US06CCHE21 : Organic Chemistry

UNIT – II : Alkaloids

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Introduction to Alkaloids

The term "alkaloids" was first of all introduced by W. Meissner in 1819. According to him, "Alkaloids (which mean alkali-like, alk-alkali, oid-like) were defined as basic-nitrogen compounds isolated from plants." In 1880, Konigs suggested the definition of alkaloids as : "Alkaloids should be defined as naturally occurring organic bases which contain a pyridine ring."

Finally it can be defined as " Alkaloids are basic nitrogenous plant products, mostly optically active and possessing nitrogen heterocycles as their structural units, with a pronounced physiological action."

However there are exceptions that some compounds although alkaloids do not confine to this definition, while other compounds which are not alkaloids confine to this definition. Examples are :

(i) Colchicine is regarded as an alkaloid because, although it is not heterocyclic and is scarcely basic, it is active pharmacologically and is of restricted botanical distribution.
(ii) Thiamine, although it is heterocyclic nitrogenous base, is not classed as an alkaloid because it is universally distributed in living matter.
(iii) A considerable number of compounds like ephedrine, hordenine, betaines, choline, muscarine, stachydrine and tryptamine, although they do not contain their nitrogen as part of a heterocyclic system, are classed as alkaloids or protoalkaloids.
(iv) Naturally occurring open-chain bases like cholines, amino acids and phenylethylamines with marked physiological activity are not referred to as alkaloids.
(v) A compound like caffeine which fully satisfies the definition of alkaloids (given as above) is not included in alkałoids.
(vi) Piperine (a compound from black pepper) neither basic nor possessing any physiological activity, is included in the list of alkaloids.

There is a great diversity, and often complexity, in the chemical structures of alkaloids.

Occurrence of Alkaloids

Alkaloids are a chemically heterogeneous group of approximately 2,500 basic nitrogen containing substances found in about 15 percent of all vascular land plants and in more than 150 plant families. They are widely distributed in higher plants particularly the dicotyledons (in abundance in the families Apocynaceae, Papaveraceae, Papilionaceae, Ranunculaceae, Rubiaceae, Rutaceae and Solanaceae) but less frequently in lower plants and fungi.

In plants, alkaloids, due to their basic nature, generally exist as salts of organic acids like acetic, oxalic, citric, malic, lactic, tartaric, tannic, aconitic acids, etc. Some feeble basic alkaloids like nerceine, nicotine, etc. occur free in nature. A few alkaloids also occur as glycosides of sugars like glucose, rhamnose and galactose (e.g., alkaloids of Solanum and Veratrum groups), as amides (piperine) or as esters (atropine, cocaine), of organic acids. Also, the structurally related alkaloids generally occur in the form of salts of the same acid, e.g., cinchona alkaloids with quininic acid, aconite alkaloids with aconitic acid, and opium alkaloids with neconic acid.

The concentration of alkaloids in plants depends upon the season, age and its locality. It is interesting to note that closely related alkaloids generally occur together in the same plant. For instance, twenty alkaloids have been isolated from opium. 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 Solanaceae contain hyoscyamine. It is also found that simple alkaloids are often found in different plants whereas the complex alkaloids in one species or genus of a family.

Functions of Alkaloids :

The functions of alkaloids within the plants are not clearly understood but it is clear that they are not produced in plants for a single function but for many functions that are summarized as follows :

(i) They may act as reserve substances to supply nitrogen.
(ii) They may be end-products of detoxification mechanisms otherwise their accumulation in plants may otherwise cause damage to the plants.
(iii) They may act as poisonous substances which afford plants safety from herbivores and insects.
(iv) They may function as plants stimulants or regulators similar to the hormones in the activities like growth, metabolism and reproduction.
(v) They may act as reservoirs for protein synthesis.

It is interesting to note that 85 to 95 percent plants carry out all their normal activities without involving alkaloids, thus indicating that the function of the alkaloids within the plants, if any is still not understood clearly.

Nomenclature of Alkaloids:

Due to the complex molecular structure of alkaloids and some historical reasons, there was no systematic nomenclature of alkaloids. However, alkaloids are named according to various methods which are as follows:

(a) A large number of alkaloids have been named according to the plants from which they are obtained. viz., papaverine from papaver someniferum and berberine from Berberis Vulgaris L.
(b) A few alkaloids are named according to their physiological action such as morphine (Ger, morphin- God of dreams), narcotine (Greek-narkoo-to benumb) and emetine (Greek-emetikos-to vomit).
(c) Some alkaloids have been named after the name of their discoverer. For example, pelletierine group has been named after its discoverer, P.J. Pelletier.
(d) The name of minor alkaloids has been derived by adding one prefix or suffix to the name of principal alkaloids as for example in cinchona series.
(e) Sometimes, related bases have been named by transpositions, as narcotine, cotarnine and tarconine.
(f) Prefixes such as epi, iso, neo, pseudo etc., or Greek letters have been used to designate isomeric or slightly modified structures. The prefix nor denotes the structure which does not have a methyl group attached to the nitrogen atom.

Classification of Alkaloids:

There are several methods of classification of alkaloids. Some of these are as follows:

(a) **Taxonomic.** This is done according to family. Thus, alkaloids may be described as solanaceous or Papilionaceous without reference to the chemical type of alkaloid present. Since both families contain alkaloids of several types (solanaceae-tropane, pyridine, steroidal, papilionaceae-quinolizidine and pyrrolizidine), then the disadvantages of the systems are obvious. It is more usual to describe alkaloids according to the genus in which they occur, e.g., Ephedra, Cinchona, etc.
(b) **Pharmacological.** Pharmacological classification lists alkaloids according to their use or physiological activity, e.g., analgesic alkaloids, cardioactive alkaloids, etc. Whereas alkaloids within a group frequently have chemical similarities, this is by no means the rule.

(c) Biosynthetic. This is more fundamental method than chemical classification, depending as it does on the types of precursors or building block compounds used by plants to synthesize complex structures. It is worth mentioning that of the hundreds of complex indole alkaloids known all are derivable from the amino acid tryptophan and mevalonic acid, as are the Ergot and Cinchona alkaloids. Similarly, morphine, papaverine, narcotine, tubocurarine and colchicine may be listed as phenylalanine tyrosine derived bases. The disadvantage with this method is that whereas it is all encompassing, the relationship of alkaloids to each other and to their precursors is not always immediately apparent.

(d) **Chemical.** The chemical classification of alkaloids is universally adopted and depends on the fundamental (frequently heterocylic) ring structure present. Thus, quinine is regarded as a quinoline type, papaverine and isoquinoline and ergometrine an indole. On the other hand, morphine, which is normally regarded as a phenanthrene derivative could easily be included with the quinolines; thus to some extent chemical classification depends on the convention adopted.

On the basis of chemical classification, numerous classes of alkaloids are possible but we shall be mentioning the names of such classes which we are going to discuss in this chapter:

1. Phenylethylamine alkaloids
2. Pyrrolidıne alkaloids
3. Pyridine or piperidine alkaloids
4. Pyridine-pyrrolidine alkaloids
5. Tropane alkaloids
6. Quinoline alkaloids
7. Isoquinoline alkaloids
8. Phenanthrene alkaloids
9. Indole alkaloids
10. Tropolone alkaloids

Isolation or Production of Alkaloids:

Isolation and purification of an alkaloid from a plant is always not a simple process because an alkaloid bearing plant generally contains a complex mixture of several alkaloids. In addition, products like glycosides, organic acids, etc. present in plants may complicate this isolation still further. Thus, the isolation of an pure alkaloid may become an extremely laborious procedure sometimes.

Some general principles underlying the isolation techniques may be summarized as follows:

(a) First of all, the presence of an alkaloid in a plant is ascertained by employing various reagents called alkaloidal reagents like Mayer's reagent (potassium mercuric iodide), Dragendorff's reagent (potassium bismuth iodide). Wegner's reagent (iodine dissolved in potassium iodide) and Hager's reagent (saturated solution of picric acid in water). Also, chloroplatunic (H_2PtCl_6), chloroauric ($HAuCl_4$,). phos-photungstic and molybdic acids, are useful precipitating reagents. These precipitates have characteristic colours and are used for the detection of alkaloids in very small amounts. Other colour reagents which are used for the detection of alkaloids are concentrated solutions of formaldehyde (Marquis reagent) or nitric acid (Erdmann's reagent) or molybdic acid (Frohde's reagent), etc.

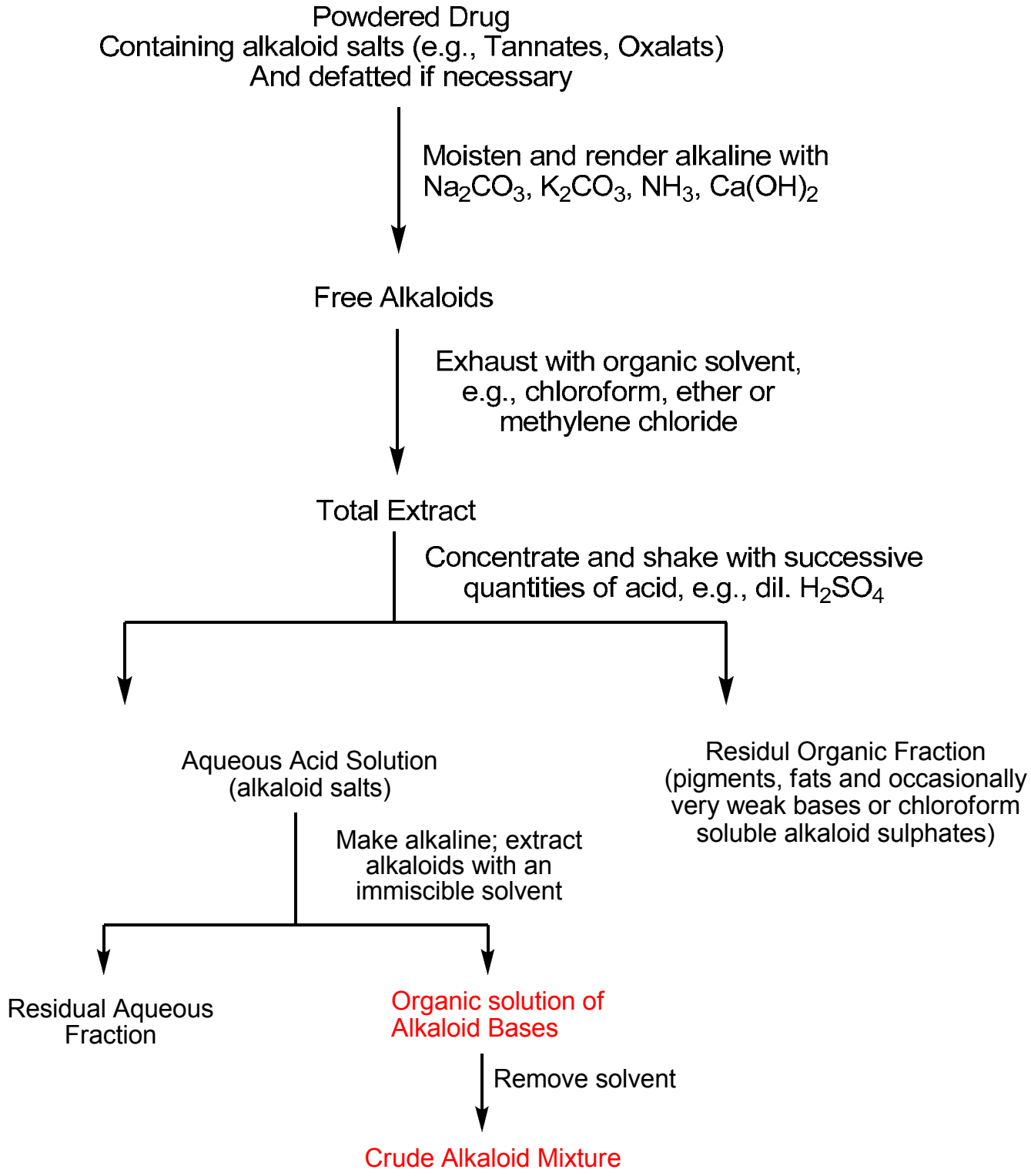
(b) After detection, the next step involves the separation of a relatively small percentage (dry weight basis) of alkaloids from a large amount of extraneous plant material. For example, opium contains 10% morphine, Cinchona 5-8% quinine, Atropa belladonna 0.2% hyoscyamine and Rauwolfia serpentina root 0.1 to 0.2% reserpine.

(c) Final step involves the separation and purification of individual alkaloids from the crude extract.

For isolation of small quantity of an alkaloids, **chromatography** is most satisfactory. This quantity may be useful for research purposes. If, however, an appreciable quantity of alkaloid is required, one of the three general methods described below is usually adopted for the initial isolation. These exploit the property that simple salts of many alkaloids are water soluble but much less soluble in organic solvents, whereas the reverse is true for free bases. The technique involves the distribution of the alkaloid bases between acid or alkaline aqueous solutions and immiscible organic solvents. It is known as the **Stas-Otto process.** The three methods of extracting the alkaloids differ in that Method -I employs water immiscible solvents such as chloroform, ether and methylene chloride for extraction, Method- 2 uses a water-miscible solvent while Method- 3 involves the use of acidulated water or alcohol.

We shall discuss these methods one by one.

Method- 1. The various steps of this method are :



Extraction of alkaloids by Method 1.

This method suffers from the following disadvantages:

(i) Mixing of the powdered material with alkali is tedious and requires special (expensive) equipment.
(ii) Deep penetration of the moist drug with solvent is unlikely; therefore a large number of extractions are required.
(iii) Ether is a fire hazard and also much of it is lost by retention in the exhausted drug, which makes the process costly.
(iv) Chlorinative solvents are a health hazard.

Method 2: In method 2, the powdered drug is extracted with methanol, ethanol or isopropanol and the resultant extract submitted to the same process as that of method 1.

Method 2 is better than 1: as it requires no alkali; gives good penetration of the drug, therefore, only four extractions may be needed, where as method-1 often requires 10 to 12 extractions, gives less solvent loss, and is less of a health and fire hazard.

Method 3. In method 3, the alkaloid is extracted from the plant material with acidulated water or alcohol. Pigments and other unwanted materials are removed from the initial extract by shaking with chloroform or other suitable solvent. The free alkaloids are then precipitated from the aqueous fraction by the addition of excess alkali and separated by filtration or with an immiscible solvent.

Method 3 is a good cheap method but water dissolves large quantities of unwanted plant constituents such as sugars, colouring matters, tannins and resins which may complicate purification of the alkaloids.

Large scale extractions based on the above methods are often carried out in the field and crude alkaloid mixtures sent to factories for separation and purification. Crude mixtures are usually purified by fractional crystallisation of salts such as sulphates, oxalates, tartrates, picrates, etc. On the small scale chromatographic methods, and sometimes counter-current distribution, may be employed.

General Properties of Alkaloids

(a) Most of the alkaloids are generally colourless crystalline solids which are insoluble in water but soluble in organic solvents like chloroform, alcohol, ether, etc. However, some alkaloids (e.g., coniine and nicotine) are liquids which are soluble in water. Also, a few alkaloids are coloured, e.g. berberine is yellow.

(b) They are generally bitter in taste and are optically active; the majority being laevorotatory. The optically active alkaloids are often useful for resolving racemic acids.

(c) Nearly, all alkaloids due to their basic character, form crystalline salts with inorganic as well as organic acids. These salts, unlike the parent alkaloids are generally soluble in water but insoluble in organic solvents. Parent alkaloids are obtained from these salts by treating them with bases. With chlorides of gold, platinum and mercury, they form double salts.

(d) Alkaloids also yield insoluble precipitates when, reacted with solution of phosphor tungstic acid, phosphomolybdic acid, picric acid, potassium nercuri-iodide, etc. Many of these precipitates have definite crystalline shapes and so may be used for the identification of an alkaloid. Some of these reagents are being employed for detecting the alkaloids especially in paper and thin layer chromotography.

(e) Most of the alkaloids contain oxygen.

(f) Most of the alkaloids contain one or two nitrogen atoms usually in the tertiary state in a ring system. Most alkaloids react with methyl iodide to form crystalline adducts, the precise nature of the adducts depends upon whether the alkaloid is a secondary or tertiary base.

General Methods Employed for Determining Structures of Alkaloids

Introduction : 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 these days to establish the molecular structures of all the known, simple as well as complex, alkaloids.

In principle, the determination of the structure of an alkaloid can be done in exactly the same way as for any other type of compound. In practice, however, the problem has been simplified considerably by using certain selective reactions as well as analytical techniques to locate and estimate quantitatively the presence of particular functional groups and substituents which are present in various alkaloids. In general, the following pattern of procedure is adopted to establish the molecular structure of an alkaloid (however, the sequence of steps in this examination need not be followed rigidly):

1. Molecular Formula Determination: After a pure specimen has been obtained, its elemental composition, and hence the empirical formula, is found by combustion analysis. Then, its molecular weight is determined by the Rast procedure (Depression of the freezing point) to establish its molecular formula. This fundamental procedure may

furnish even more useful information by calculating the number of double bonds equivalent's corresponding to the found molecular formula. Its calculation is based upon the simple fact that introduction of a double bond or cyclization of the chain decreases the molecular formula by two hydrogen atoms relative to the corresponding saturated aliphatic hydrocarbon. For example, the difference between hexene (C_6H_{12}) from hexane (C_6H_{14}) is two hydrogens and this difference is called a double bond equivalent. Similarly, the difference between benzene (C_6H_6) and hexane (C_6H_{14}) is eight hydrogens which will correspond to 8/2 or 4 double bond equivalents (accommodated by the three double bonds and one ring).

The above procedure is valid for simpler compounds only. However, for complex formulae, where elements other than hydrogen and carbon are present, the simpler method is that for any formula $\mathbf{C_aH_bN_cO_d}$

the number of double bond equivalents (**DBE**) is given by the following expression:

$$\mathbf{a - \frac{1}{2}\, b + \frac{1}{2}\, c + 1}$$

The above method for the calculation of double bond equivalents is also useful to calculate the number of rings in a given compound. For example, hygrine has the molecular formula, $C_8H_{15}NO$ which corresponds to [a=8, b=15, c= 1]

$$\mathbf{8 - 15/2 + \frac{1}{2} + 1 = 2}$$

double bond equivalents. However, chemical tests reveal that hygrine contains only one carbonyl group (one double bond equivalent) and does not show any other form of unsaturation. Thus, hygrine must be monocyclic to account for the other double bond equivalent.

Another simple example is mescaline, $C_{11}H_{17}NO_3$ which corresponds to [a=11, b=17, c= 1]

$$\mathbf{11 - 17/2 + \frac{1}{2} + 1 = 4}$$

double bond equivalents. Experimentally, it is found that mescaline does not contain unsaturated groups. This indicates that mescaline is probably aromatic because four double bond equivalents correspond to aromatic ring.

The presence of unsaturation in an alkaloid may also be ascertained by treating the alkaloid with bromine or halogen acid or alkaline potassium permanganate when a glycol is obtained. If the alkaloid is optically active, its specific rotation is also measured.

2. Functional Group Analysis. Application of classical techniques of organic analysis (especially if the alkaloid is available in appreciable amounts) and/or infra-red examination (especially if the alkaloid is available only in small amounts) can reveal the nature of the functional groups present. This will also reveal the aromatic or aliphatic nature of the alkaloid and the unsaturation, if present.

3. Functional Nature of Oxygen. If an alkaloid contains oxygen, it may be present as -OH (phenolic or alcoholic), methoxy ($-OCH_3$), acetoxyl ($-OCOCH_3$), benzoxyl ($-OCOC_6H_5$), carboxylic (-COOH), carboxylate (-COOK) or carbonyl (>C=O) groups. Occasionally, lactone ring systems have also been encountered (e.g., narcotine, hydrastine). These functions have been detected by the usual methods of organic analysis including infrared examination. Various oxygen functional groups can be characterized according to the following characteristics :

(a) Hydroxyl Group. Its presence in an alkaloid can be ascertained by the formation of acetate, on treatment with acetic anhydride or acetyl chloride or by the formation of benzoate on treatment with benzoyl chloride in the presence of sodium hydroxide.

$$R\text{-}OH + (CH_3CO)_2O \longrightarrow ROOCCH_3 + CH_3COOH$$

$$R\text{-}OH + CH_3COCl \longrightarrow ROOCCH_3 + HCl$$

$$R\text{-}OH + C_6H_5COCl \longrightarrow ROOCC_6H_5 + HCl$$

However the above test for oxygen should be applied carefully because primary amines if present in an alkaloid also yield acetyl and benzoyl derivatives. Then the number of hydroxyl groups is determined by or Zerewitnoff's method. In the former method, the number of hydroxyl groups is determined by acetylating the alkaloid and hydrolyzing the acetyl derivative with a known volume of 1 N NAOH.

$$R\text{-}OH \xrightarrow{CH_3COCl} R\text{-}OCOCH_3 \xrightarrow{NaOH} R\text{-}OH + CH_3COONa$$

The excess of alkali is estimated by titration with a standard solution of HCl acid. The number of acetyl groups or hydroxyl groups can be calculated from the volume of alkali used for hydrolysis. In the latter method, hydroxyl groups (and any N-H groups) can be detected and quantitatively estimated by treatment with methylmagnesium iodide.

$$-O-H + MeMgI \longrightarrow -O-MgI + CH_4$$

$$>N-H + MeMgI \longrightarrow >N-MgI + CH_4$$

In this method, CH_4 is obtained quantitatively and therefore can be estimated volumetrically, giving the confirmation about the number of -OH and >NH groups. Thus,

1-OH group = 1 >NH Group = 22.4 litres of N_2 at S.T.P.

(b) Phenolic hydroxyl group (>C-OH) or Alcoholic hydroxyl group (>C-OH) The next problem is to ascertain whether the hydroxyl group is alcoholic or phenolic. It is said to be phenolic if the alkaloid is :
(i) soluble in sodium hydroxide;
(ii) reprecipitated by carbon dioxide and
(iii) giving a coloration with ferric chloride.

If the alkaloid does not respond to the above tests of phenol, the hydroxyl group may be assumed to be alcoholic. However, one can verify this assumption by the action of dehydrating agents on alkaloids (the most alkaloids having an alcoholic group are readily dehydrated by sulphuric acid or phosphorus acid). Thus, the behaviour of the alkaloid towards oxidizing agents will also reveal the presence of an alcoholic group. It is further confirmed by characteristic absorption spectrum in the infrared in the 3.0 μ region.

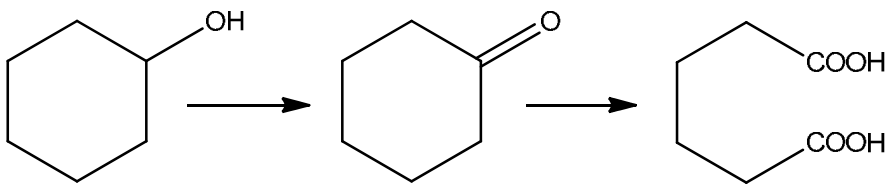
If alcoholic hydroxyl group is present, then the nature of the alcoholic group, i.e. primary, secondary or tertiary, is determined by oxidation or by dehydration to unsaturated compound.

(i) Primary alcoholic group ($-CH_2OH$) on oxidation yields first an aldehyde (-CHO) and then acid having the same number of carbon atoms as the parent alcohol.

$$-CH_2OH \longrightarrow -CHO \longrightarrow -COOH$$

(ii) On oxidation, secondary alcohol (>CHOH) first yields ketone having the same number of carbon atoms and then acid having the lesser number of carbon atoms. However, if the secondary alcoholic group is attached to cyclic carbon atom, then the compound gets oxidized to open chain dicarboxylic acid having the same number of carbon atoms.

$$>CHOH \longrightarrow >C=O \longrightarrow \text{Acids with lesser number of carbon atoms}$$

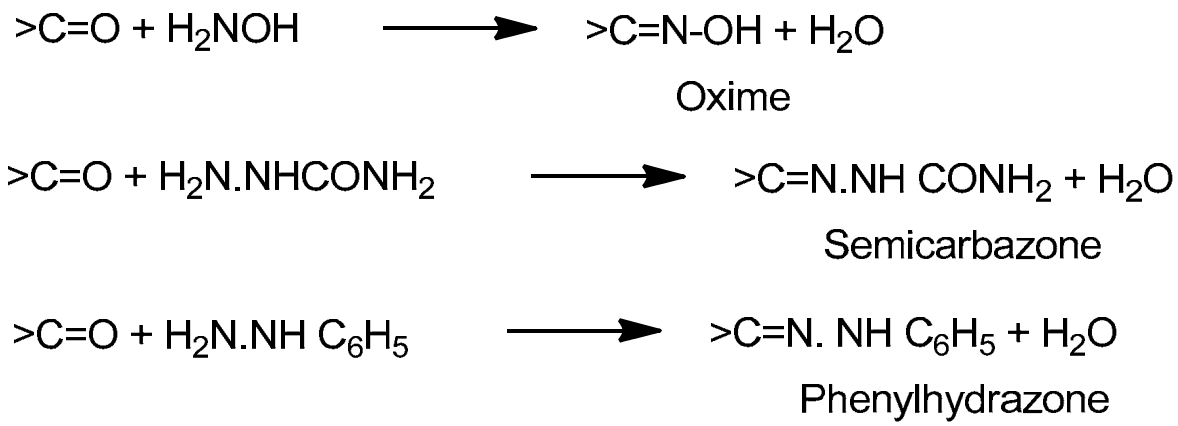


(iii) Tertiary alcohols on oxidation yield ketone and acid having the lesser number of carbon atoms.

(c) Carboxylic Group. The solubility of the alkaloid in aqueous sodium carbonate or ammonia reveals the presence of a carboxylic group. The formation of ester on treatment with an alcohol also reveals the presence of carboxylic group.

The number of carboxylic groups may be determined volumetrically by titration against a standard barium hydroxide solution using phenolphthalein as an indicator or gravimetrically by silver salt method.

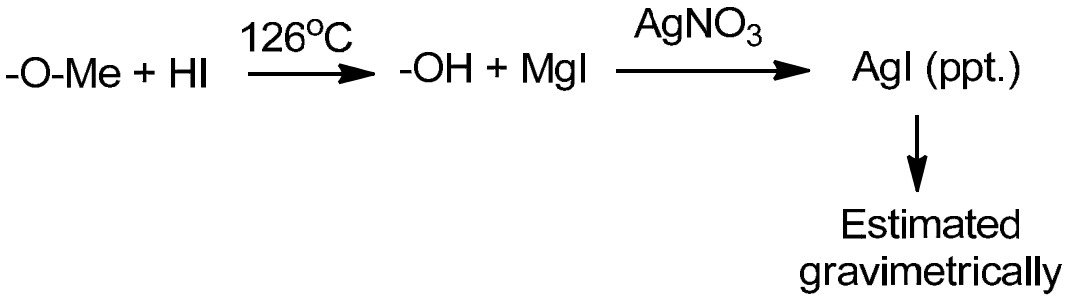
(d) Oxo Group. The presence of this group is ascertained by the reaction of an alkaloid with hydroxylamine semicarbazide or phenylhydrazine when the corresponding oxime, semicarbazone or phenylhydrazone are formed.



Distinction between an aldehyde and a ketone can be made on the basis of reduction and oxidation reactions.

The presence of an oxo group and distinction between an aldehyde and a ketone may be further confirmed by several physical methods such as infra-red, ultraviolet and NMR techniques.

(e) Methoxy Group. The detection of this group and its number may be determined by the Zeisel determination, analogous to the Herzeg-Meyer method for N-methyl groups. In this method, a known weight of alkaloid is heated with hydroiodic acid at its boiling point (126°C) where the methoxy groups are thereby converted into methyl iodide which is then absorbed by ethanolic silver nitrate and the precipitated silver iodide is filtered, dried and weighed. From the weight of silver iodide, the number of methoxyl groups may be calculated.

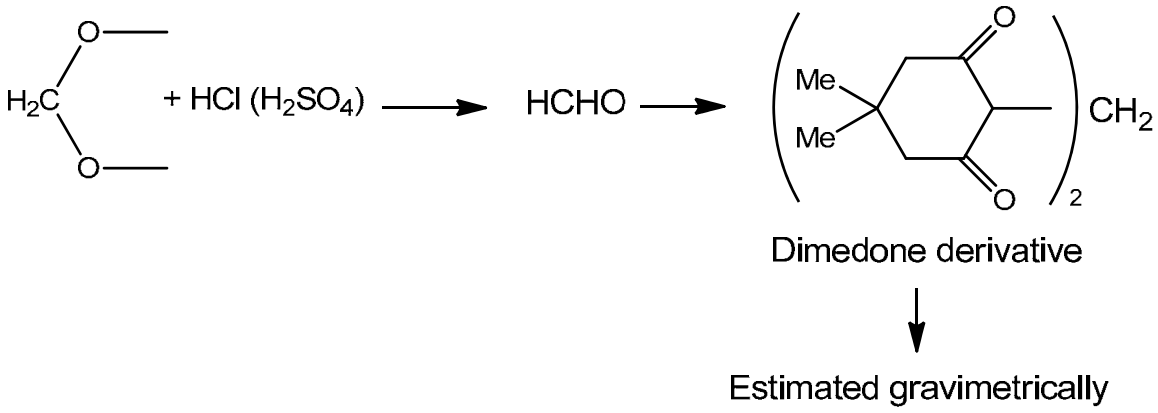


For example, papaverine, $C_{20}H_{21}O_4N$, when treated with hydrogen iodide, consumes four moles of hydrogen iodide, producing 4 moles of silver iodide and thus confirming the presence of four-OCH_3 groups.

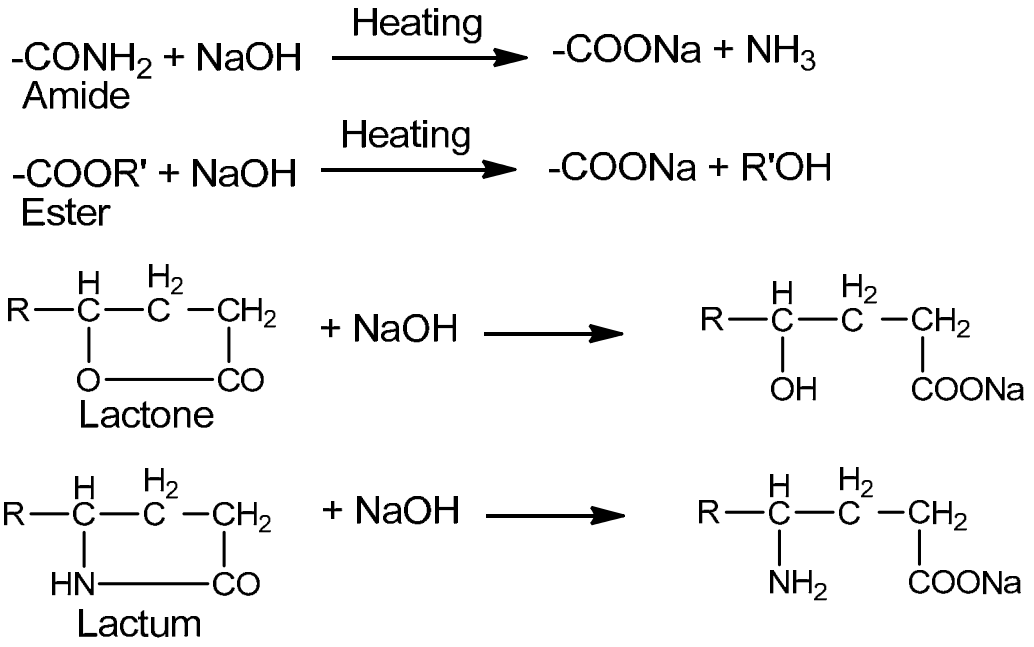
$$C_{16}H_9N(OCH_3)_4 + 4HI \longrightarrow C_{16}H_9N(OH)_4 + 4CH_3I$$

$$4CH_3I + 4AgNO_3 \longrightarrow 4AgI\downarrow + 4\ CH_3NO_3$$

(f) Methylenedioxyl Group (-OCH_2OO-). If an alkaloid contains this group, formaldehyde is obtained when this alkaloid is heated with hydrochloric or sulphuric acid. Formaldehyde obtained in this reaction is converted into dimedone derivative, which can be estimated gravimetrically, thus giving the information about the number of –OCH_2O- groups.



(g) Ester, Amide, Lactone and Lactum Groups. These groups can be detected and estimated by observing the products of their alkali or acid hydrolysis.



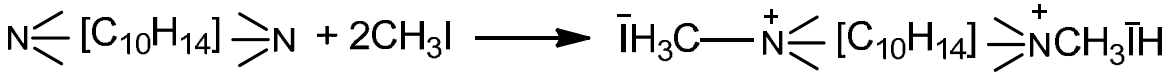
4. Nature of Nitrogen. All alkaloids contain nitrogen. But in the majority of alkaloids it is present as a part of a heterocyclic system. Therefore, it must be either a secondary (>NH) or tertiary (>N-CH_3 or >N-). However, there are phenyl alkyl amine type of alkaloids (adrenaline, ephedrine, etc.) which do not contain nitrogen as a part of a heterocyclic ring but in the form of a primary amino (-NH_2) group

(a) The general reactions of the alkaloid with acetic anhydride, methyl iodide and nitrous acid often show the nature of the nitrogen. However, these reactions must be interpreted with caution as occasionally subtle changes such as ring scission occur.

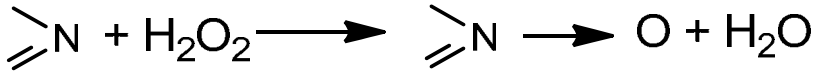
If the alkaloid reacts with one mole of methyl iodide to form N-methyl derivative, it means that a secondary nitrogen atom is present. For example, coniine, $C_8H_{17}N$ reacts with one mole of methyl iodide to form an N-methyl derivative, indicating that coniine must contain secondary nitrogen atom.

$$(C_8H_{16})\,NH + CH_3I \longrightarrow (C_8H_{16})\,N\text{-}CH_3 + HI$$

If an alkaloid reacts additively with one mole of methyl iodide to form crystalline quaternary salt, this indicates that nitrogen atom present in this alkaloid is tertiary. For example, nicotine reacts additively with two moles of methyl iodide, indicating that it contains both nitrogen atoms as tertiary.

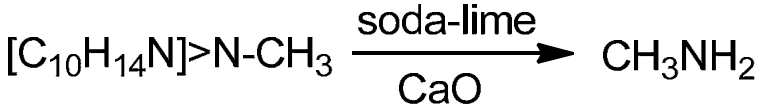


One can detect the tertiary nitrogen atom in an alkaloid by treating it with 30 percent hydrogen peroxide (H_2O_2) when tertiary nitrogen is oxidized to amine oxide.

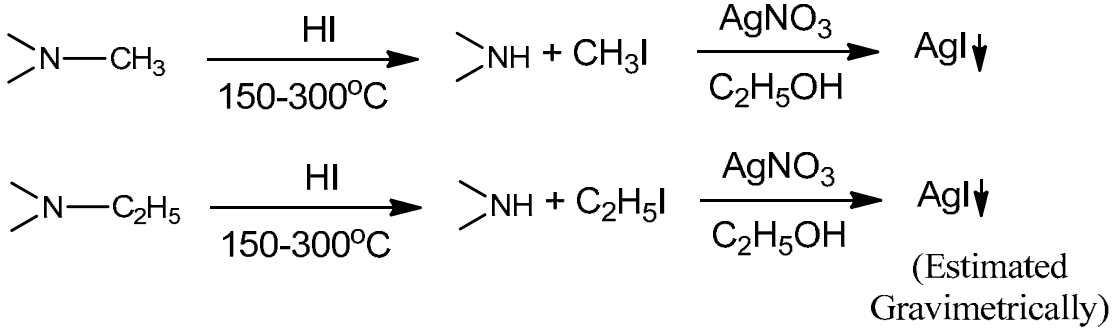


(b) When an alkaloid is distilled with aqueous potassium hydroxide (KOH), the nature of products formed leads to the information regarding the nature and number of alkyl groups which are attached to nitrogen. The formation of methyl amine, dimethylamine or trimethyl amine indicates respectively the attachment of one, two or three methyl groups to a nitrogen atom, the formation of ammonia shows the presence of an amino group.

(c) The presence of N-methyl group is often detected by distillation of alkaloid with soda-lime when methyl amine is obtained. For example, nicotine on heating with soda-lime yields methylamine indicating that it must contain a N-methyl group.



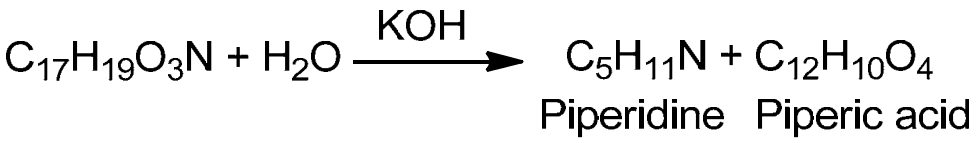
(d) Herzig-Meyer's method is used to detect and estimate the number of methyl groups attached to N-atom. This method consists in cleaving N-methyl amine present in an alkaloid with hydroiodic acid [HI] at 150-300°C and estimating the amount of methyl iodide so formed by conversion to silver iodide (AgI) with silver nitrate solution.



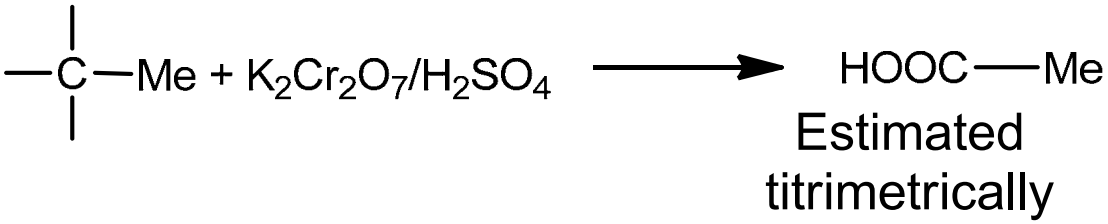
It must be kept in mind that methoxy group is also estimated by the above method but the temperature in that case is not 150-300°C but 126°C.

(e) The amide linkage, if present, shall be indicated by hydrolysis followed by the characterization of acid and amine moieties. For example, piperine ($C_{17}H_{19}O_3N$), when hydrolyzed with alkali, yields piperidine and piperic acid. But piperidine is a base

and piperic acid is a monobasic acid. Therefore, piperine is the piperidine amide of piperic acid.



5. Estimation of C-Methyl Groups. C-Methyl groups are quantitatively estimated by the Kuhn- Roth oxidation, the acetic acid formed being distilled off and the distillate titrated against standard base.



6. Degradation of Alkaloids. The analytical steps, described as above, establish the nature of nitrogen atom (s) and usually at least some of the oxygen atoms in the alkaloid molecule. In those cases, where these preliminary investigations fail to identify nitrogen and oxygen atoms, then one must perform usual laboratory tests for the common functional groups like aldehyde, ketone, ester, amide, etc. The problem now remains of discovering the structural system which incorporates these substituent groups and is tackled by degradation of the molecule and identification of the fragments formed from each reaction. Most of the reactions used in such work are follows:

(a) Hofmann exhaustive methylation method.

(b) Emde's degradation.

(c) Von Braun's method.

(d) Reductive degradation and zinc dust distillation

(e) Alkali fusion

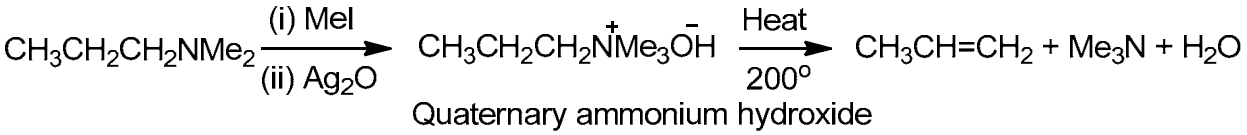
(f) Oxidation

(g) Dehydrogenation

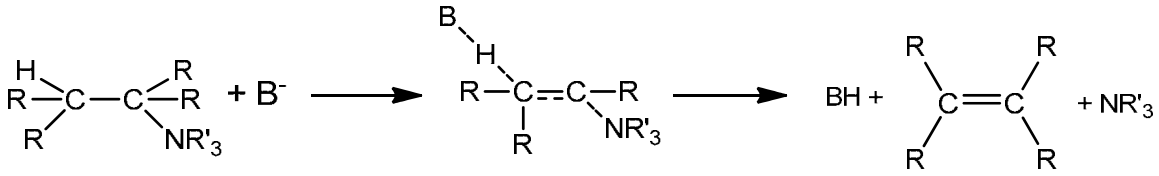
Let us discuss these steps one by one.

(a) Hofmann's Exhaustive Methylation Method. This is an important step in chemistry because by its means 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 ascertained.

The principle of this method is that compounds, which contain the structural unit -CH-C-NR,OH, eliminate a trialkylamine on pyrolysis at 200°C or above to yield an olefin.



The above step is very important and generally proceeds by an E_2 mechanism in which the requisite β-hydrogen, and quaternary nitrogen group are present in the trans-antiparallel configuration:

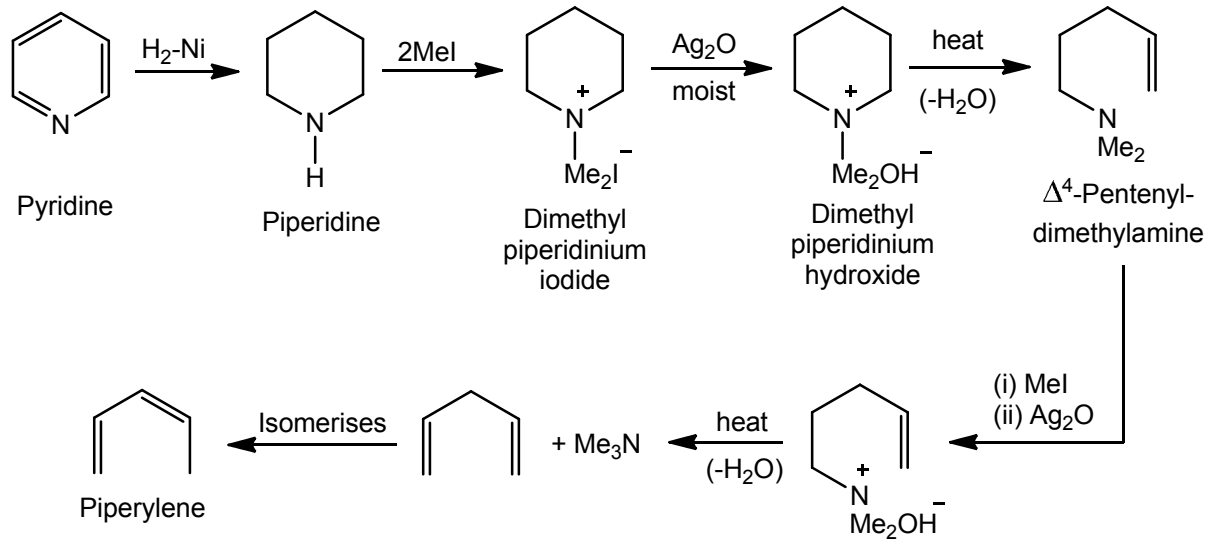


In practice, the alkaloidal amine is hydrogenated, followed by its conversion into the quaternary iodide by treatment with excess of methyl iodide and this salt is then converted into the more basic hydroxide by reacting with silver oxide. Then, the resultant product is heated at 200°C to give an olefin, with the elimination of a tertiary amine. Identification of the olefin by further degradation then often enables the position of the nitrogen atom in the original compound to be ascertained.

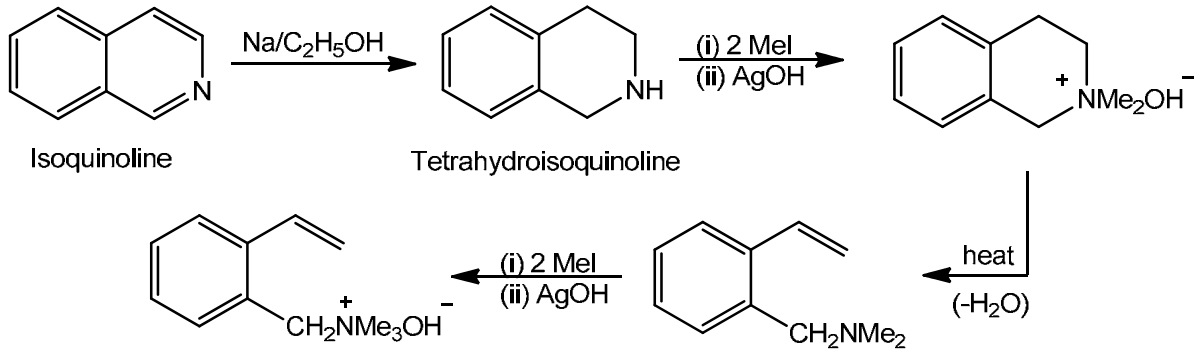
If the nitrogen atom forms a part of a cyclic structure, two or three such cycles are essential to liberate the nitrogen and expose the carbon skeleton. However, this method is applicable only to reduced ring systems such as piperidine and actually fails with analogous unsaturated compounded such as pyridine and therefore the latter should be first of all converted into the former. We will demonstrate this general phenomenon with the degradation of pyridine.

First of all pyridine is reduced to piperidine by catalytic dehydrogenation. Then, piperidine is treated with excess of methyl iodide to form quaternary ammonium iodide. The latter is reacted with moist silver oxide or aqueous potassium hydroxide to yield quaternary ammonium hydroxide which on heating loses a molecule of water with the cleavage of the C-N bond from the side from which β-hydrogen atom is eliminated. Now the process involving methylation, treatment with moist silver oxide and heating is

repeated on the product when there occurs the elimination of nitrogen as trimethylamine with the formation of water and unsaturated compound The latter then on isomerisation yields the more stable conjugated diene.

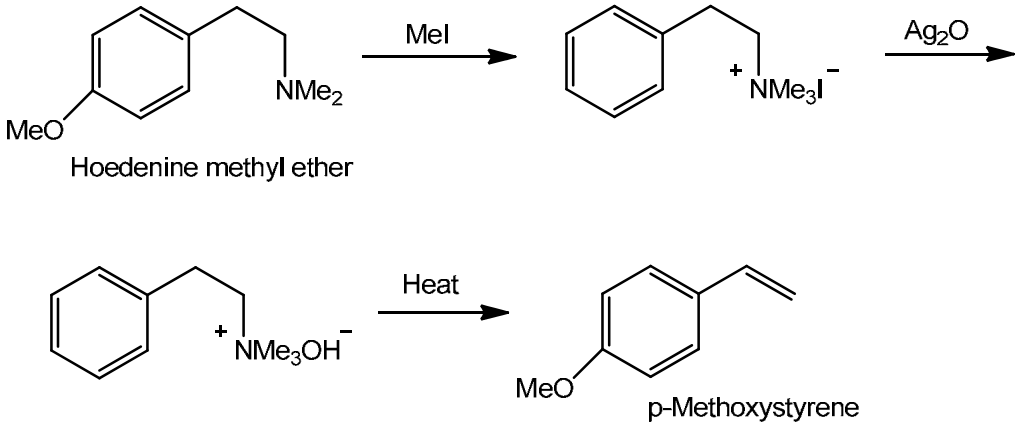


When a molecule of water is eliminated from quaternary ammonium hydroxide, hydrogen atom is always eliminated from the β-position, if this hydrogen is not available, the reaction fails. This can be understood from the degradation of isoquinoline only one time by Hofmann s method and nitrogen will not be removed from this product by this method.



In the above example, there is no β-hydrogen atom with respect to nitrogen. Therefore, it does not undergo Hofmann's degradation method.

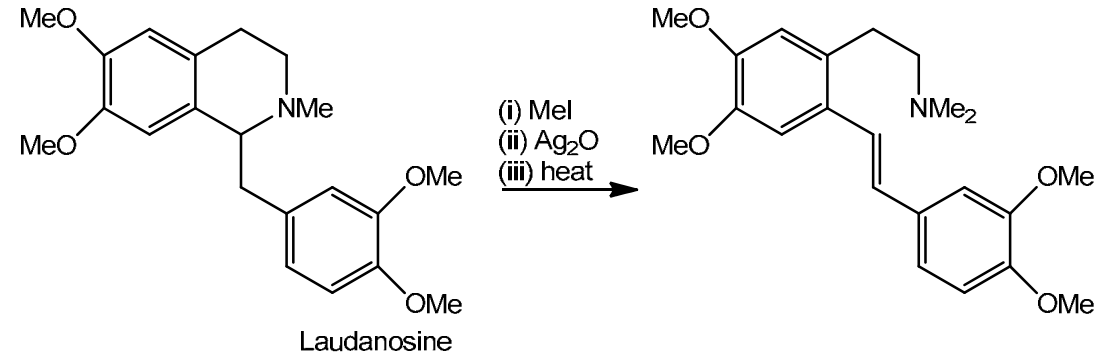
The Hofmann's degradation method can be applied to hordenine methyl ether which yields p- methoxy styrene.



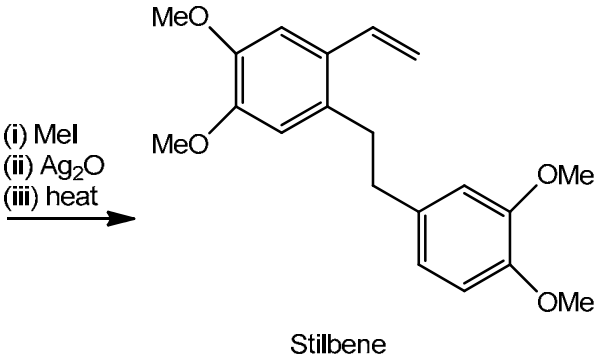
Hoedenine methyl ether

p-Methoxystyrene

If the ring incorporates the nitrogen atom, two complete sequences are to be carried out to eliminate it from the molecule. For example, laudanosine is converted into the stilbene derivative as follows:



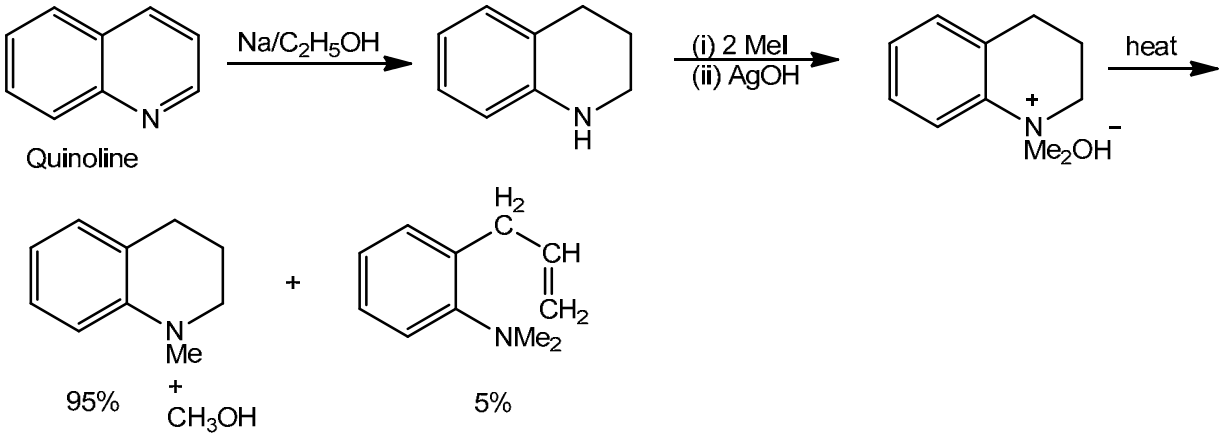
Laudanosine



Stilbene

When more than one sequence is required for eliminating the nitrogen atom, the overall process is sometimes known as exhaustive methylation and it is generally convenient in practice to hydrogenate the olefin formed after each elimination step, thus removing the possibility of double bond isomerism under the basic reaction conditions.

Hoffmann's exhaustive methylation fails (i) with unsaturated heterocyclic rings, (ii) when there is no β -hydrogen atom and (iii) with tetrahydroquinoline. For example,



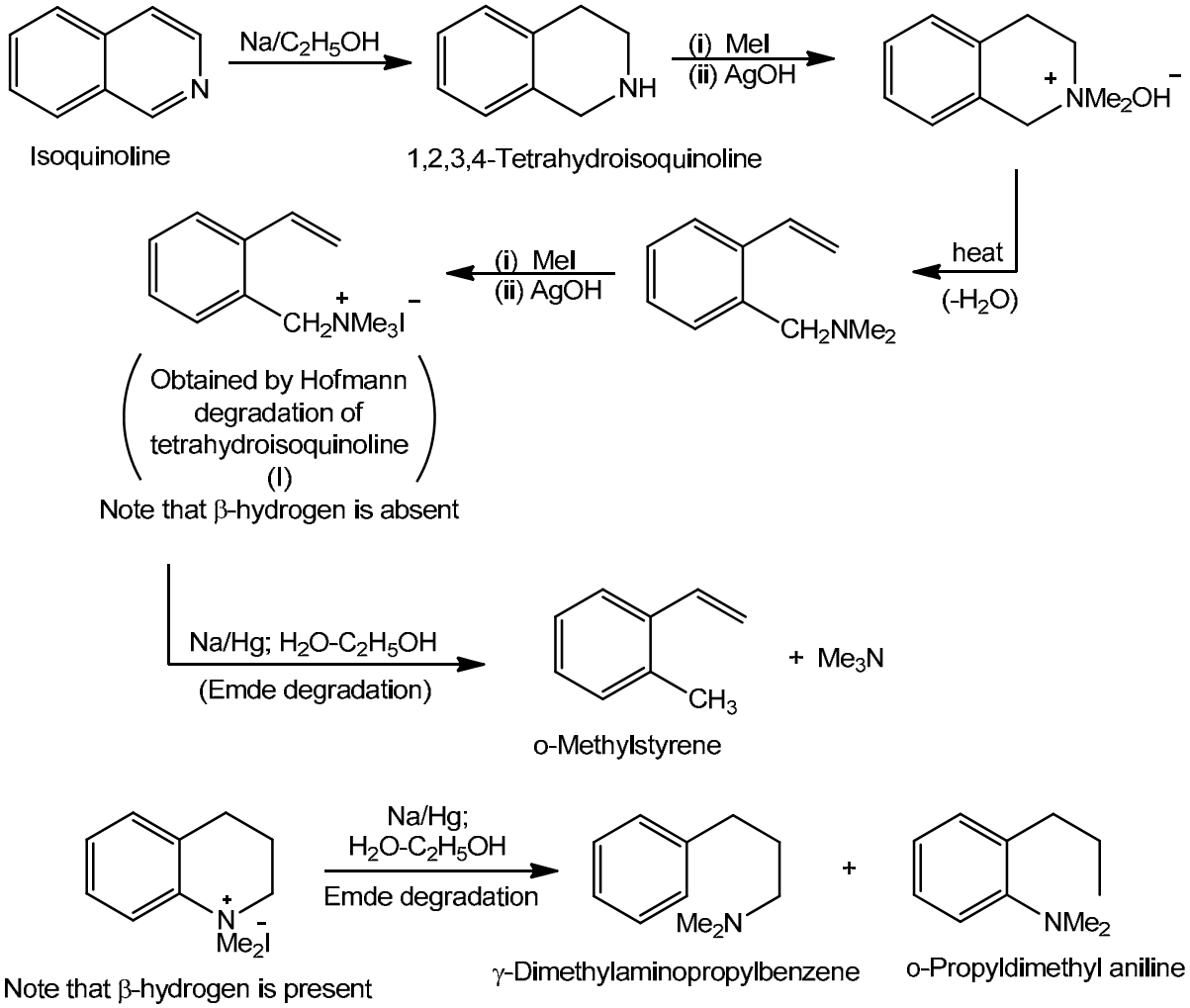
Even though the compound contains a, β - hydrogen atom, the exhaustive methylation method may fail.

We have stated earlier that for exhaustive methylation, the quaternary hydroxide is to be heated at about 200°C. However, in some cases, the reaction can be carried out by refluxing an aqueous or ethanolic solution of potassium hydroxide having the methiodide or methosulphate of the base.

(b) Emde's Degradation. If the alkaloid does not contain a, β - hydrogen atom, the Hofmann's exhaustive methylation method fails. In such cases, Emde's method may be employed. In this method, the final step involves reductive cleavage of quaternary ammonium salts either with sodium amalgam or sodium in liquid ammonia or by catalytic hydrogenation :

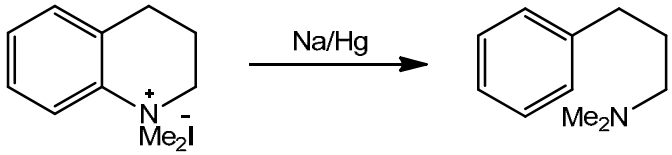
$$R\text{-}CH_2\text{-}N^+R_3'X^- \longrightarrow R\text{-}CH_3 + NR_3'.HX$$

Emde's method can be demonstrated by considering the case of isoquinoline.

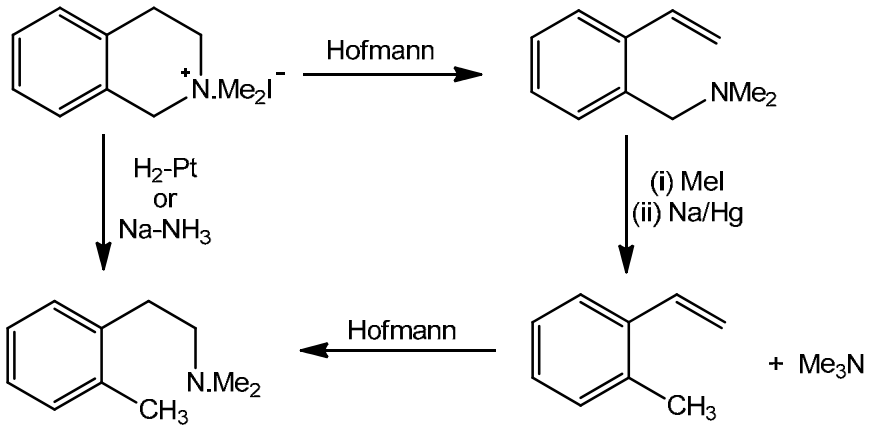


Hofmann's method cannot be applied to compound (I) because it does not contain β -hydrogen.

We have earlier stated that tetrahydro-quinoline does not respond to Hofmann's exhaustive methylation method. However, the heterycyclic ring in this compound is opened by the Emde degradation.



The Emde degradation of tetrahydroisoquinoline is also interesting:



Occasionally, successive Emde degradations have been employed as a means of eliminating a nitrogen atom from an alkaloid but where possible the preferred sequence is Hofmann elimination followed by Emde reaction.

(c) Von Braun's Method. This method is of two types:

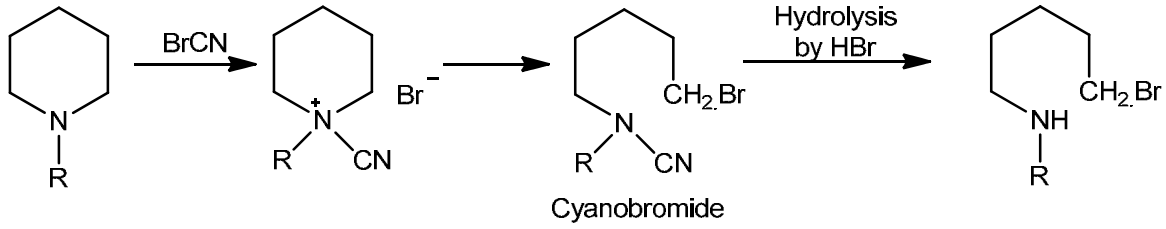
(i) In the first method, the tertiary amine, which contains at least one alkyl substituent, is treated with cyanogen bromide. This results in cleavage of an alkyl-nitrogen bond to give an alkyl halide and a substituted cyanamide.

$$R_3N + CN\text{-}Br \longrightarrow R\text{-}Br + R_2N\text{-}CN$$

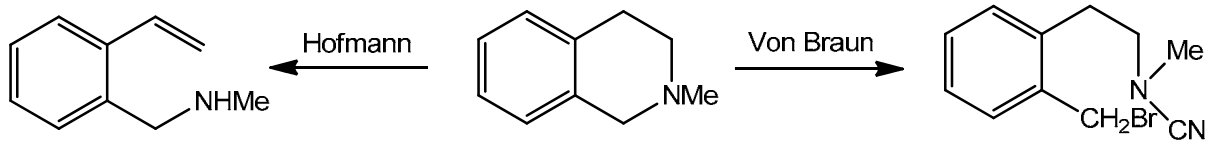
Fission of unsymmetrically substituted amines generally takes place to yield the alkyl halide derived from the smallest alkyl substituent.

$$Et_2NMe + CN\text{-}Br \longrightarrow MeBr + Et2N\text{-}CN$$

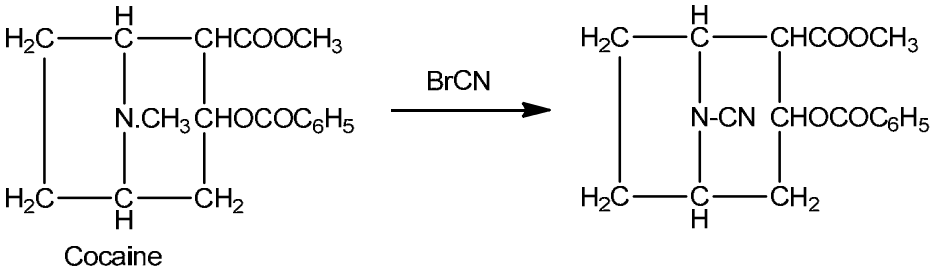
Now we will apply Von Braun's method to tertiary cyclic amines.



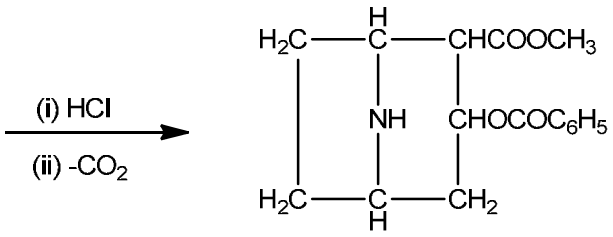
Von Braun's cyanogen method is often applicable to such compounds which do not respond to Hofmann's method. Furthermore, where both methods are applicable, ring-opening takes place at different points of the ring, e.g.



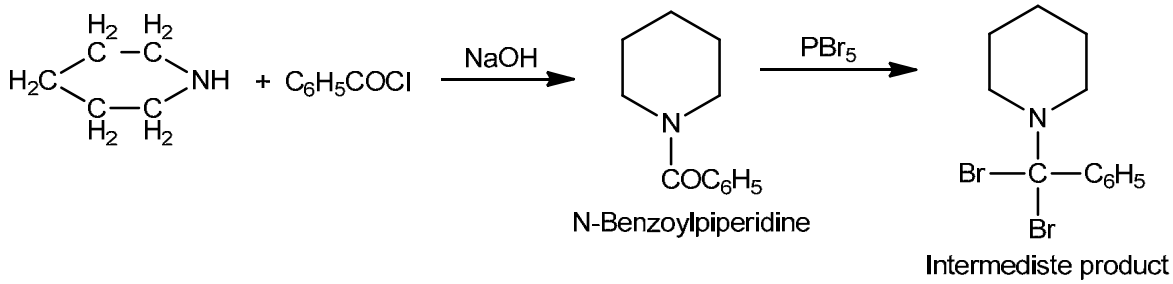
In the above examples, there occurs the opening of the ring. However, in some cases dealkylation takes place with formation of the cyclic N-cyano derivative e.g., cocaine.



Cocaine

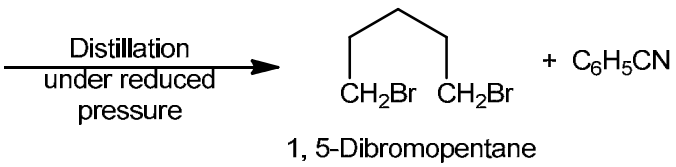


(ii) The second Von Braun's method is used for secondary cyclic amines. In this method, the cyclic amine is treated with benzoyl chloride in the presence of NaOH to yield the benzoyl derivative which on treatment with phosphorus halide followed by distillation under reduced pressure yields α : w-dihalo compound with the elimination of benzonitrile, taking piperidine for example,



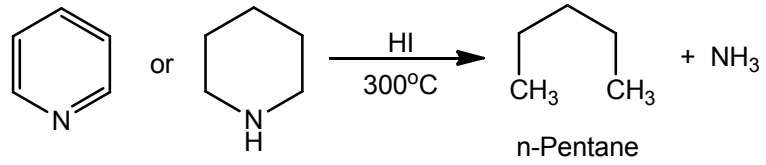
N-Benzoylpiperidine

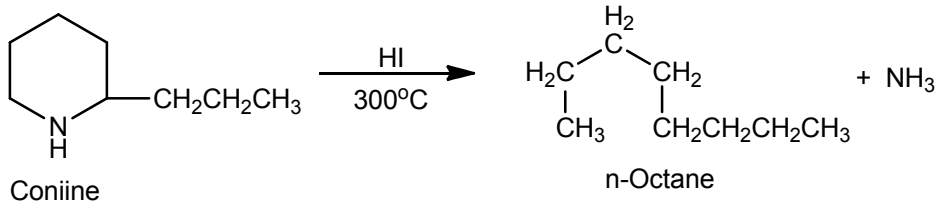
Intermediste product



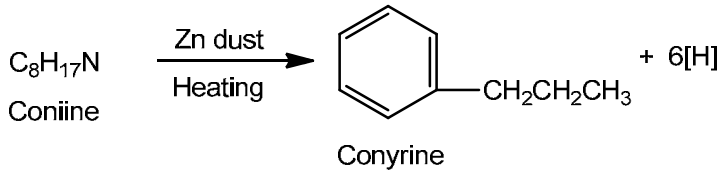
1, 5-Dibromopentane

(d) Reductive Degradation and Zinc Dust Distillation. In some cases the ring may be opened by heating with hydriodic acid at 300°C, e.g.,



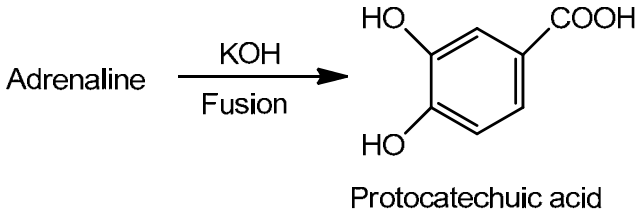


Zinc dust distillation produces simple fragments from which one can draw the conclusion about the carbon framework of the alkaloid molecule. Zinc dust distillation also brings about dehydrogenation or removal of oxygen if present. For example



As conyrine is formed by loss of six hydrogen atoms, it means that coniine must contain a piperidine ring. It must however, be noted that the interpretation of data from such drastic experiments should be done cautiously as these may occasionally lead to subtle skeletal changes.

e) Alkali Fusion. This is a very drastic method which is often employed to break down the complex alkaloid moleeule into simpler fragments, the nature of which will give infotmation on the type of nuclei present in the alkaloid molecule... For example, adrenaline when fused with solid potassium hydroxide yields protocateohuic acid, indicating that adrenaline is a catechol derivative.



Similarly, papaverine on fusion with alkali yields an isoquinoline derivative indicating that papavarine must contain an isoquinoline unit. Also, cinchonine when

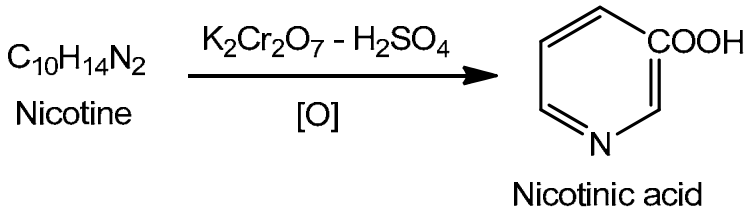
fused with alkali yields quinoline showing that quinoline nucleus is present in cinchonine.

(f) Oxidation. This method gives quite useful information about the structure of alkaloid. By varying the strength of the oxidising agents, it is possible to obtain a variety of oxidation products. For example,

(i) In order to carry out mild oxidation, hydrogen peroxide, iodine in ethanolic solution, or alkaline potassium ferricyanide are usually used.

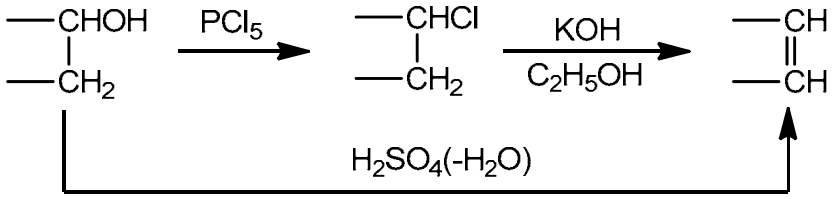
(ii) In order to carry out moderate oxidation, acid or alkaline potassium permanganate or chromium trioxide in acetic acid are generally used.

(iii) For carrying out vigorous oxidation, potassium dichromate-sulphuric acid, chromium trioxide-sulphuric acid, concentrated nitric acid or manganese dioxide-sulphuric acid are used. These reagents usually break up an alkaloid into smaller fragments whose structures are either already known or can be readily ascertained. For example,



Nicotinic acid

From the above reaction, it can be concluded that nicotine contains a pyridine ring having a side chain in β -position. The above classification of oxidizing agents is not rigid because the strength' of an oxidizing agent depends to some extent on the nature of the alkaloid which is being oxidized. In some cases, where this can be done, one may get better results by first dehydrating the compound to the unsaturated compound followed by its oxidation, which is readily affected at a double bond.



Recently, mercuric acetate has been employed to hydrogenate certain alkaloids, thereby introducing olefinic bonds. By knowing the oxidation products, position of the double bond is easily established. Various examples of the importance of oxidation in alkaloid chemistry will be found in the individual alkaloids.

(g) Dehydrogenation. When an alkaloid is distilled with a catalyst such as sulphur, selenium or palladium, dehydrogenation takes place to form relatively simple and easily recognisable products which provide a clue to the gross skeleton-of the alkaloid. During dehydrogenation, there occurs the elimination of peripheral groups such as hydroxyl and C-methyl.

From the above degradation methods of an alkaloid, one is able to establish the nature of the nucleus. the various fragments constituting the alkaloid and also some types of linkages present in it Then, one may arrange the different fragments obtained during degradation in different ways and that structure is selected which explains most of the characteristics.

Synthesis. The structure of the alkaloid arrived at by the exclusive analytical evidence based on the foregoing methods is only tentative. The final confirmation of the structure must be done by the unambiguous synthesis.

8. Physical Methods. During the last thirty years, the structure of alkaloids has been elucidated by involving modern instrumental techniques which have rendered the above methods unnecessary. In alkaloid chemistry, the most important instrumental methods are as follows:

(a) Ultraviolet spectroscopy,

(b) Infra-red spectroscopy,

(c) Nuclear magnetic resonance spectroscopy,

(d) Mass spectrometry,

(e) Optical rotatory dispersion and circular dichroism,

(f) Conformational analysis, and

(g) X-Ray diffraction.

The first four of these techniques are generally used to determine the gross structure of the alkaloid and the remainder to clarify stereochemistry.

We will now describe the above methods in a concise manner.

(a) Ultraviolet Spectroscopy. This is mainly used to establish the class and/or structural type to which the alkaloid being investigated belongs. Such assignments are made because ultraviolet spectrum of a compound is not a characteristic of the whole molecule but only of the chromophoric system (s) present.

The usual practice is to record the ultraviolet spectra of a very large number of different types of alkaloids. Then, the data are analysed and categorised with respect to structure correlation. We know that each group of alkaloids having a particular chromophoric system benzene, pyridine, indole quinohne etc. yields characteristic absorption maxima and extinction coefficients. Therefore, the comparison of these data with those observed for a new alkaloid may allow the identification of the exact nature of the aromatic or heterocyclic system in the new compound.

(b) Infra-red Spectroscopy. Even for simplej alkaloids, infra-red spectra contain many relatively sharp absorptions. Therefore, it becomes impossible to make an accurate assignment or every individual absorption and information is only qualitative, usually being confirmed either by other spectroscopic or by chemical means. Hence, infra-red spectroscopy in alkaloid chemistry is mainly used to ascertain the presence and sometimes the absence of particular functional groups.

The presence of aldehyde, ketone, alcohols, phenols, ester, amide. lactone, carboxylic acid carbonyl groups, and primary and secondary amines and amides can rapidly be identified and distinguished by comparison of the observed frequencies with those reported for structural related compounds.

One can also ascertain the presence of O-methyl, N-methyl and aromatic groups from the infra-red spectrum of an alkaloid but the quantitative analysis of such groups is best accomplished by nuclear magnetic resonance spectroscopy.

(c) Nuclear Magnetic Resonance Spectroscopy This technique is mainly used for the identification and quantitative estimation of the substituents like O-methyl, N-methyl; O, O-methylenedioxy, C-methyl and phenolic groups present in alkaloids. The normal chemical shifts for these substituents are given in given Table.

Table : Chemical Shifts for Certain Substituent's

Group	**Chemical Shift**	**Multiplicity**
O-Me	6.2-6.5	Singlet
N-Me	7.0-7.09	Singlet
O-CH_2O	3.8-4.2	Singlet
C-Me (aliphatic)	8.9-9.1	Singlet, doublet or triplet depending upon the number of α-H atoms
C-Me (aromatic)	7.5-7.7	Singlet
Ar-OH	-2 - +5	Singlet

Nuclear magnetic resonance spectroscopy is not only used to obtain an accurate estimation of the number of aromatic and heteroaromatic protons but also to know the exact substitution pattern (s) of the ring (s).

From the above Table, it can be seen that the chemical shift of phenolic protons varies widely because it depends on the concentration of the solution and also on the degree of inter-and intramolecular association

However, one can confirm a phenolic hydroxyl group, simply by adding deuterium oxide to the solution and redetermining its NMR spectrum. There occurs rapid exchange of hydrogen for deuterium, ArOH→ ArOD, and the signal due to the proton of the phenol disappears.

(d) Mass Spectrometry. This technique is quite useful because it gives quite useful information about the alkaloid like.

(i) The molecular weight,

(ii) The empirical formula by accurate mass measurement of the molecular ion, and

(iii) Knowledge of the molecular structure by comparison of the fragmentation pattern with those of analogous systems.

Much of the success has been achieved in the case of polycyclic indole alkaloids because the indole nucleus of these substances gives rise to an abundant, stable molecular ion which subsequently undergoes decomposition by highly specific bond fission involving the alicyclic portion of the molecule containing the other nitrogen atom (s). In some alkaloids, it is possible to deduce the total structure of the alkaloid by further analysis of the mass spectrum with respect to the nature and position of substituent groups.

(e) Optical Rotatory Dispersion and Circular Dichroism. These are only instrumental methods which are mainly used for elucidation of the stereochemistry of alkaloids but their application is restricted to those compounds which are optically active, ie., to those in which a rotation-reflection symmetry axis is absent. Due to this reason, few alkaloids of the yohimbine aprophine, morphìne and benzylisoquinoline series have been examined so far by these techniques.

(f) Conformational Analysis. The principles of conformational analysis have been widely used to establish the stereochemistry as well as physical properties and chemical reactivity of alkaloids. The approach is mainly experimental which involves determination, correlation, and interpretation of the kinetics and product ratios obtained from simple chemical transformations such as reduction of double bonds and carbonyl

groups, hydrolysis and esterification, oxidation of alcohols and quaternization of amines, epimerization, etc.

(g) X-ray Diffraction. This technique is widely used to study alkaloids because it gives the exact structure of the molecule, including bond angles and bond lengths; it also gives the information about the relative stereochemistry, including information on overcrowding twisted bonds, etc. X-ray diffraction method is also useful to reveal the absolute configuration of the molecule.

Owing to the introduction of computers it becomes possible to quickly perform the calculations from X-ray data, and so the complete stereochemical structure can be obtained from a single crystal. An interesting example is that of thelepogine CH NO the structure of which has been determined by X-ray analysis without doing any chemical analysis.

PYRIDINE-PYRROLIDINE ALKALOIDS

1. Nicotine

Introduction. It is the most important töbacco alkaloid occurring in Nicotiana tobacum L and other Nicotianan species. It usually occurs in the form of its salts with malic and citric acids. Although it is distributed throughout the plant, its highest concentration is found in the leaves in varying amounts from 0.6 to 8 percent. Although tobacco is the commercial source of nicotine, it occurs not only among other flowering plants (eg., in the biting stonecrop, Sedum acre L.), but also in vascular cryptogams (Pteridophyta) such as the common horsetail, Equisetum arvense L. and the club-moss, Lycopodium clavatum L.

The name nicotine was given in the honour of Sir J. Nicot, Ambassador of the King of France to Portugal from 1559-1561.

Isolation. The leaves and stems of tobacco plants are dried and powdered and then distilled with milk of lime when nicotine distils over. The distillate is extracted with ether. When the solvent is evaporated. nicotine is left as an oily liquid which is further purified by fractional crystallization of is salt like oxalate.

Properties. For human consumption tobacco of low alkaloid content is desirable as nicotine is extremely toxic. For instance, the fatal does for man is said to be 40 mg approximately. Enough evidence is available which reveals that cigarette smoking increases the heart beat and thus causes constriction of blood vessels, resulting in an increase in blood pressure and hence disturbing the blood distribution.

When freshly prepared, it is a colourless, very hygroscopic liquid which becomes discoloured in air (b.p. 247°). It is volatile in steam and is miscible with water in all proportions below 60° (as a hydrate) and above 210°C.

The natural nicotine is laevorotatory, [α], = -166.4) The salts of (-)-nicotine are dextro rotatory. The (+) nicotine has only one-half the physiological activity of natural (-)-nicotine.

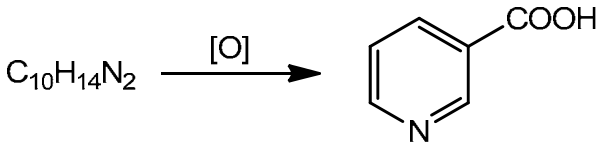
Constitution:

1. Molecular weight determination and chemical analyst reveal that the molecular formula of nicotine is $C_{10}H_{14}N_2$.

2. Both the nitrogen atoms in nicotine are shown to be in a tertiary state because nicotine takes up two moles of methyl iodide to form a dimethiodide. Under suitable conditions, it also forms two isomeric monomethiodides, one of the tertiary nitrogen atoms is found to be N-methyl group.

$$C_{10}H_{14}N_2 + 2CH_3I \longrightarrow \bar{I}H_3C.\overset{+}{N} \leq [C_{10}H_{14}] \geq \overset{+}{N}.CH_3\bar{I}$$

3. When nicotine is oxidized with chromic acid or potassium permanganate, it forms nicotine acid (pyridine e-3-earboxylic acid) showing thereby that nicotine is a pyridine derivative containing a side- chain in 3-position.

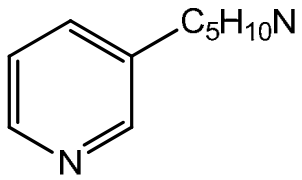


Nicotinc acid

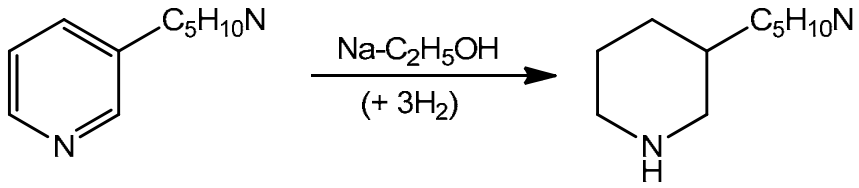
From the above reaction it is revealed that:

(i) Nicotine must have a pyridine nucleus,

(ii) The side chain $C_5H_{10}N$, obtained by subtracting the molecular formula of a substituted pyridine (C_5H_4N) from the molecular formula of nicotine ($C_{10}H_{14}N_2$), must be present in the 3-position of the pyridine nucleus. Therefore, the structure of nicotine must be written as follows:



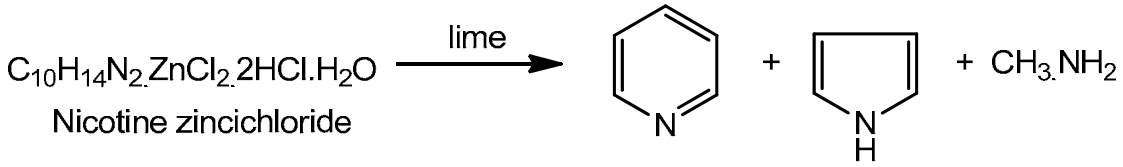
The presence of the pyridine nucleus is further confirmed by the formation of a hexahydro derivative when reduced with sodium and alcohol. It means that one of the two nitrogen atoms is present as a pyridine nucleus of the nicotine.



4. Nature of the side-chain. As the side-chain $C_5H_{10}N$ has the same composition as the piperidyl group, it was thought for sometimes that nicotine was piperidyl-pyridine. However, further work showed that this was incorrect. For instance,

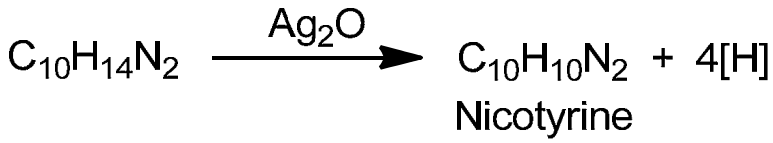
(a) As the nitrogen atom of pyridine moiety is present as N, the side chain must possess the methyl group (point 2). This is confirmed by the fact nicotine, when heated with concentrated hydriodic acid to about 150°C, yields methyliodide **(Herzig-Meyer method)**. Hence, the side- chain must contain an N-methyl group.

(b) With zinc chloride, nicotine forms an addition product nicotine zinc-chloride. Nicotine zinc chloride, when distilled with soda-lime, yields pyridine, methylamine and pyrrole. This reaction reveals that nicotine might contain a five-member heterocyclic ring containing nitrogen (i.e, a pyrrolidine or a pyrrole ring). Thus, now the side-chain having N methyl group can be extended as $C_4H_8NCH_3$.



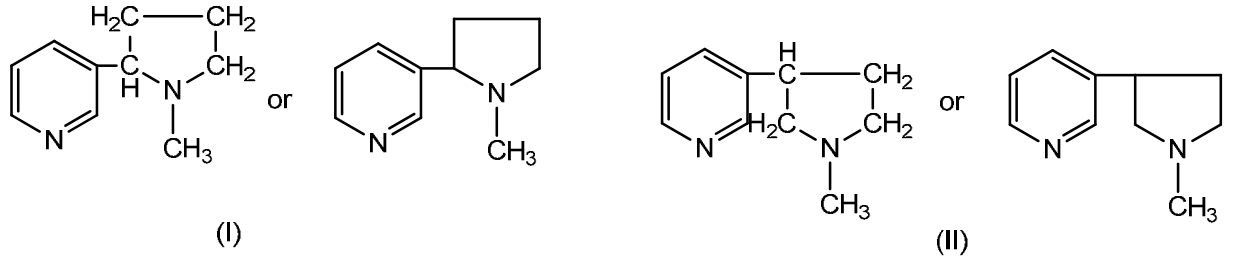
This step clearly revealed that the side chain is pyrrole derivative, But we have already stated that the side-chain is reduced and is having one N-CH, group, it is N-methylpyrrolidine.

(c) Nicotine when oxidised mildly with silver oxide yields nicotyrine by loss of four hydrogen atoms



From the above, facts, one may draw conclusion that nicotine must contain a pyrrolidine nucleus and therefore, the side-chain in nicotine must be N-methylpyrrolidine.

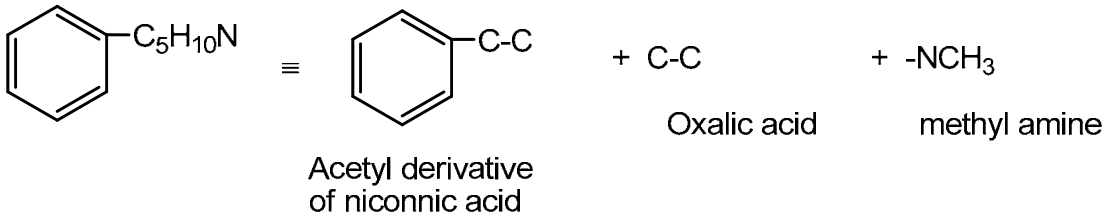
5. Point of attachment of N-methylpyrrolidine to the pyridine nucleus. The pyrrolıdine sıde-chain may be attached to the pyridine ring only in two possible ways, i.e. either through position - 2 or 3 (α or β) resulting in two structures (I) and (II) for nicotine.



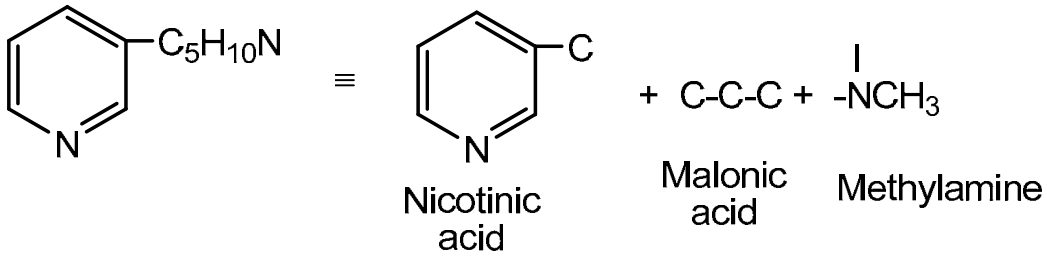
(I) (II)

The exact nature of side-chain was ascertained by Pinner (1892, 1893). According to him,

(a) When nicotine is treated with bromine, in acetic acid, it yields many products including the hydrobromide perbromide $C_{10}H_{10}Br_2N_2O$. HBr. Br_2 which when treated with aqueous sulphurous acid is converted into dibromonicotine $C_{10}H_{10}Br_2N_20$. Dibromonicotine when heated with a mixture of sulphurous and sulphuric acids at 130-140°C yields 3-acetylpyridine, oxalic acid and methyl amine. This means that the structure (I) of nicotine has to explain this fragmentation, i.e

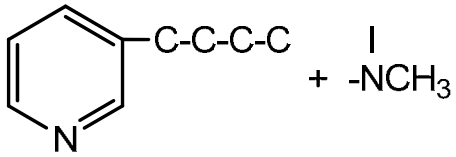


(b) When nicotine is treated with bromine in the presence of hydrobromic acid, dibromonicotine, $C_{10}H_8Br_2N_2O_2$ is obtained which on heating with barium hydroxide at 100°C yields nicotinic acid, malonic acid and methylamine. It means that the structure of nicotine must also explain the following skeletal structures:



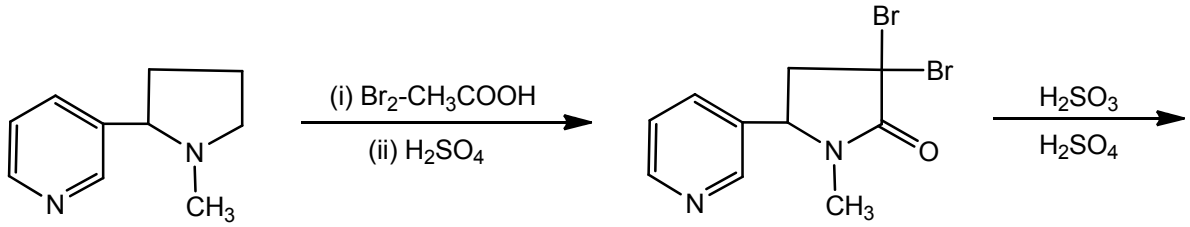
The formation of malonic acid, a three carbon acid, shows that the carbon atom appearing in the -COOH group of nicotinic acid must be the end atom of a chain of four carbons. This is possible only if N-methylpyrrolidine moiety is linked to pyridine through an e-position. Hence the structure (II) for nicotine is ruled out and the only possible structure for nicotine is (I).

The formation of the two sets of reaction products (a) and (b) can only be explained if nicotine has the following structure :



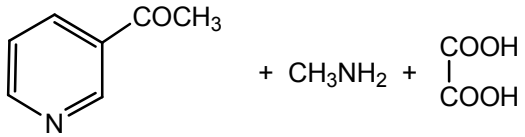
(c) Now the question arises What is the position of N-methyl group? This can be found out as follows:

As nitrogen is a di-tertiary base, it forms two isomeric methyl iodide addition products. Therefore, the nitrogen atom in the side-chain must be of the type-C-$N(CH_3)$-C- Also. it is quite difficult to reduce nicotine beyond hexahydronicotine, (the pyridine part is reduced to piperidine) indicating that the side-chain must be saturated and this is only possible if it is cyclic, i.e., N-methyl-pyrrolidine ($C_5H_{11}N$). The presence of this pyrrolidine in the side-chain also explains the formation of pyrrole when the distillation of nicotine zincichloride is carried out.

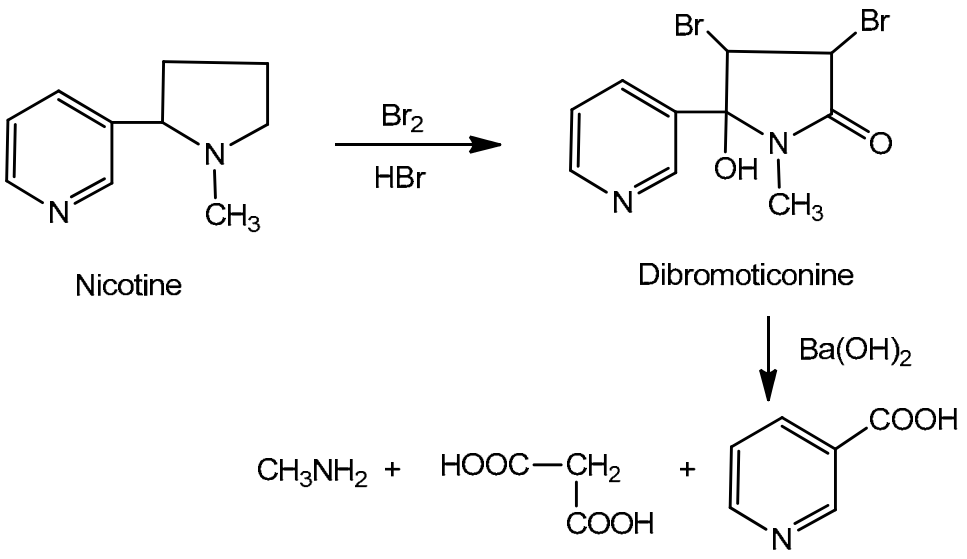


Nicotine

Dibromocotinine

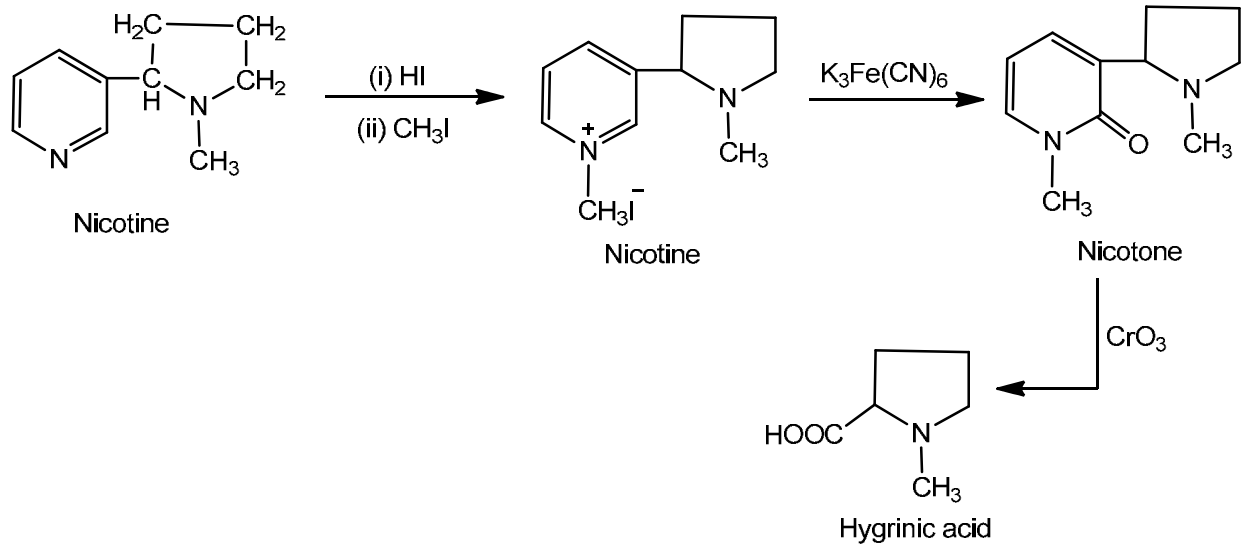


3-Acetylpyridine



All the above facts can be explained by considering the structure (I) of nicotine. On the basis of this structure the formation of Pinner's dibromo-derivatives and their further decomposition is explained as above.

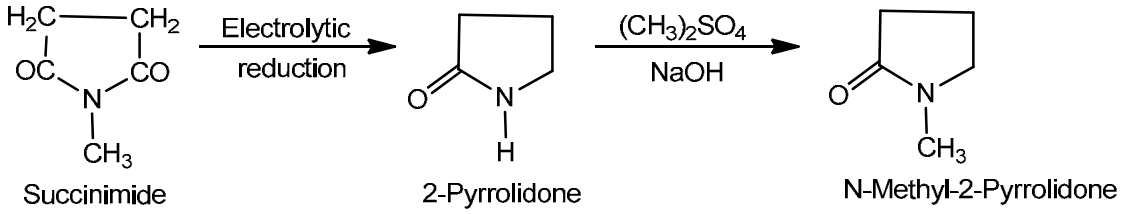
P. Karrer (1923, 1925) gave a direct evidence for the presence of N-methyl-pyrrolidine ring and its point of attachment to the pyridine nucleus. According to him, nicotine hydroidide when warmed with methyl iodide yields nicotine isomethiodide and this on oxidation with potassium ferricyanide is converted into nicotine which is further oxidized with chromic acid to yield L (-)-hygrinic acid.



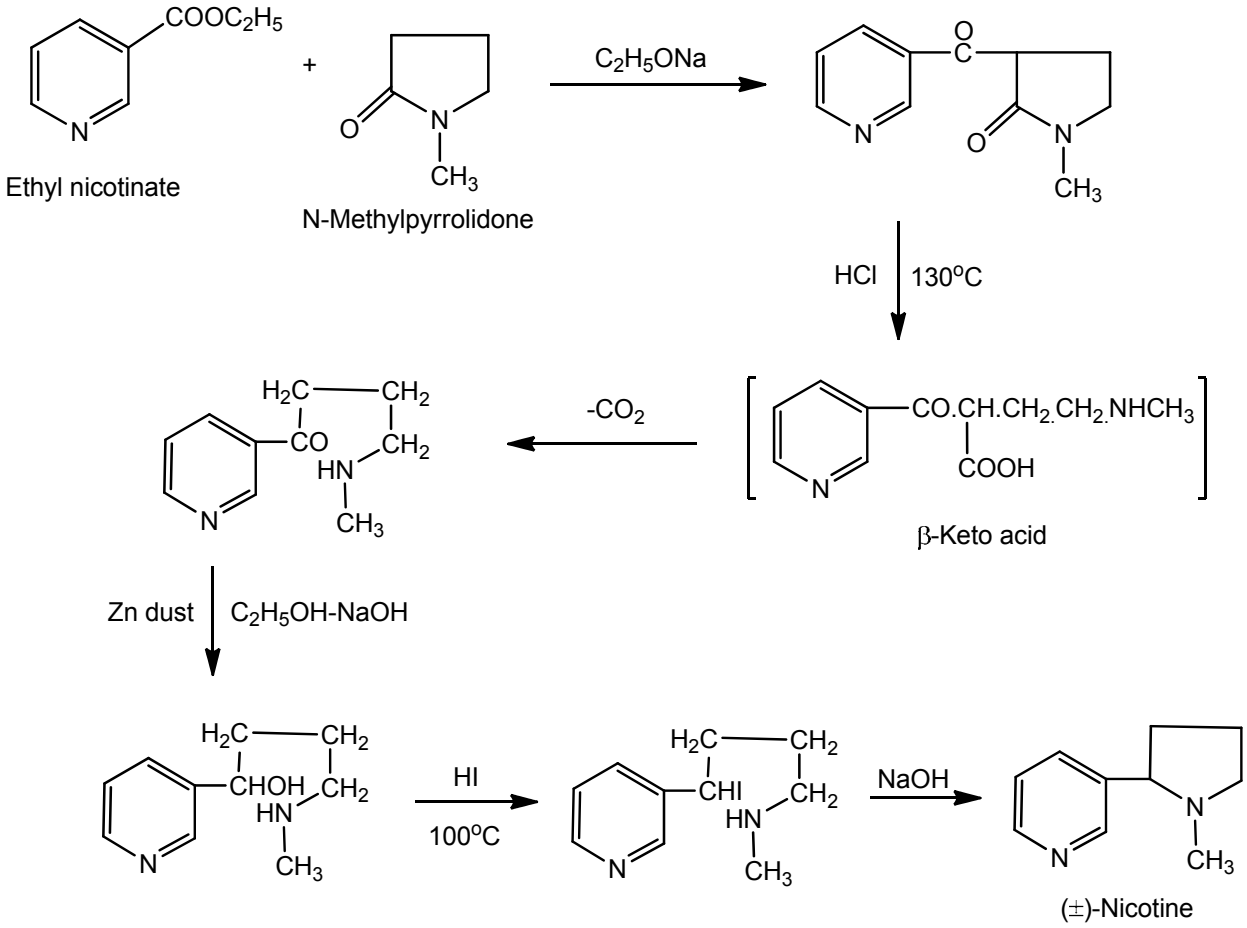
This structure of nicotine is confirmed by the following syntheses:

1. By Spath and Bretschneider (1921)

(a) Synthesis of N-methyl-2-pyrrolidone

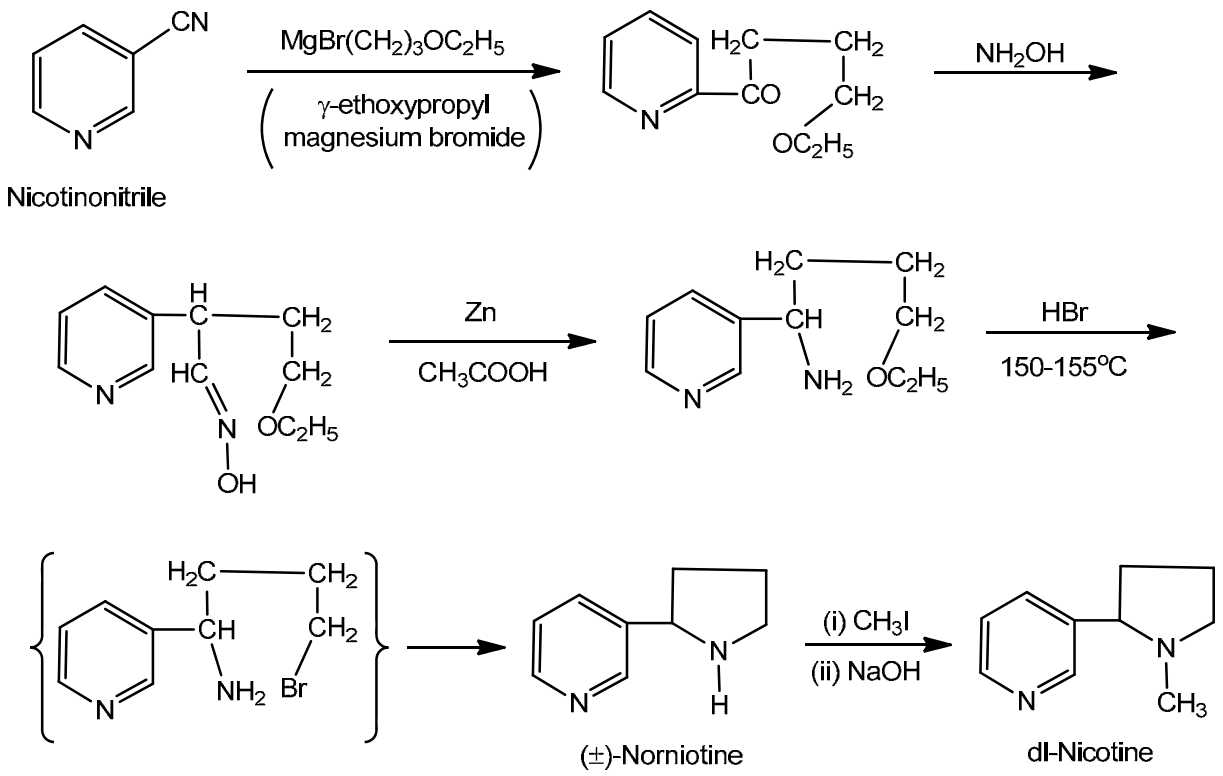


(b) Synthesis of nicotine N-methyl-2-pyrrolidone produced as in step (a) further undergoes reactions to yield nicotine.



The dl-nicotine is resolved by means of (+)-tartaric acid the synthetic (-)-nicotine is identical with the natural compound.

2. By Craig (1933)



(+)-Tartaric acid is able to resolve (+)-nicotine into (-)nicotine which is identical with the natural product. Spath et. al, (1936) resolved (+)-nornicotine into (-) form that on methylation with formaldehyde and formic acid yields (-)-nicotine which was identical with the natural product.

Reference Book : Organic chemistry of natural products by Gurdeep R. Chatwal, Vol. I.