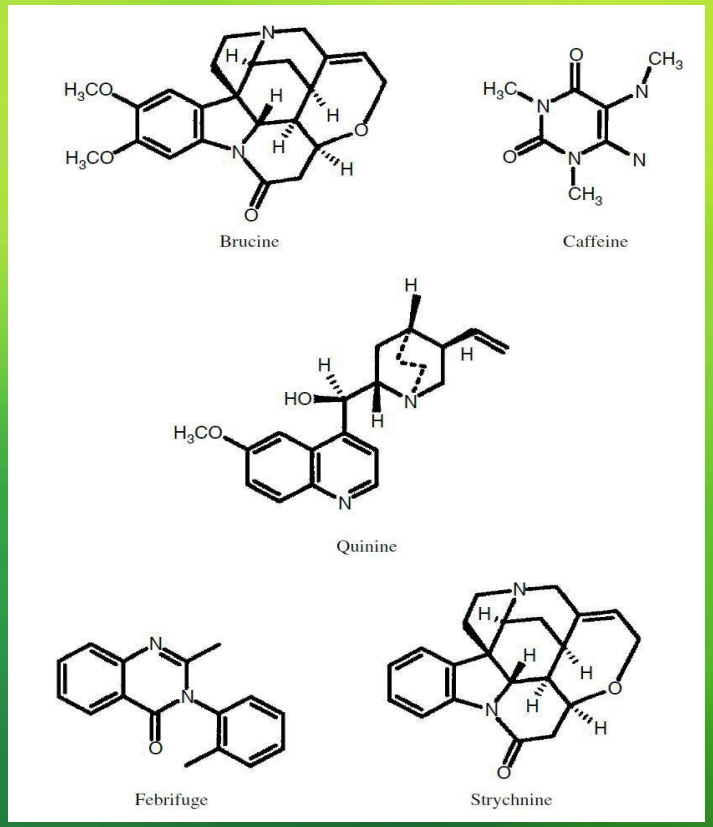
Notes on Alkaloids

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, especiallyin 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

Naturaloccurrence

❖ Alkaloids encompass an enormous class of approximately 12,000 natural products, distributed throughout inknown vascular plants. They are rarely found in lower plants like algae, fungi etc. The alkaloids occur in the leaves, seeds, roots and bark of nearly40 plant species. Alkaloid contentof plants varieswith theseason, age and itslocality. 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 themore complicated onessuchas quinine, nicotine, colchicine, etc. generally occur in one species.

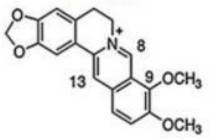
Since alkaloids are basic in nature, it is expected that in plants they exist as salt of plant acids such as acetic, oxalic, citric, malic, lactic, tartaric, tannic acid etc. Some alkaloids are also found to occur free, as glycosides, as amides or as esters or organic acids.

General structural featuresofalkaloids

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.

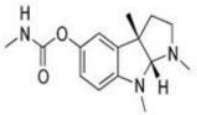
Berberis vulgaris

Berberine



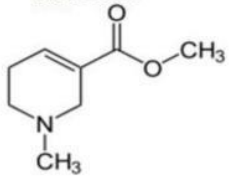
Physostigmine venosum

Physostigmine



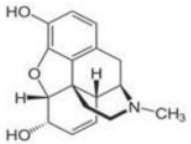
Areca catchu

Arecoline



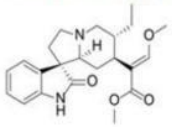
Papaver somniferum

Morphine



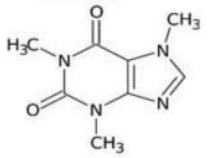
Uncaria rhynchophylla

Isorynchophyline



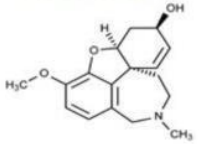
Coffee arabica

Caffeine



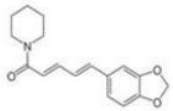
Galanthus nivalis

Galantamine



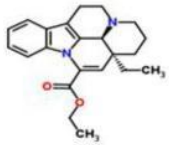
Piper nigumv

Piperine



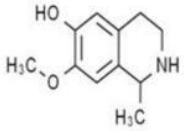
Vincia Minor

Vinopectine



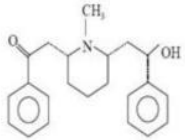
Salsola oppositefolia

Salsoline



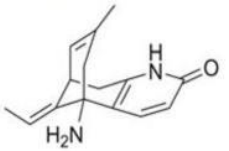
Lobela inflata

Lobeline



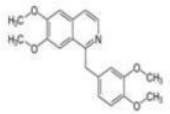
Huperzia serrate

Huperzine A



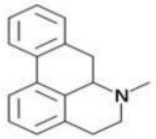
Hippeastrum vittatum

Montanine



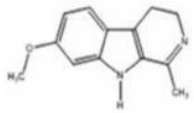
Nandina domestica

Nantenine



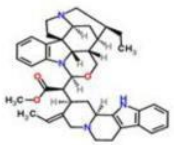
Pegnum harmala

Harmine



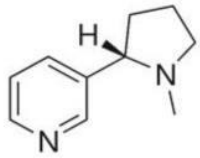
Geissospernum vellosii

Geissospermine



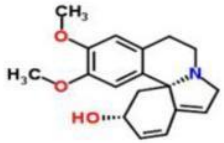
Nicotiana tobaccum

Nicotine



Erythrina mulungu

(+)-erythravine



Hussain,G.,Rasul,A.,Anwar,H.,Aziz,N.,Razzaq, A.,Wei,W.,...&Li,X.(2018).Roleofplantderivedalkaloidsandtheirmechanisminneurodegenerative disorders.*Internationaljournalofbiologicalsciences*,*14*(3),341.

Generalpropertiesofalkaloids

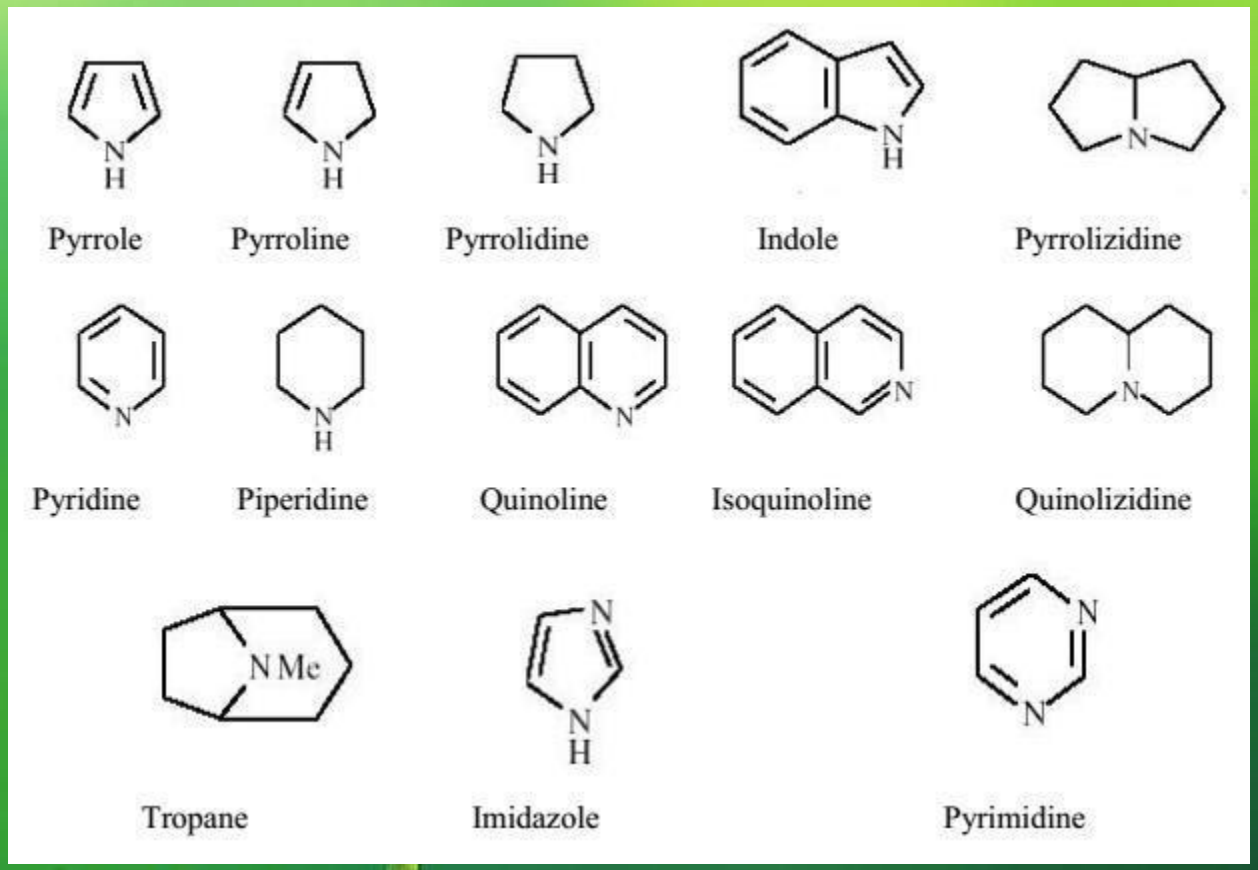
- The alkaloids are usually colourless, crystalline, non-volatile solids which are insoluble in water, but are soluble in ethanol, ether, chloroform, etc.
- Some alkaloids are liquids which are soluble in water, e.g. coniine and nicotine.
- Afewarecoloured,e.g.berberine isyellow.
- Most alkaloids have a bitter taste and are optically active (laevorotatory).
- Theopticallyactive alkaloids areveryusefulforresolving 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.

Classificationofalkaloids

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

- Phenylethylamine alkaloids
- Pyrrolidone alkaloids
- Pyridineorpiperidinealkaloids
- Pyridine-pyrrolidine alkaloids
- Tropane alkaloids
- Quinolinealkaloids
- Isoquinolinealkaloids
- Phenanthrenealkaloids
- Indolealkaloids
- Tropolonealkaloids

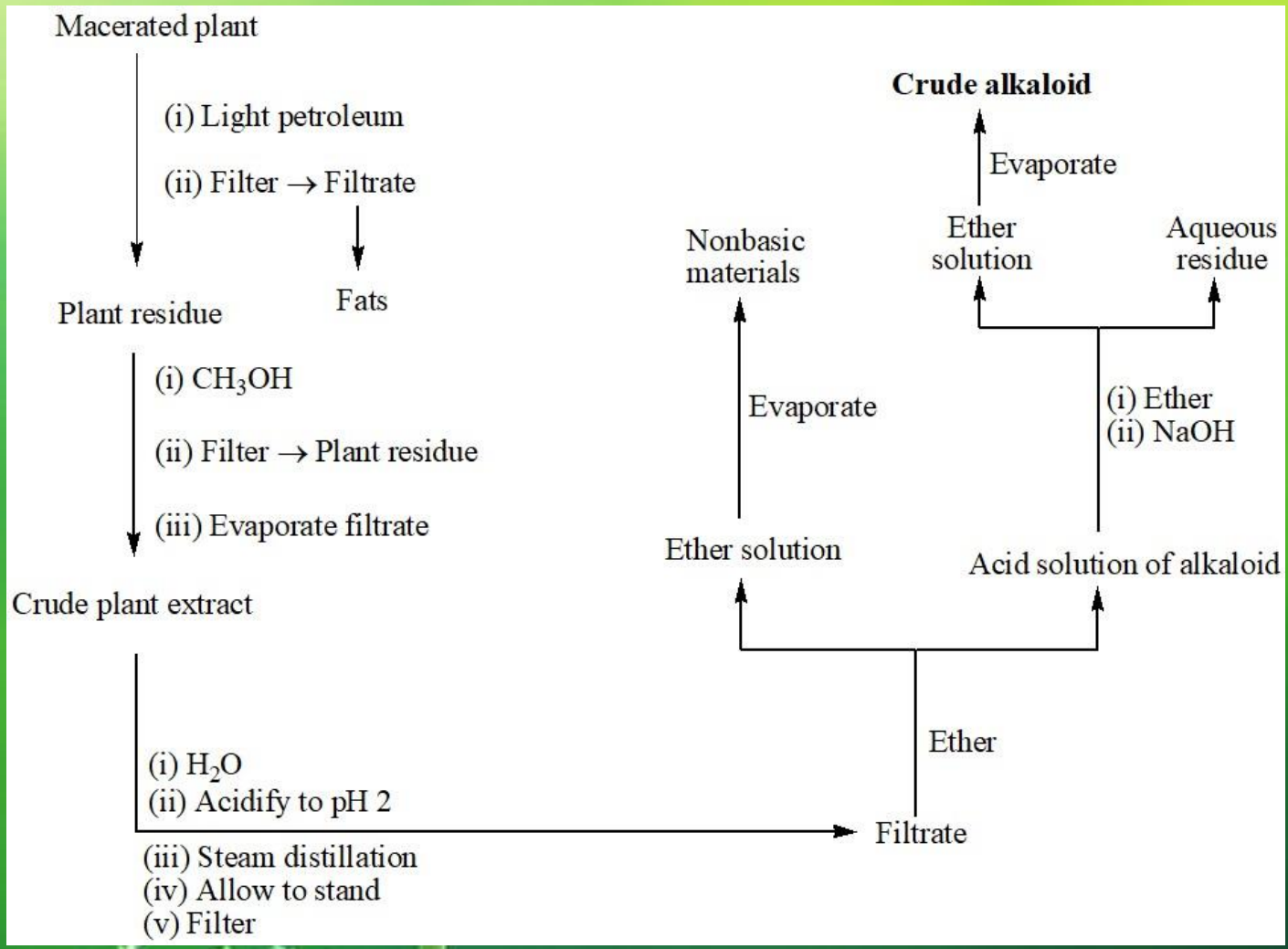
Heterocyclicstructureofskeletonconstitutinggroupofalkaloids



Isolationofalkaloids

Acommonmethod ofisolationofalkaloidsasfollows:

- **Firsttheplantisdried,andthen finelypowdered.**
- **The dried and powdered plant material is first extracted with petroleum ether (if it is rich in fat) and then filtered forthe removal of soluble fats.**
- **Theresidueisthenextractedwithmethanoltoremovecellulosicandotherinsolublematerialandthefiltrateso obtained is evaporated.**
- **The evaporated massis dissolvedinwater,acidifiedtopH 2 andfinallysteamdistilled toremovemethanol.**
- **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 againextractedwith ether orchloroform 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.**


Macerated plant
(i) Light petroleum
(ii) Filter → Filtrate
Fats
Plant residue
(i) CH_3OH
(ii) Filter → Plant residue
(iii) Evaporate filtrate
Crude plant extract
(i) H_2O
(ii) Acidify to pH 2
(iii) Steam distillation
(iv) Allow to stand
(v) Filter
Filtrate
Ether
Ether solution
Acid solution of alkaloid
Evaporate
Nonbasic materials
(i) Ether
(ii) NaOH
Ether solution
Aqueous residue
Evaporate
Crude alkaloid

Physiologicalactionofalkaloids

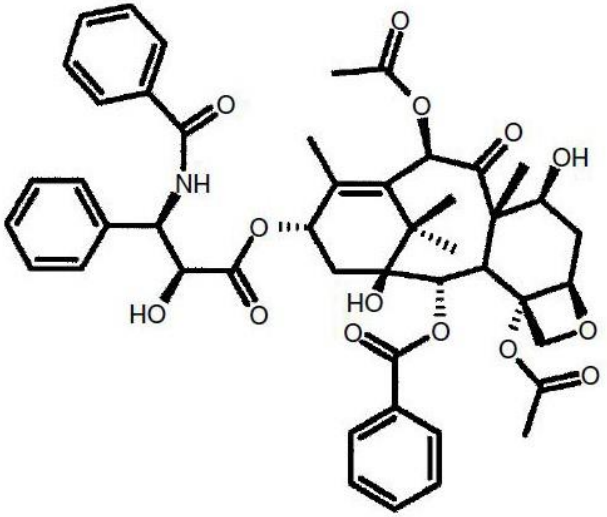
Alkaloids showed diverse medicinal properties. From the beginning of civilization, alkaloid containing plant extracts have been used in all cultures as medicine and poisons. Due to the physiological effects of alkaloids, they are considered as important compounds in medicine. Many alkaloids are sufficiently 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 narcoticwhich is used for the relief of pain, but its usefulness is limited because of addictive properties

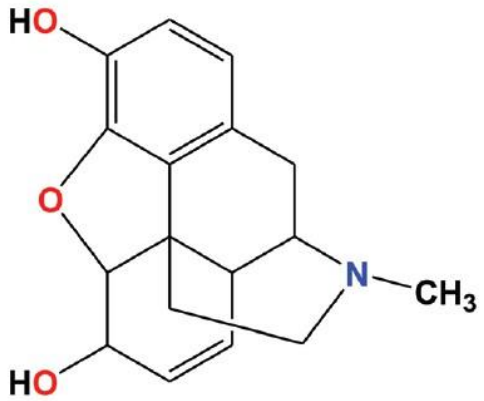
Alkaloid	Physiologicalaction	Alkaloid	Physiologicalaction
Palmatine, jatrorrihizine, and tetrahydropalmatine	Antimalarialactivity	Tetrahydropalmatine	Analgesic, bradycardial, hypotensiveandsedative activities
zephyrantine	antitumoractivity	secocepharantine	antiviraleffect
noscapine	anti-coughremedy	Berberine	anti-HIV, anti-fungal, cardioprotective, immunoregulative, anti-malarial, anti-inflammatory, antioxidant, cerebro-protective, anti-mutagenic, vaso-relaxing, anxiolyticandanalgesicactivities
Proaporphines andcrotsparine isolated from Cocculussparciflorus	hypotensiveandanticancer activity	Homoerythrine derivedalkaloids isolated fromstemofGalipea bracteata	molluscicidalactivity
Taxol	cytostaticdrug,forthetreatment of lung cancer, breast cancer, neck cancer and ovarian cancer	Coniine, tropine, vendoline,morphine and tyrosine	anticanceractivity

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.

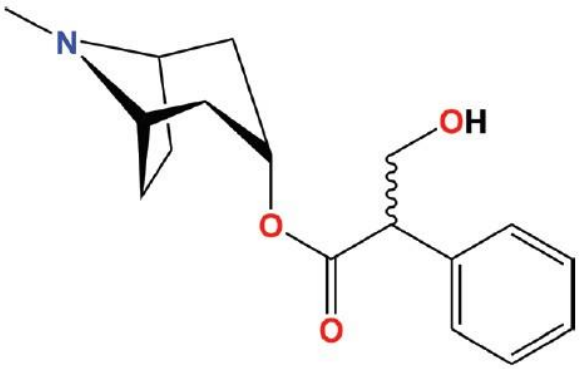
- Nicotine isolatedfromNicotiana tabacumoffamilySolanaceaeisahighlyaddictive stimulantofthenervoussystem in small doses, such as those obtained by smoking tobacco in cigarettes, whereas higher doses can be extremely toxic.
- Nicotineisalso usedasaninsecticideinthe form ofnicotinesulfate.
- Various alkaloids like codeine, heroin, morphine and opium, derived from the sap of Papaversomniferum 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,abittertasting alkaloidextractedfromCinchonaledgerianaiswellknownforits antimalarialactivity.
- Morphineisapowerfulpainkiller, oftengiventoterminallyillpatients.
- An addictive narcotic drug cocaine, derived from the foliage of Erythroxylon coca used as a stimulant and local anaesthetic
- Reserpine has usefultranquillizing propertiesandis usedin thetreatmentofmentaldisordersandfor thereduction of hypertension.



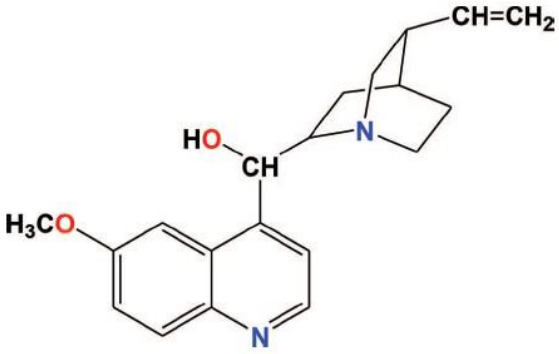
Taxol



Morphine



Atropine



Quinine from cinchona species

Determinationofmolecularstructureofalkaloids

Ingeneral,molecularstructureofanalkaloid iselucidatedaccordingtothefollowing steps:

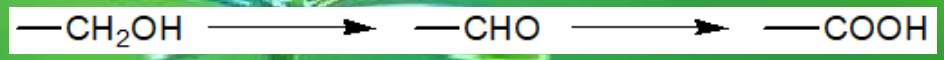
1. **The first step in determining the structure of a pure alkaloid consists in ascertaining its molecular formula and optical rotatory power.**
2. **Thepresenceofunsaturationinanalkaloidmaybeascertainedbytheadditionofbromineorhalogenacidsorby hydroxylationwithdilutealkalinepermanganate.**

   Reduction mayalso be used to show the presence of unsaturation, preferablyby 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 mayeasily 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 orin its fragments obtained by hydrolysis as in step 3.**
5. **Functionalnatureof oxygen:Theoxygen atommaybepresentintheformofalcoholic orphenolic hydroxyl(-OH), methoxy (-OCH_3), acetoxyl (-$COCH_3$), benzoxyl (-$OCOC_6H_5$), carboxyl (-COOH) or carbonyl (-C=O) group. Various functional groups can be characterized according to the following characteristics.**

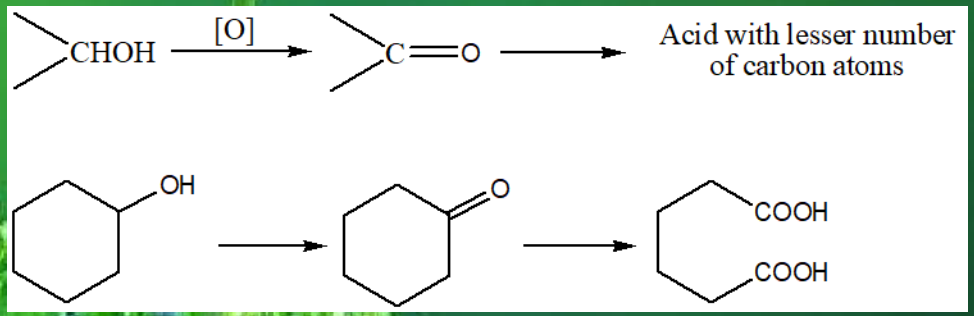
(i) Phenolic hydroxyl group (=C-OH): The phenolic hydroxyl group is characterised by alkali solubility followed by reprecipitation by carbon dioxide, a colour reaction with ferric chloride, acylation to an ester and alkylation to an ether. The number of phenolic hydroxyl group is estimated by acetylation.

(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 ($-CH_2OH$) on oxidation gives first an aldehyde and then acid both having the same number of carbon atoms as the parent alcohol.

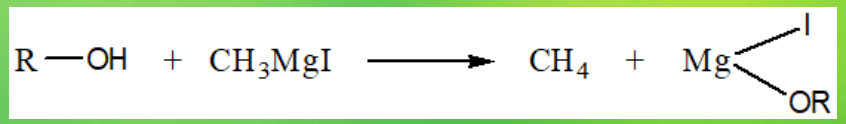


(b) Secondaryalcohol (>CHOH) on oxidation first gives ketone having same number of carbon atoms and then acid with fewer number of carbon atoms. However, if the secondary alcoholic group is constituted by cyclic carbon atom, the compound is oxidised to open chain dicarboxylic acid, although with the same number of carbon atoms.



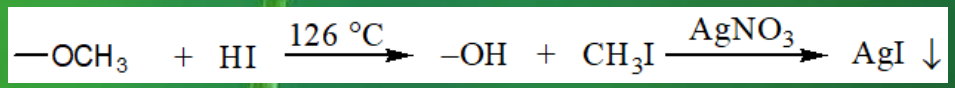
(c) Tertiaryalcoholonoxidationgives ketoneandacidbothhavingfewernumberofcarbon atoms.

Thenumberofalcoholichydroxylgroupscanbedeterminedbyheatingthealcoholwithmethyl 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.

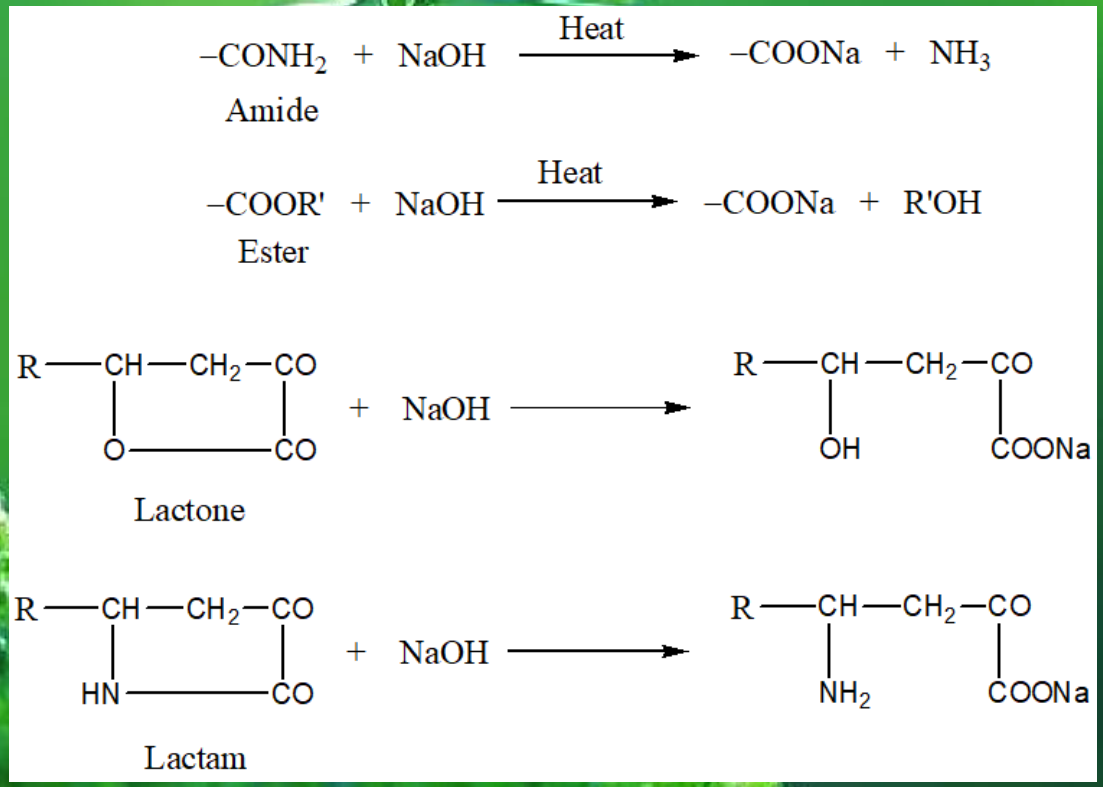
(iv) Alkoxyl group (-OR): Thealkoxygroups, generallymethoxy(-OCH_3) and sometimes–OC_2H_5, occur frequentlyin the alkaloids. It is detected as well as estimated by zeigel method which involves boiling of the alkaloid with concentrated hydriodic acid at its boiling point (126 ºC) when alkoxy groups are converted into alkyl halides which can be easily estimated as silver iodide by treatment with ethanolic silver nitrate.



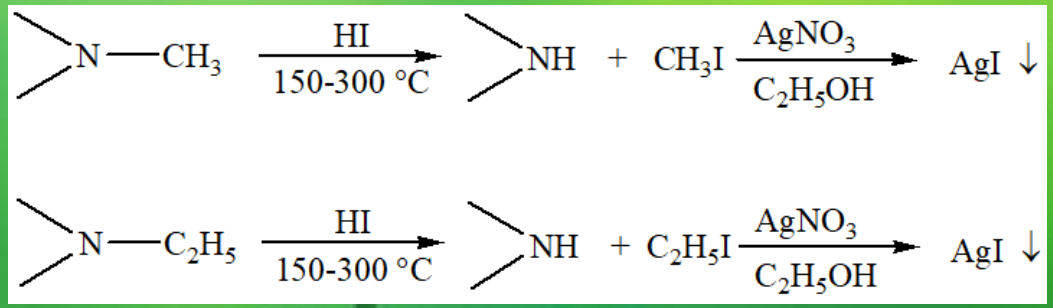
(v) Carbonyl group (C=O): Carbonyl groups such as aldehydes or ketones are detected by the usual carbonyl reagents, *viz*. hydroxylamine, phenylhydrazine, 2,4-dinitrophenylhydrazine, etc. Distinction between aldehyde and ketonic group can be made on the basis of reduction and oxidation reactions.

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 $-OCOCH_3$, $-OCOC_6H_5$) and related groups like amides, lactone, lactam and betaines are detected bytheir hydrolysis with water, dilute acids, alkali to the hydroxyl and acidic compounds. The nature is established by knowing the nature of the acid.



6. **Functionalnature of nitrogen:**Since in majority of the alkaloids, the nitrogen atom is involved in a ring structure,it must be a secondaryor tertiary. The N-alkyl groups are frequentlyestimated byHERZIG-Meyer method where the alkaloid is heated with hydriodic acid at about 150-300 ºC under pressure whereby the alkyl groups are converted into alkyl iodides which are estimated as silver iodide by means of alcoholic silver nitrate.

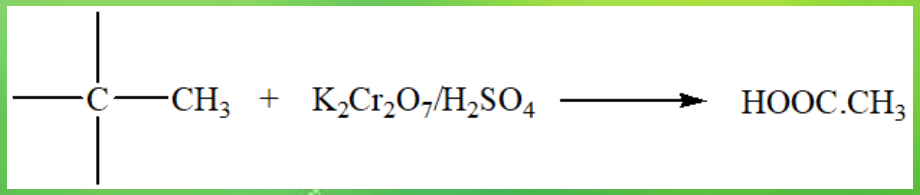


Thesecondaryandtertiaryamino groupscanbe distinguishedonthebasisofthefollowingreactions-

(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 aminestake two moles of alkyl halides while tertiary amines only one to form quaternary salt.

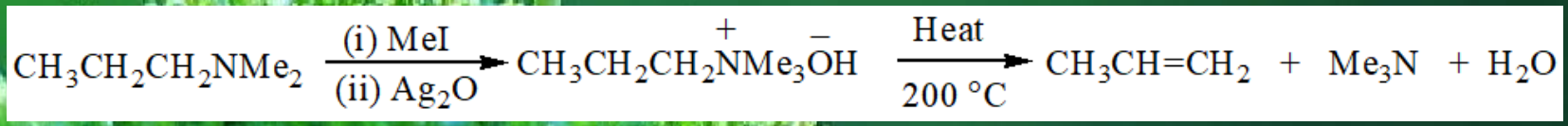
(ii) Tertiaryaminesareconverted intoamineoxide ontreatmentwith30%hydrogenperoxide.

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.

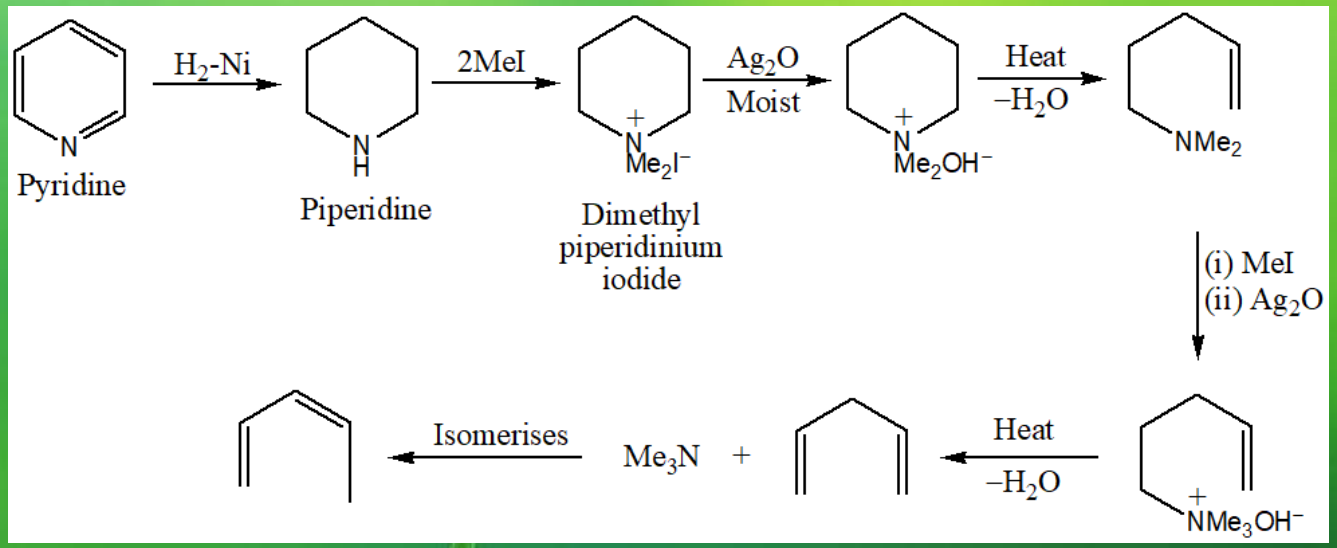


8. **Degradation of alkaloids:** This is the most important step in elucidating the structure of a compound since it gives rise to certain identifiable products of well known structure and hence by knowing the changes during the degradation and the structure of the degraded products, it will be very 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 byHofmann 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.

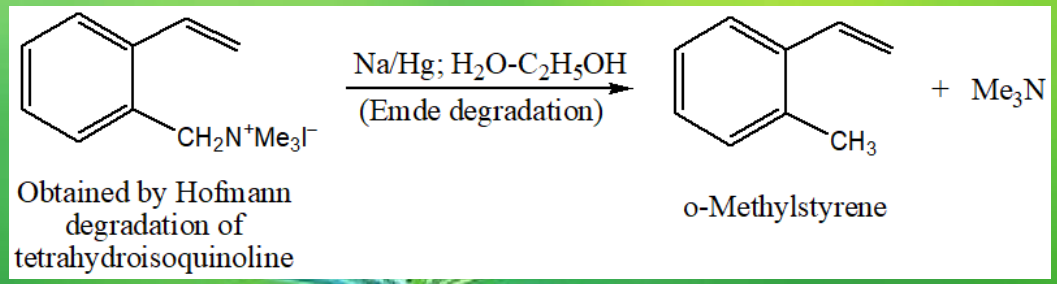


If the nitrogen atom is present in a cyclic structure, two or three such cycles are necessaryto liberate the nitrogen and expose the carbon skeleton. The method is only applicable to reduced ring systems like piperidine and actually fails with the analogous unsaturated compounds like pyridine and hence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



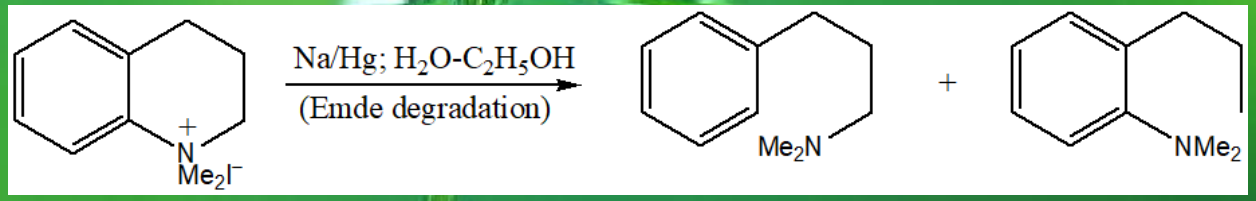
Since in the elimination of a molecule of water from quaternary ammonium hydroxide, hydrogen atom always eliminates from β position, in case it is not available the reaction fails. However, Hofmann's method suffers from the defect that some compounds even though containing β-hydrogen atom are not degraded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

(B) Emde method: The above two types of compounds which are not degraded byHofmann'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.



Obtained by Hofmann degradation of tetrahydroisoquinoline

o-Methylstyrene



Thus withthehelp of degradationof thealkaloids, thenatureof thenucleus, thevariousfragmentsconstituting 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) Ultravioletspectroscopy

(iii) X-rayanalysis

(iv) NMRspectroscopy

(v) Massspectrometry

(vi) Opticalrotatorydispersionandcirculardichroism.

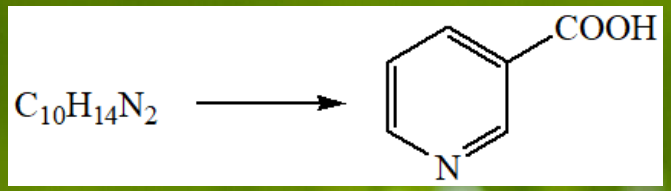
10. Finally,thestructureproposed bydegradativemethods isconfirmedbytheunambiguoussynthesis.

Pyridine-Pyrrolidinealkaloids:Nicotine

- Nicotine isthemostimportantand widelydistributed ofthe tobacco.
- Itisoneofthe mosttoxic alkaloidsknown,afataldosefor menbeing40mg.
- 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 isacolourlessleavorotatoryliquid(b.p.246ºC)
- Itbecomesdarkenedonexposuretoairdue toauto-oxidation
- Nicotineismisciblewithwaterinallproportionsat temperaturesbelow60ºC.
- 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.
- Nicotineinlargeamountisused asaninsecticide.

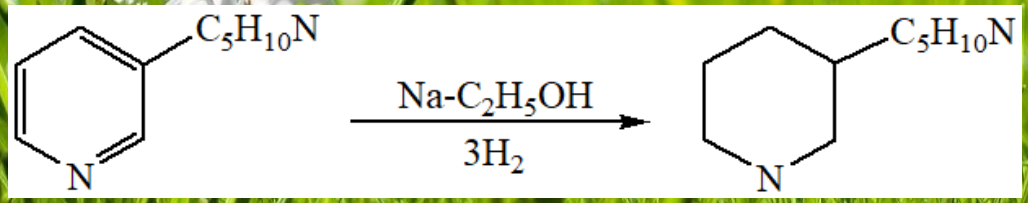
StructureElucidation

1. Itsmolecularformulais$C_{10}H_{14}N_2$.
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.



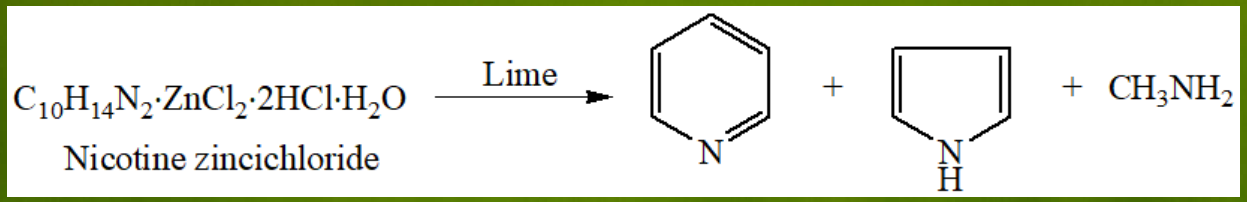
Bysubtractingthemolecular formulaofa substitutedpyridine (C_5H_4N) fromthemoleculare formula of nicotine ($C_{10}H_{14}N_2$), it is obvious that side-chain at position 3 is $C_5H_{10}N$.

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.



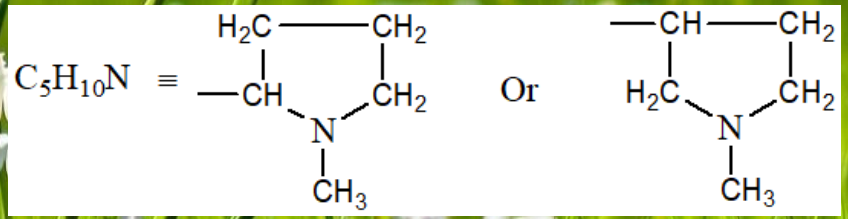
(ii) Since nitrogen atom of the pyridine moiety is present as $\equiv N$. The nitrogen atom of the side chain must possess the methyl group. This is confirmed by the fact that when nicotine is heated with concentrated hydriodic acid at 150 °c (Herzig-Meyer method), methyl iodide is formed. Thus, now the side-chain having the N-methyl group can be extended as $C_4H_7.NCH_3$

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

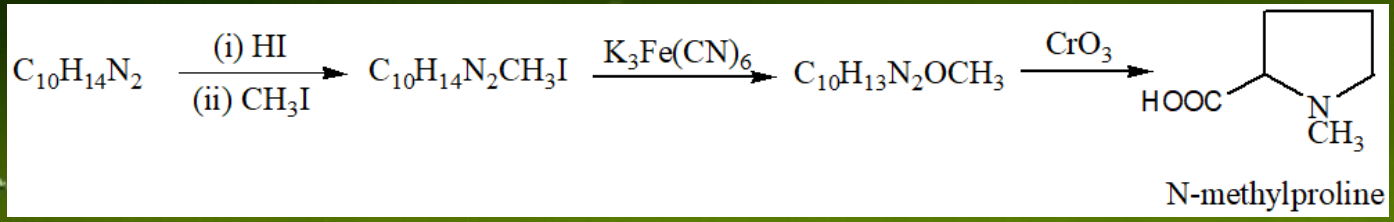


This step clearly indicated that the side-chain is pyrrole derivative. But as it already has been pointed out that the side chain is reduced and has one N-CH_3 group, it is N-methylpyrrolidine.

Thepointofattachmentofthesidechain(N-methylpyrolidine)tothe3-positionofthepyridine nucleus could be either 2 or 3. Thus, the side chain of the nicotine may be represented as below-

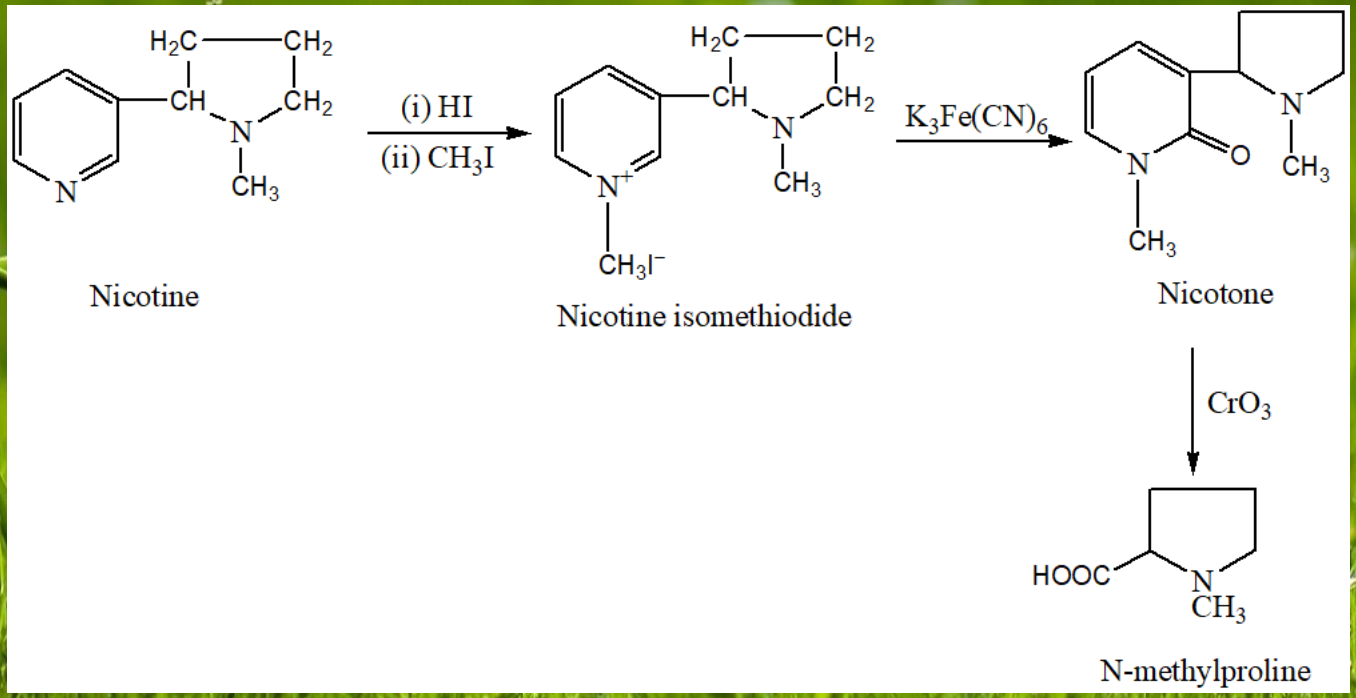


(iv) On treatment with CH_3I nicotine hydriodide give nicotine isomethiodide which on oxidation with potassium ferricyanide followed by dichromate oxidation gives N-methylproline



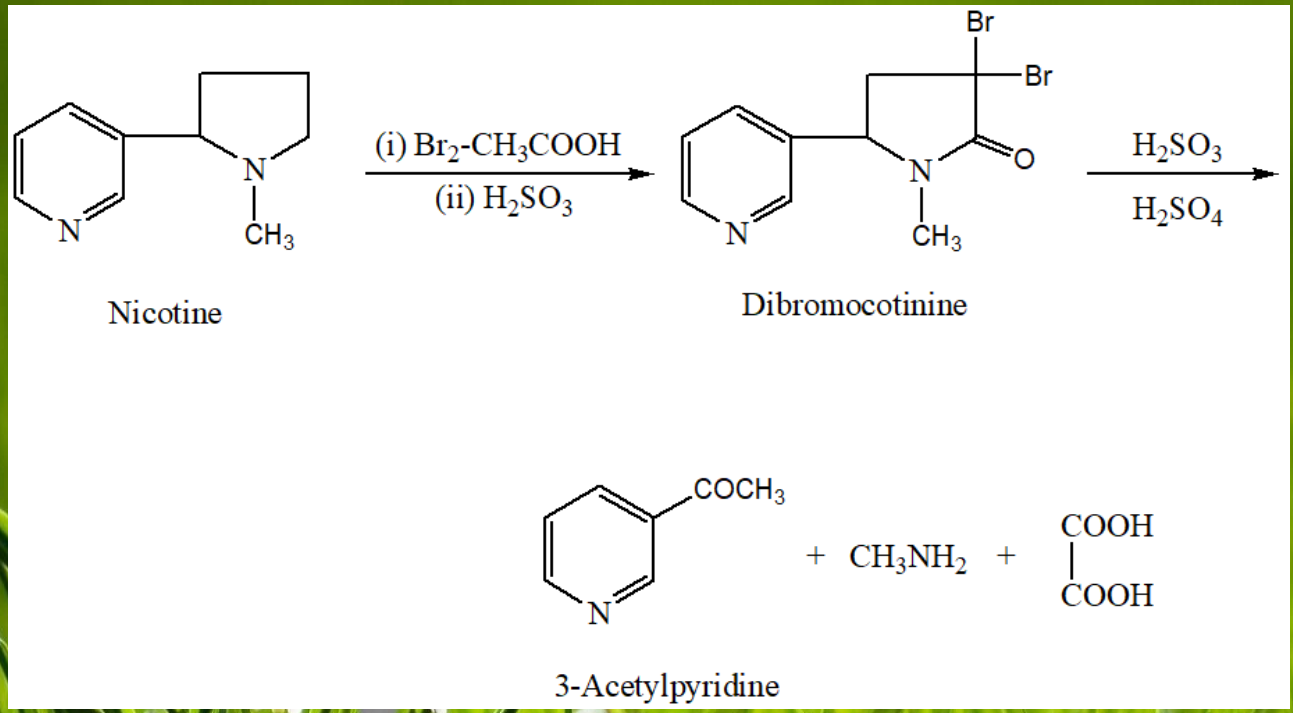
The formation of N-methylproline suggests beyond doubt that the pyrrolidine unit is attached to position 3 of the pyridine nucleus by means of α-position.

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



6. **Theproposedstructure alsoexplains thefollowingtwoPinner's observations,actuallytheabovestructurewas 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.

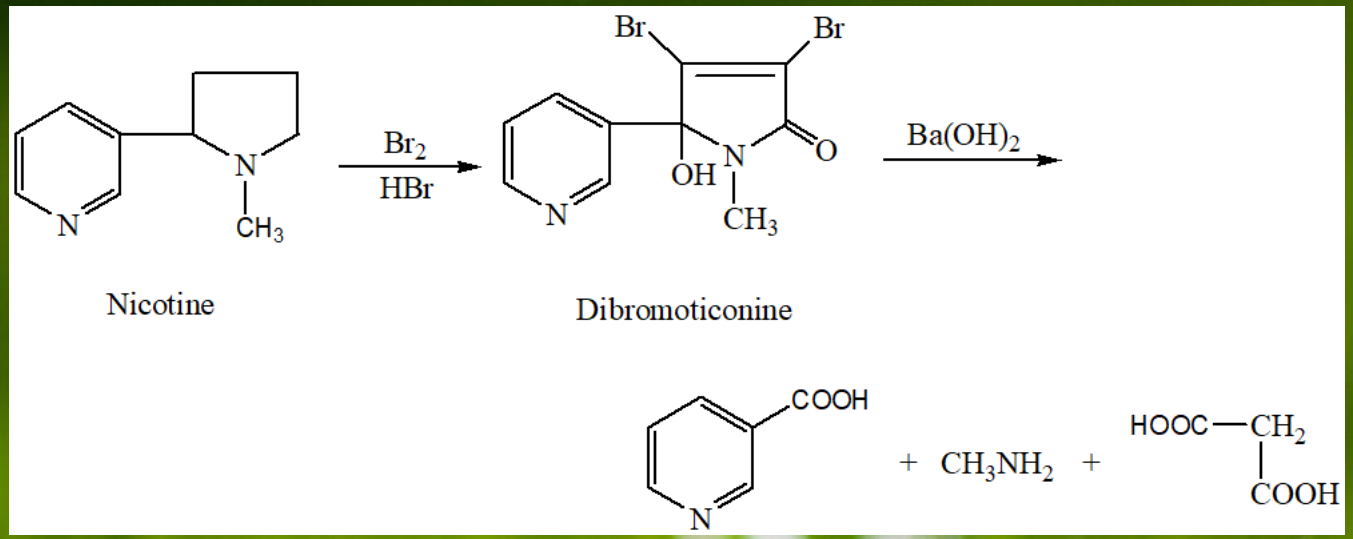


Nicotine

Dibromocotinine

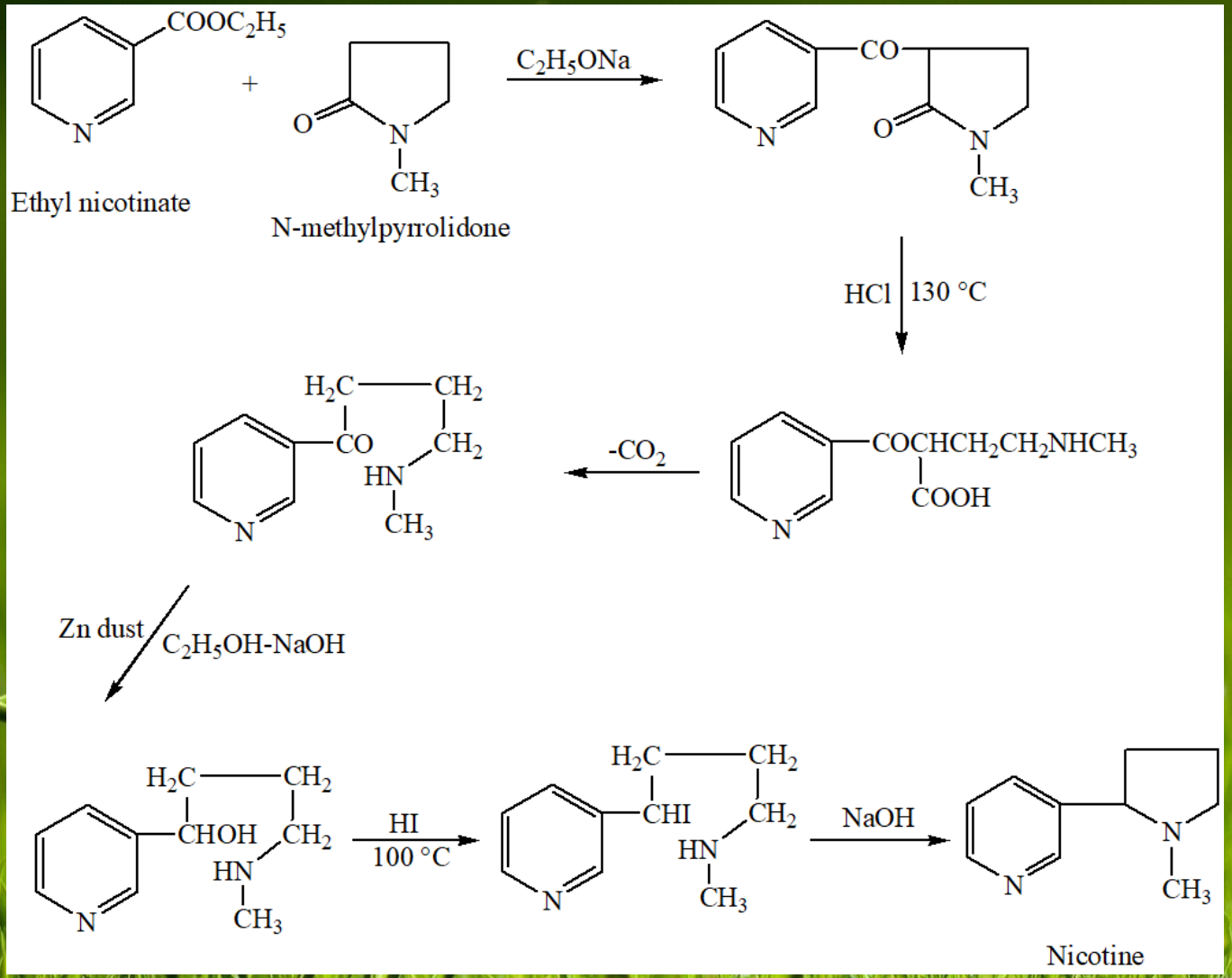
3-Acetylpyridine

(ii) Nicotineontreatmentwithbromineinpresenceofhydrobromicacidgivesdibromoticoninewhichonheatingwith $Ba(OH)_2$ solution at 100 °C affords nicotinic acid, malonic acid and methylamine.

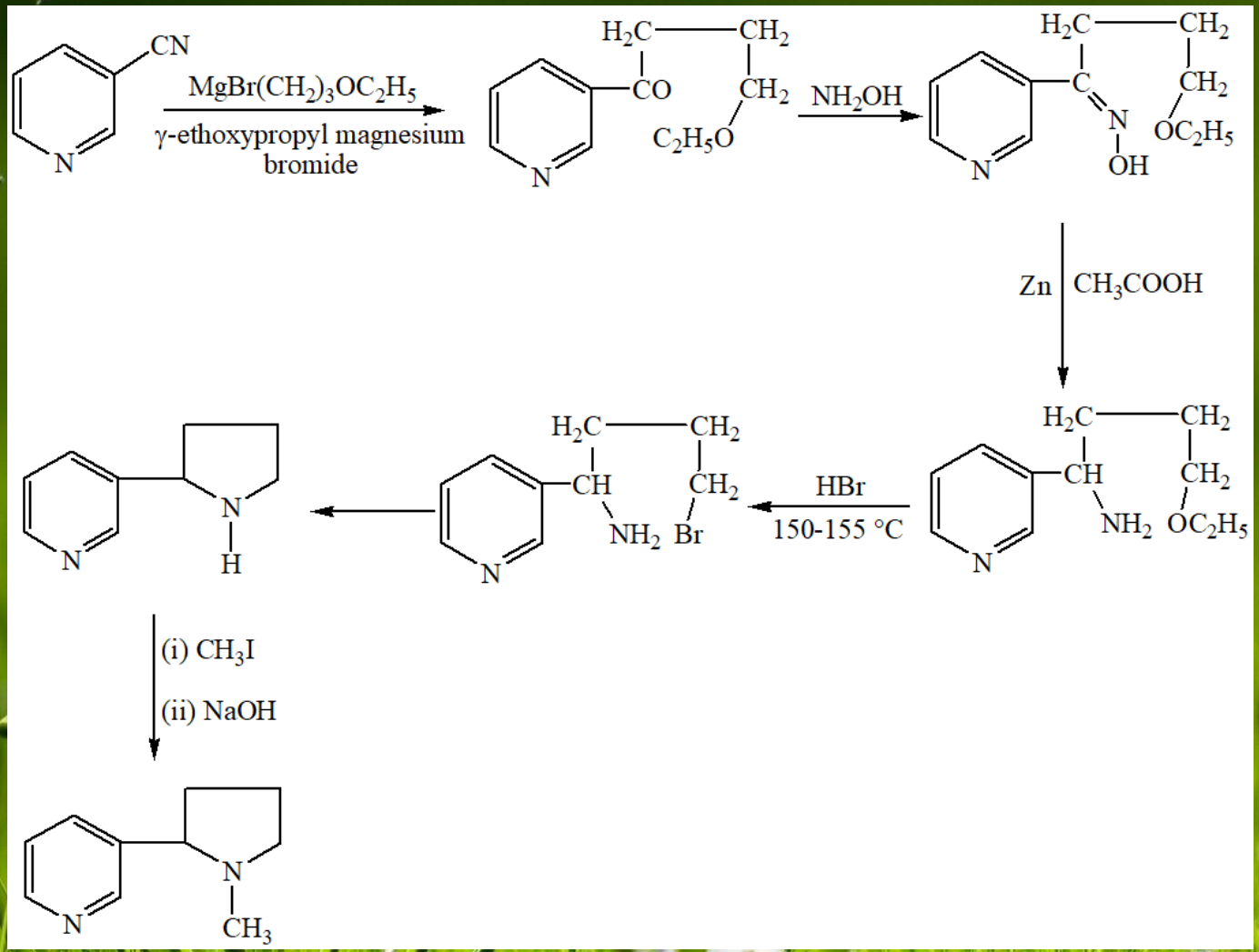


7. Lastlythe structureofnicotineisprovedbyits synthesis.

Synthesis:(i)Spathetal.(1928).ThisinvolvestheClaisencondensationofethylnicotinatewithN-methyl-2- pyrrolidone.



(ii)Craigetal.(1933):



(iii)Hellmanand Dieterich, 1962: