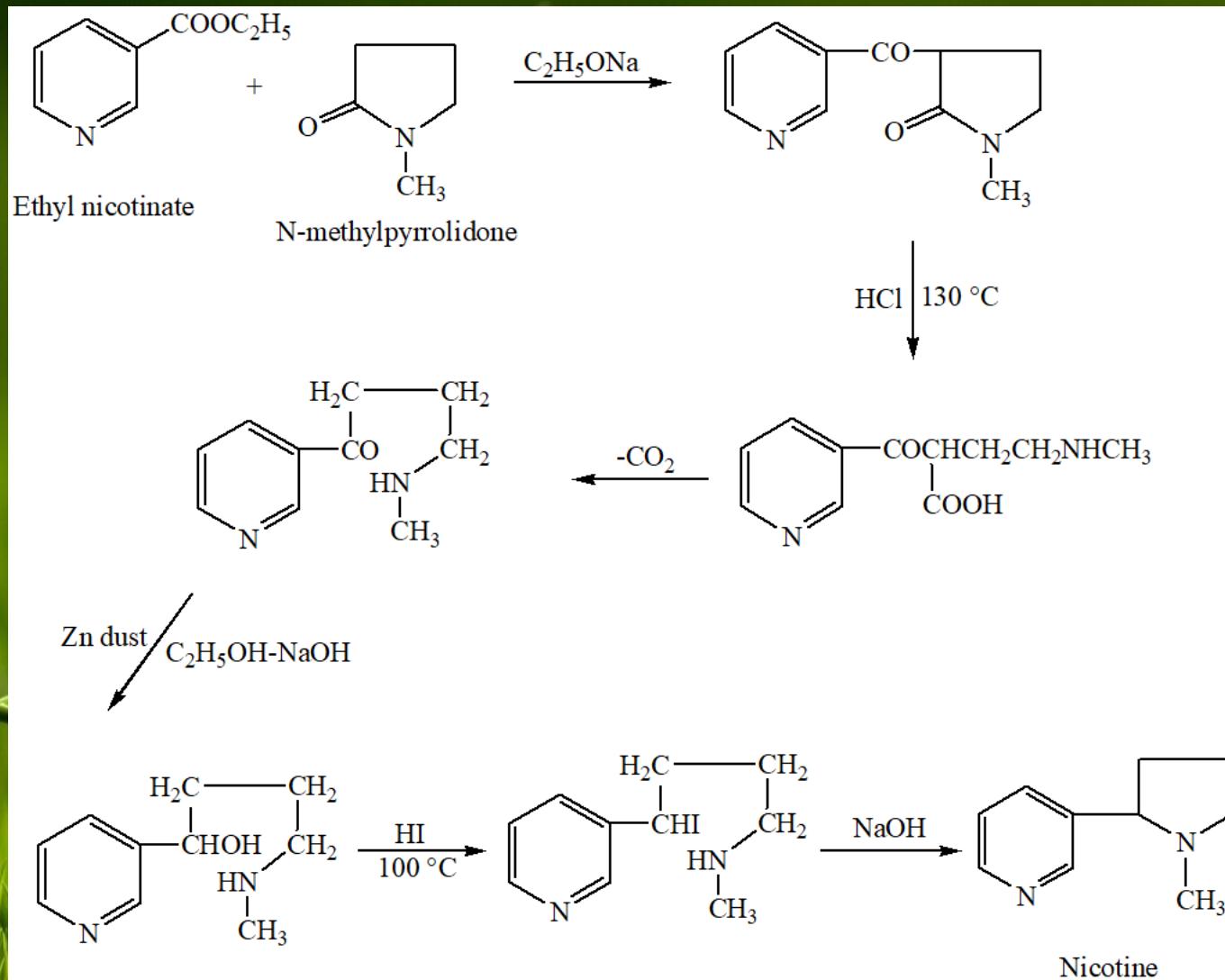
(ii) Nicotine on treatment with bromine in presence of hydrobromic acid gives dibromoticonine which on heating with $\text{Ba}(\text{OH})_2$ solution at $100\text{ }^\circ\text{C}$ affords nicotinic acid, malonic acid and methylamine.



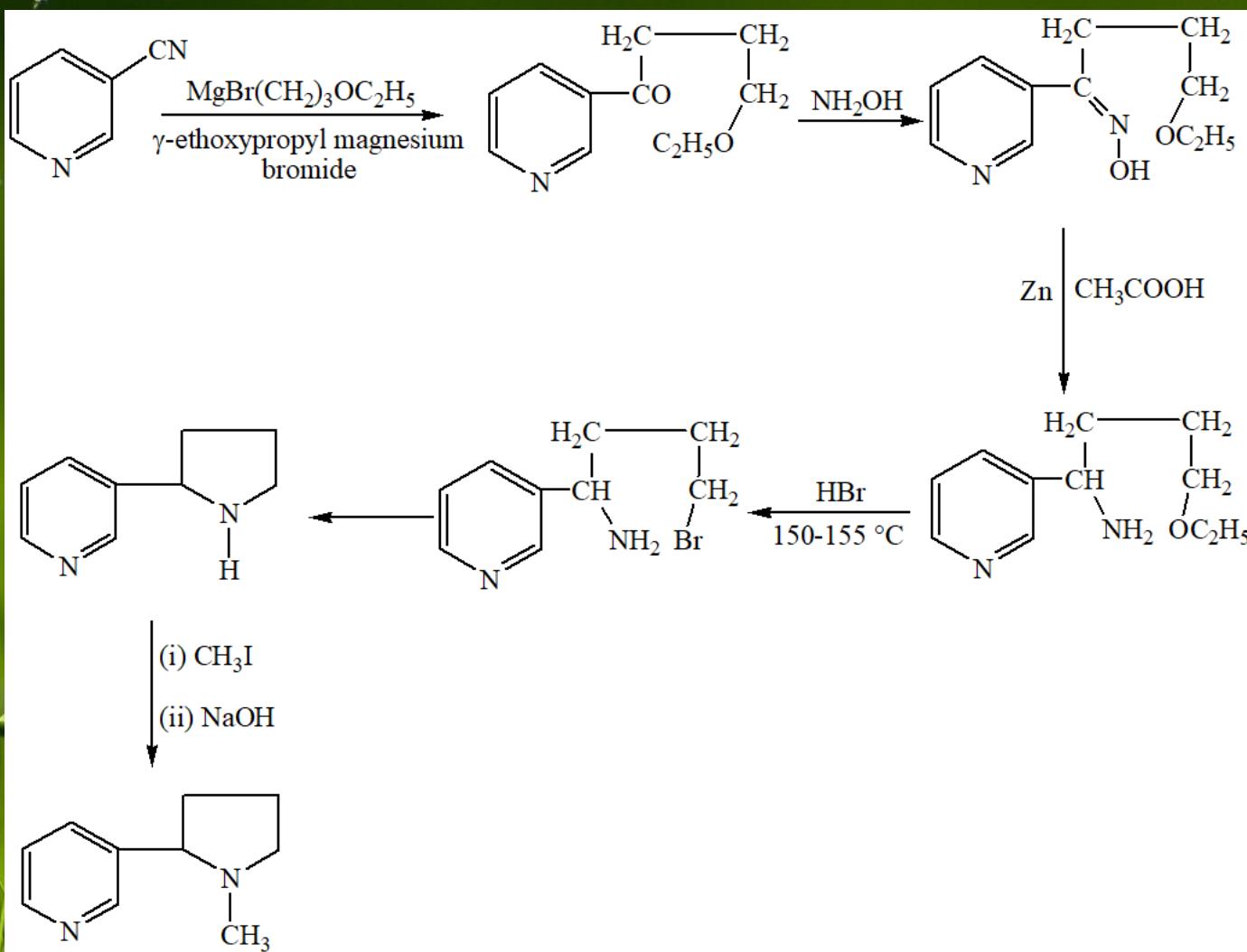
7. Lastly the structure of nicotine is proved by its synthesis.



Synthesis: (i) Spath et al. (1928). This involves the Claisen condensation of ethyl nicotinate with N-methyl-2-pyrrolidone.



(ii) Craig et al. (1933):



(iii) Hellman and Dieterich, 1962:

