Chapter 4…

Natural Products

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(B) ALKALOIDS

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4.1 Introduction of Natural Products

A natural product is a chemical compound or substance produced by a living organism such as plants, animals, microbes, insects, plant pathogens, endophytes and marines.

Natural products can also be prepared by chemical synthesis (both semisynthesis and total synthesis) and have played a crucial role in the development of organic chemistry by providing many important synthetic compounds.

Natural products sometimes have pharmacological activity that can be of therapeutic benefit in treating diseases.

Classification : Natural products are classified according to biological functions, biosynthetic pathway and source.

Type 1 : Classification of natural products according to function : Natural products are often divided into two major classes :

1. **Primary metabolites :** They are directly involved in normal growth, development, and reproduction. In other words, they perform an intrinsic function.
   Examples : Amino acids, sugars, vitamins, lipids, DNA, RNA, etc.
2. **Secondary metabolites :** Secondary metabolites in contrast have an extrinsic function that mainly affects other organisms. These are not essential for survival but do increase the competitiveness of the organism within its environment. These are formed due to enzymatic reactions of primary metabolites.
   Examples : Phenols, polyphenols, tannins, **terpenoids** and **alkaloids**.

alkaloids.

Type 2 : Classification of natural products according to biosynthetic pathway :

1. **Carbohydrates :** These are obtained by gluconeogenesis (in animals) and photosynthesis (in plants).
2. **Lipids and polypeptides :** These are obtained by acetate biosynthetic pathway.

Type 3 : Classification of natural products according to source :

1. **Plants :** Plants are major sources of complex and highly structurally diversed natural products called phytochemicals (e.g. Phenols, polyphenols, tannins, terpenes, and alkaloids).
2. **Microbes :** Microbes are also main sources of many natural products.
3. **Animals :** Animals contain many natural products like steroids.
4. **Marenes :** Marene organisms also contain many natural products.

Organic natural products : These are classified according to structures.

1. **Terpenoids :** These are a large class of natural products that are constructed from ‘isoprene’.
2. **Alkaloids :** These are secondary metabolites that contain nitrogen as a main component of their organic structure.
3. **Phenylpropanoids :** These are a diverse family of organic compounds that are synthesized from amino acids.
4. **Polyketides :** These are assembled from the building blocks of acetate and malonate to form large complex structures.

4.2 Terpenoids

4.2.1 Introduction

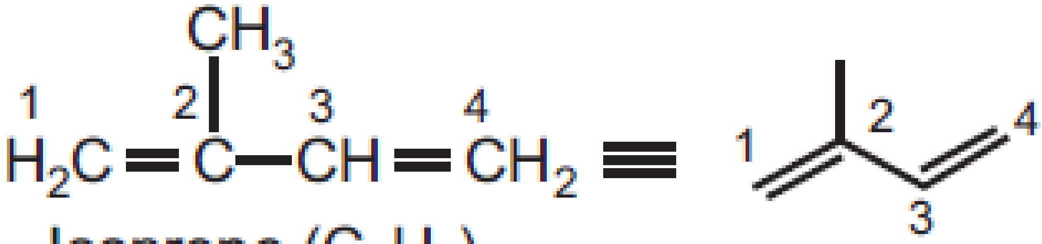
Terpenoids are a group of organic compounds the majority of which occur in the plant kingdom. A few terpenoids have been obtained from other sources.

The term ‘Terpene’ was referred to only volatile C_{10} and C_{15} hydrocarbons that were isolated from various parts of plants, even from the wood in some cases. This was then modified and all the naturally occurring hydrocarbons having multiples of five carbon atoms in their structures as well as their functionally substituted derivatives (such as alcohols, aldehydes, etc.) were called terpenes.

Nowadays they are generally called as ‘Terpenoids’ and sometimes called ‘Isoprenoids’ which belong to the biggest class of secondary metabolites and basically consist of five carbon isoprene units which are assembled to each other by thousands of ways.

Analyses of oils of turpentine were made in 1818 by Houston, and it was in 1866 when Dumas proposed the name “terpene” derived from turpentine, the suffix “ene” indicating the presence of olefinic bonds.

In 1887, Wallach proposed that, all terpenes are found to contain isoprene (C_5H_8) as their basic unit. Isoprene, the “building block” of terpenoids, is 2-methylbuta-1,3-diene named as ‘hemiterpene’.



$H_2C=\overset{\overset{\displaystyle CH_3}{|}}{C}-CH=CH_2 \equiv$

Isoprene (C_5H_8)

Isoprene itself, a gaseous hydrocarbon, is emitted from the leaves of various plants as a natural byproduct of plant metabolism. Next to methane it is the most common volatile organic compound found in the atmosphere.

When the compounds contain additional elements, usually oxygen, then they are termed as terpenoids.

4.2.2 Occurrence

Terpenoids are naturally occurring hydrocarbons produced by a wide variety of plants. More than 55,000 terpene molecules have been discovered to date and this number has almost doubled in each decade.

1. Monoterpenoids are chiefly found in essential oils which are extracted from various parts of plants such as fruits, flowers, leaves, roots etc. They are steam volatile.

   The oil has been used as flavors and perfumes since centuries. e.g. Oil of rose, oil of lavender, oil of jasmine etc. A few of them such as Eucalyptus oil have been used in medicine and some turpentine oil have industrial value.
2. Many of the latex-producing plants contain sesquiterpene, and these are potent antimicrobial and anti-insecticidal agents.
3. Sesquiterpenes are naturally present in the fungus, marine organism, insects, sponges, lichens, and protective waxes of insects.

4. Geraniol is produced by geranium, rose and lemon.
5. Di- and tri- terpenoids are obtained from gums and resins of plant and tree origin. They are not steam volatile.
6. Tetra terpenoids are yellow or red pigments of plant matter and can be extracted from it.
7. Natural rubber, the most important polyterpenoid is obtained from rubber trees.

4.2.3 Isolation of Terpenoids

Chemically, terpenoids are generally lipid-soluble compounds. Most of them are colourless liquids which are lighter than water and boil between 150 °C and 180°C. These are steam volatile.

Essential oils are first extracted from plants and then individual terpenoids are separated from these essential oils by using techniques like fractional distillation, column chromatography, etc. Plants containing essential oils usually have the greatest concentration at some particular time e.g. jasmine at sunset. Thus terpenoids can be isolated in two steps :

Step I : Isolation of essential oils from plants : In general, there are four methods used for isolation of terpenoids from plants.

(i) Steam distillation,

(ii) Extraction with fat and lard,

(iii) Solvent extraction,

(iv) Expression.

1. **Steam distillation :** This is widely used method for the isolation of mono and sesquiterpenoids.

In this method, the plant material is manerated (softened by soaking in H_2O) and then steam distilled to get essential oils into the distillate which are extracted by using pure organic volatile solvents. If compound decomposes during steam distillation, it may be extracted with petrol at 50˚C. After extraction solvent is removed under reduced pressure to give essential oils.

2. **Extraction with fat and lard (fat of a hog) :** In this method, fat is saturated with leaves or petals of flowers. It is then warmed to about 50°C. Extraction of oil takes place. This is then digested with ethyl alcohol. This alcohol extract is cooled to 20°C to remove the fat present in dissolved conditions. Ethyl alcohol is then distilled off under reduced pressure to get essential oil.

3. **Solvent extraction :** The oils may be extracted with suitable organic solvents like petroleum ether (40-60°C) or diethyl ether. Then

4. **Expression :** The plant material is crushed and the juice is filtered to remove large particles. The juice is centrifuged when major part of the essential oil is obtained in the centrifugate. Some oil is obtained by distillation of the residual material

Step II : Separation of terpenes from essential oils : The essential oils obtained from above steps generally contain a mixture of terpenoids and are separated by various physical and chemical methods.

1. **Physical methods :**
   - (a) **Fractional distillation method :** The various terpenoids present in essential oils are separated by fractional distillation method.
   - (b) **Chromatography :** More recently chromatography in its various forms has been widely used both for isolation and separation of terpenoids.

2. Chemical methods :

These methods are less used today. However, various chemical methods are as follows :

- **(a)** When essential oils containing terpenoid hydrocarbons are treated with nitrosyl chloride in chloroform, crystalline adducts of hydrocarbons having sharp melting points are obtained. These are separated and decomposed into their corresponding hydrocarbons.
- **(b)** When essential oils containing alcohols are treated with phthalic anhydride to form diesters. After extracting with sodium bicarbonate, diesters are decomposed by alkali to the parent terpenoid alcohols.
- **(c)** Terpenoid aldehydes and ketones are separated from essential oils by forming their adducts with the common reagents like $NaHSO_3$, 2,4-DNP, phenylhydrazine, etc. After separation, these are decomposed to regenerate terpenoid aldehydes and ketones.

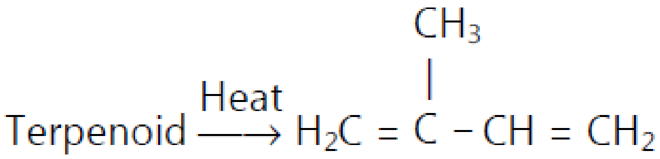
4.2.4 General Characteristics

As far as physical properties of terpenoids are concerned, most of them are colourless liquids, which are lighter than water and boil between 100-150°C. A few are solids which are lighter than water,

volatile in steam, usually highly refractive and insoluble in water but soluble in organic solvents. Many of these are optically active.

The various general chemical properties of terpenoids are as listed below :

1. Terpenes are organic compounds found in plants and they provide flavor, fragrance, and colour to the plant. The aroma, flavor and colour of a plant depend on type, strength, and quantity of terpenes within that particular plant.
2. They are open chain or cyclic unsaturated compounds having one or more double bonds.
3. Due to presence of C=C bonds, terpenoids undergo addition reactions with hydrogen, halogens, HX. Some of them form hydrates. They also form characteristic addition products with NOCl and NOBr.
4. The addition products of terpenoids are found to be useful in identification of terpenoids. A number of addition products have antiseptic properties.
5. They undergo polymerization, also dehydrogenation in the ring.
6. As they have olefinic bonds, they are very easily oxidized by all oxidizing agents.
7. A number of terpenoids are highly labile and hence they readily undergo isomerisation into more stable forms in the presence of acids.
8. On thermal decomposition, most of the terpenoids yield isoprene as one of the products.



$$\text{Terpenoid} \xrightarrow{\text{Heat}} H_2C = \overset{\overset{\displaystyle CH_3}{|}}{C} - CH = CH_2$$

Isoprene

4.2.5 Classification of Terpenoids

The classification of terpenoids is mainly based on the number of isoprene units $(C_5H_8)_n$ present in the molecule. Each class of terpenoids is further classified into subgroups on the basis of acyclic, cyclic and number of rings present in terpenoids.

1. **Acyclic Terpenoids :** They contain open chain structure.
2. **Monocyclic Terpenoids :** They contain one ring in the structure.
3. **Bicyclic Terpenoids :** They contain two rings in the structure.
4. **Tricyclic Terpenoids :** They contain three rings in the structure.
5. **Tetracyclic Terpenoids :** They contain four rings in the structure.

The general formula of terpenes with a number of isoprene units present and example is given in Table 4.1.

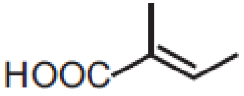
Table 4.1 : Classification of Terpenoids based on the Number of Isoprene Units

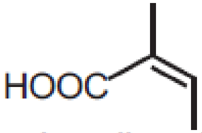
Sr. No.	Class	Number of isoprene units	Number of carbon atoms	General formula	Examples
1.	Hemiterpenoids	1	C_5	C_5H_8	Isoprene
2.	Monoterpenoids	2	C_{10}	$C_{10}H_{16}$	Camphor dipentene
3.	Sesquiterpenoids	3	C_{15}	$C_{15}H_{24}$	Zingiberene
4.	Diterpenoids	4	C_{20}	$C_{20}H_{32}$	Phytol
5.	Sesterpenoids	5	C_{25}	$C_{25}H_{40}$	(Recent discovery)
6.	Triterpenoids	6	C_{30}	$C_{30}H_{48}$	Squalene
7.	Tetraterpenoids (carotenoids)	8	C_{40}	$C_{40}H_{64}$	β-carotene
8.	Polyterpenoids	> 8	> C_{40}	$(C_5H_8)n$	Natural Rubber

1. **Hemiterpenoids :** These are simplest terpenoids. The most prominent hemiterpene isoprene (boiling point 34°C) is emitted from the leaves of many trees (including conifers, oaks and willows) and herbs (e.g. hamamelis japonica).

   Examples : Other known hemiterpenoids found in plants are tiglic and angelic acids.

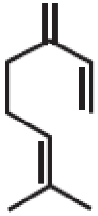

Isoprene

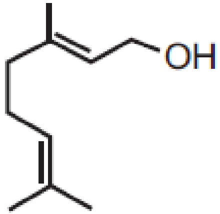

Tiglic acid

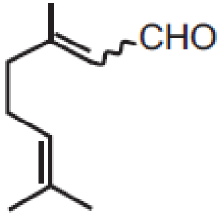

Angelic acid

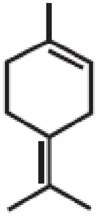
2. **Monoterpenoids** : These consist of two isoprene units (10 carbon backbone) in its structure and can be divided into three subgroups : acyclic, monocyclic, and bicyclic.

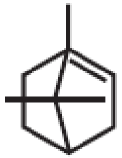
   Examples : Myrcene, citral, geraniol, α-terpineol, limonene, thymol, menthol and carvone.

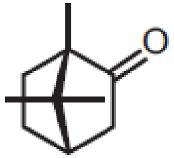

Myrcene

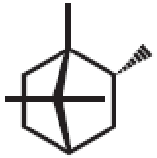

Geraniol


Citral


Limonene

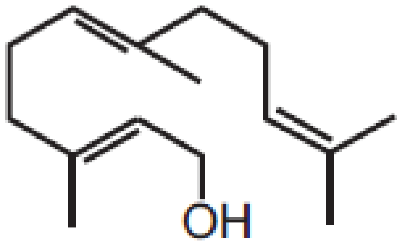

α-Pinene


Camphor

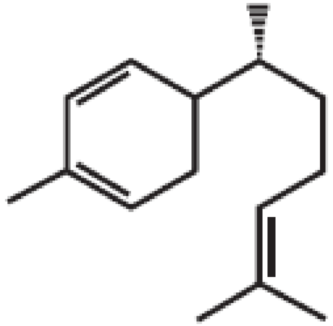

Borneol

3. **Sesquiterpenoids** : Sesquiterpenoids are derived from three isoprene units (15 carbon backbone) and exist in a wide variety of forms, including linear, monocyclic, bicyclic and tricyclic frameworks. They are the most diverse group of terpenoids.

   Examples : Farnisol and α-Zingiberene



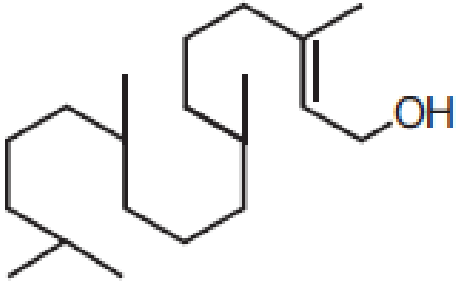
Farnisol



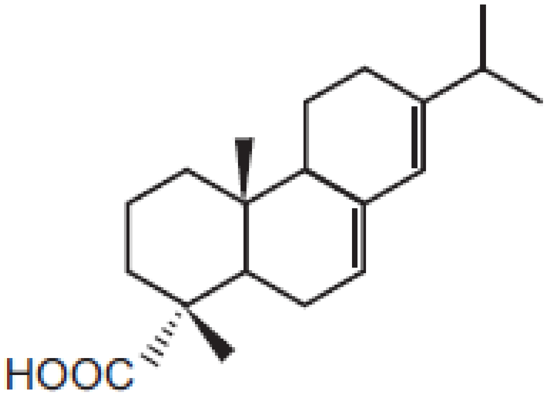
α-Zingiberene

4. **Diterpenoids** : Diterpenoids are derived from four isoprene units (20 carbon backbone). They can be classified as linear, bicyclic, tricyclic, tetracyclic, pentacyclic or macrocyclic diterpenes depending on their skeletal core.

   Examples : Phytol and Abietic acid.



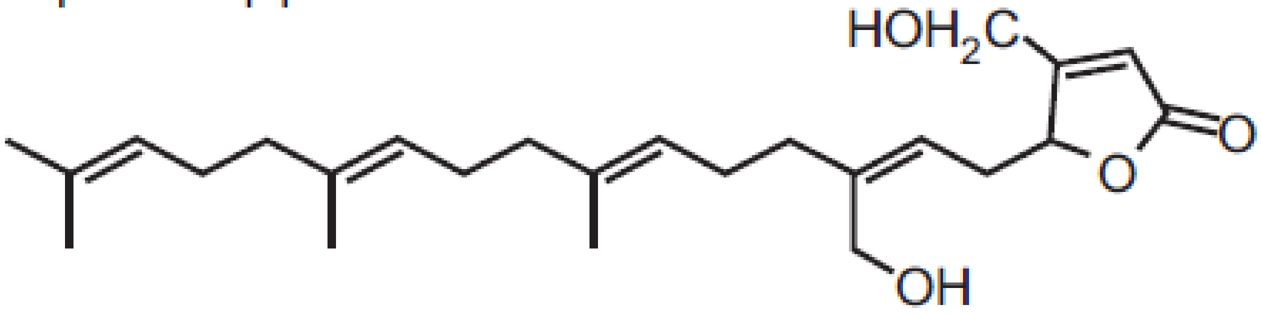
Phytol



Abietic acid

5. **Sesquiterpenoids :** Sesquiterpenoids are derived from five isoprene units (25 carbon backbone). They exist in a wide variety of forms, including linear, monocyclic, bicyclic, tricyclic, tetracyclic and macrocyclic frameworks.

   Example : Hippolide E.

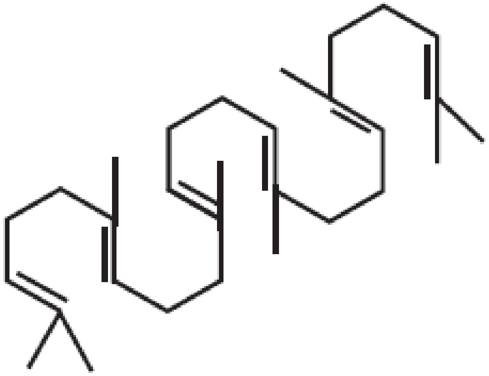


Hippolide E

Hippolide E

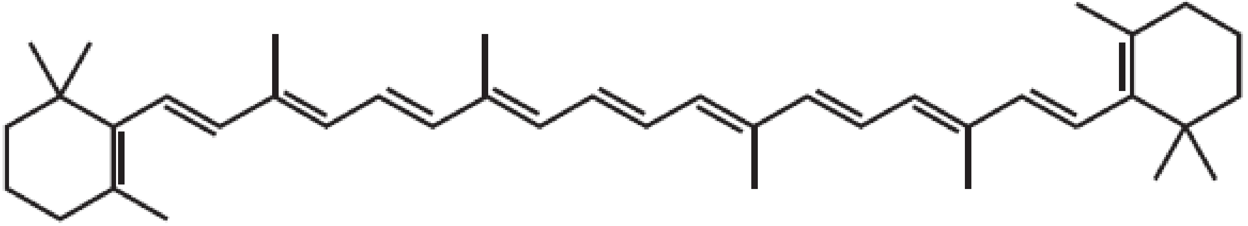
6. **Triterpenoids** : Triterpenoids are derived from six isoprene units (30 carbon backbone) which are derived biosynthetically from the acyclic C30 hydrocarbon, squalene. They have relatively complex cyclic structures, most being either alcohols, aldehydes or carboxylic acids. Sterols are triterpenes which are based on cyclopentane perhydrophenanthrene ring system.

   Example : Squalene



Squalene

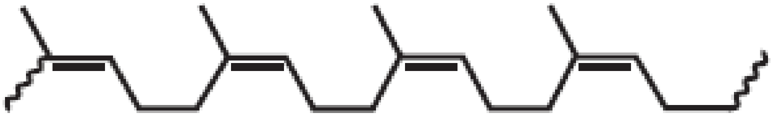
7. **Tetraterpenoids :** Tetraterpenoids are derived from eight isoprene units (40 carbon backbone). The most common tetraterpenoids are carotenoids, which are natural fat-soluble pigments.



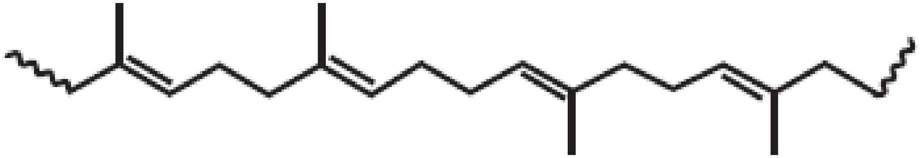
β-Carotene

8. **Polyterpenoids :** Polyterpenoids are polymeric isoprenoid hydrocarbons, which consist of more than eight isoprene units.

Example : Natural rubber.



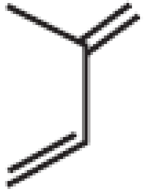
Natural rubber
(cis-configuration)



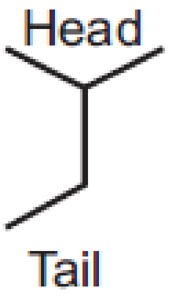
Gutta percha/balata
(trans-configuration)

4.2.6 Isoprene Rule

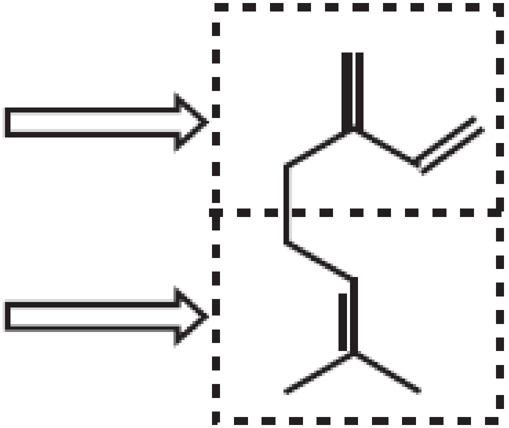
It was shown by Wallach (1887) that all terpenoids are made up of two or more isoprene units of molecular formula C_5H_8. Thus the molecular formulae of terpenoids are multiple of C_5H_8 with or without addition of oxygen and water. This is known as "Isoprene Rule".



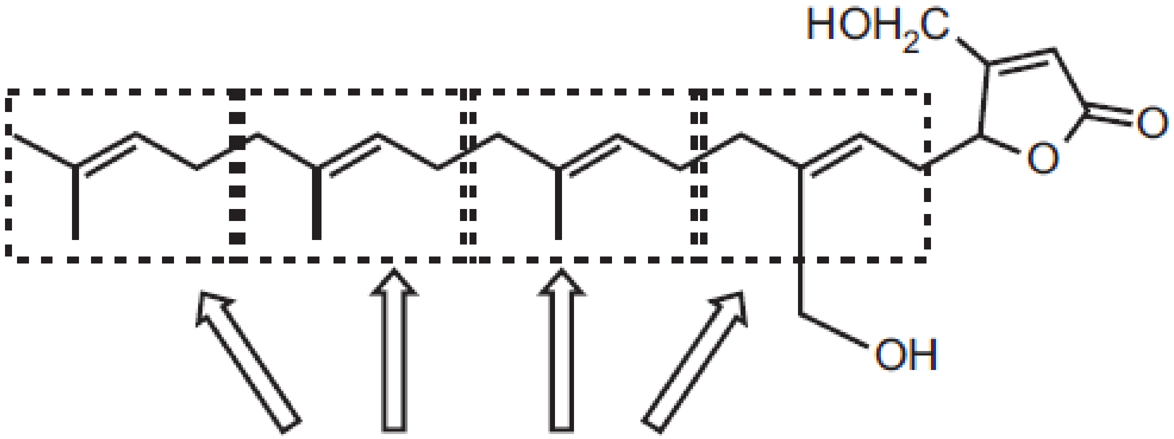
Isoprene unit



Examples :



Two isoprene units in monoterpenoids Myrcene



Four isoprene units in
sesterpenoids
Hippolide E

It is supported by following facts :

1. The thermal decomposition of almost all terpenoids gives isoprene as one of the products.

Example : Rubber on destructive distillation yields isoprene as one of the products.

$$\text{Natural rubber } (C_5H_8)_n \xrightarrow{\text{Pyrolysis}} \text{n Isoprene } (nC_5H_8)$$

2. Isoprene may be polymerised to yield a rubber like product.

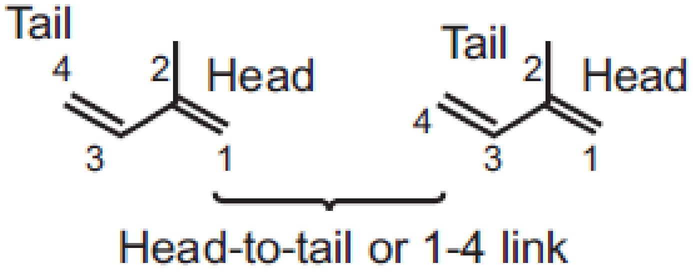
$$\text{Isoprene } n(C_5H_8) \xrightarrow{\text{Polymerisation}} (C_5H_8)_n \text{ Rubber}$$

3. Isoprene when heated to 300°C gets dimerised to yield a widely distributed terpenoid called dipentene.

$$\underset{\text{Isoprene}}{2(C_5H_8)} \rightarrow \underset{\text{Dipentene}}{C_{10}H_{16}}$$

4. The isoprene rule has helped to elucidate the structures of simple as well as complex terpenoids.

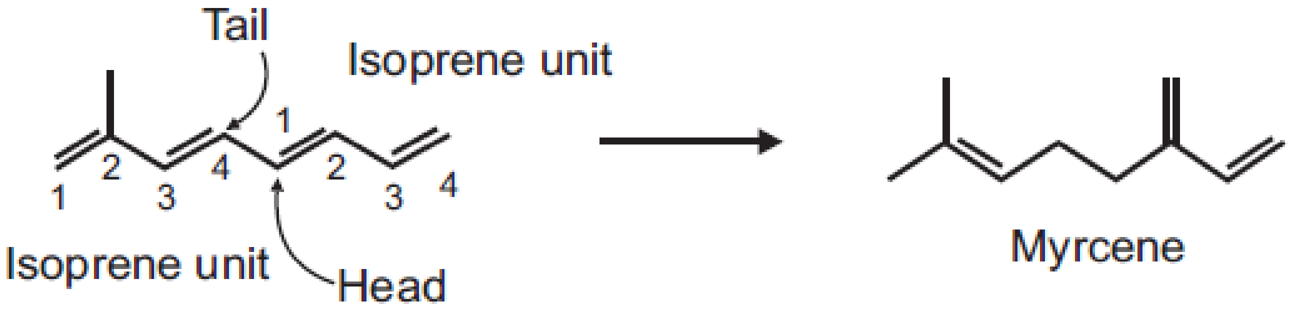
Special Isoprene Rule : It has been shown by Ingold (1925) that in many terpenoids the isoprene units are joined in a **head (H)** to **tail (T)** fashion. Head of one molecule joined to the tail of another molecule. Head being the branched end of the isoprene molecule.

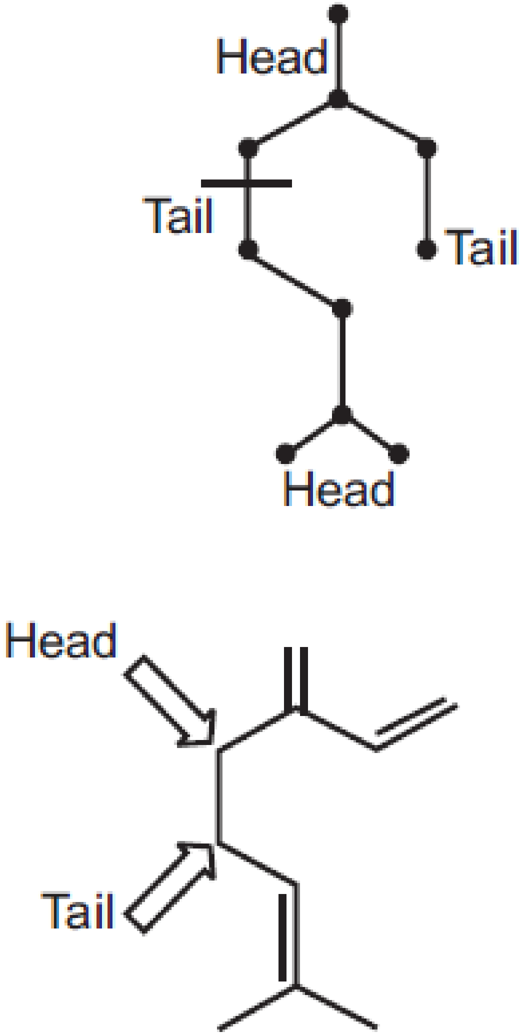


- This link is called a head-to-tail or 1-4 link.
- Carbon 1 is called the 'head' and carbon 4 is 'tail'.
- The head is always directed to the free end of a molecule and tail to the inner part.

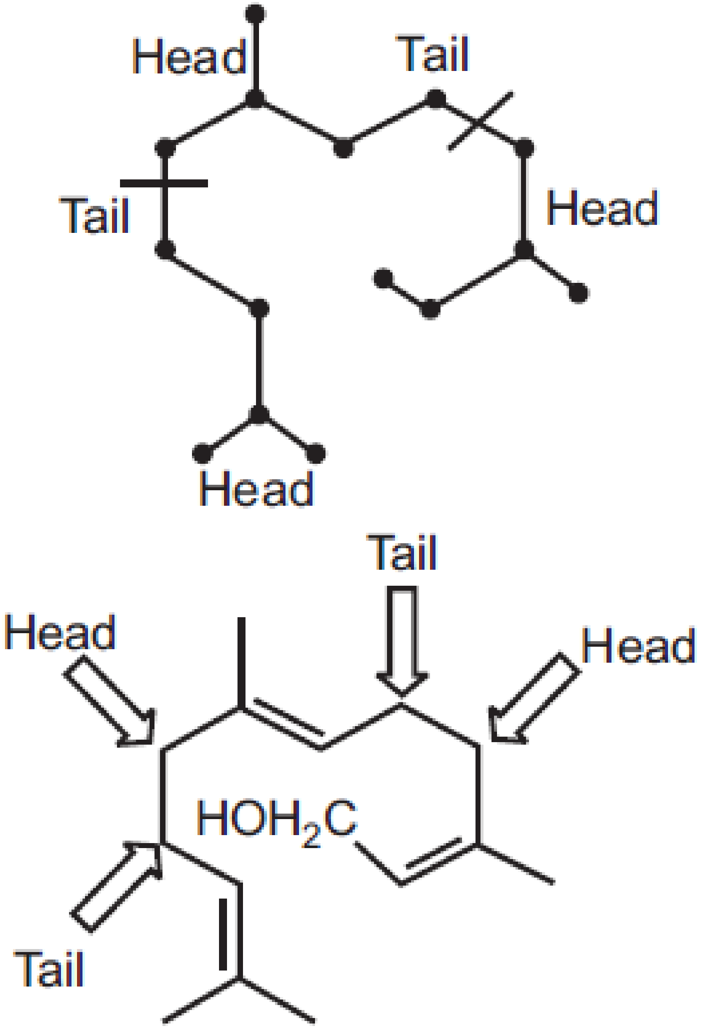
Examples :

1. Myrcene is a simple 10 carbon containing terpenoid formed from the head-to-tail union of two isoprene units as follows.





Myrcene



Farnisol

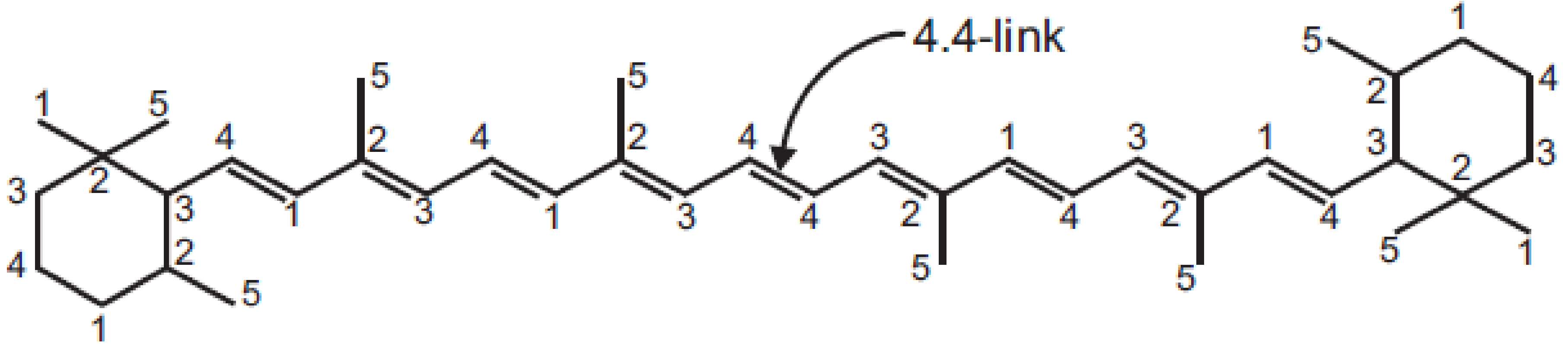
13 and 14

Exceptions :

Though this rule has proved very useful, it can only be used as a guiding principle and not as a fixed rule. This is because there are several exceptional terpenoids, which do not follow this special isoprene rule.

Examples :

1. **Tail-to-tail joining (4-4 linkage) :** Lavandulol consisting of just two isoprenes has tail-to-tail condensation.



2. **Head-to-head joining :** Does not occur in nature.

4.2.7 General Methods for Structure Determination of Terpenoids

The fundamental research in elucidating the complicated structures of terpenoids were done by Wallach, Baeyer, Perkin, Semmler, Simonson, Ruzicka, etc.

The following methods were used for the determination of structure of terpenes :

I. Chemical methods (Analytical evidences)
II. Physical methods
III. Synthesis

The following brief account gives an indication of various methods which have been particularly useful (especially oxidative degradation) in elucidating the structures of terpenoids.

I. Analytical evidences :

(A) Molecular formula :

(a) The molecular formula of a pure compound is determined by qualitative and quantitative elemental analysis. Elemental analysis of the sample estimates the percentage of different elements from which empirical and molecular formula can be determined.

(b) Molecular weight of terpenoids is obtained by mass spectrometry and other methods.

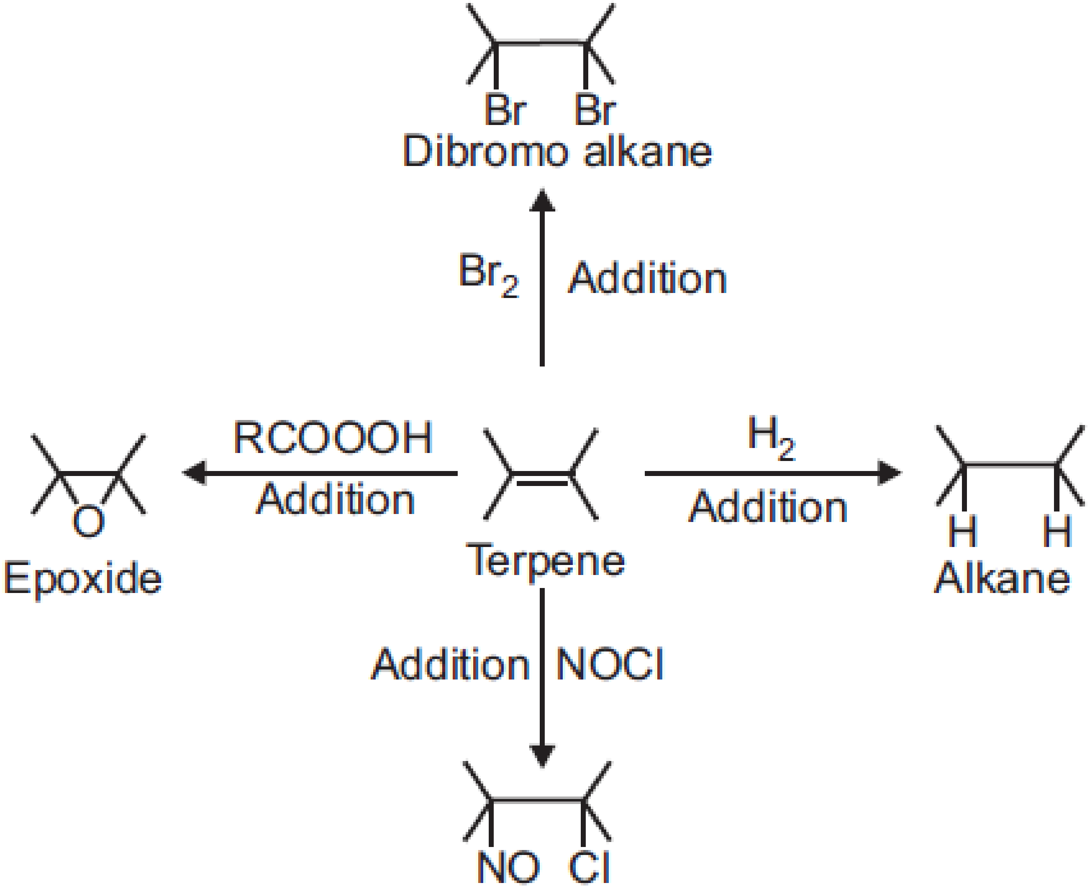
(B) Detection of unsaturation :

The presence of unsaturation (qualitative) as well as number of unsaturation (quantitative) is ascertained by addition reaction.

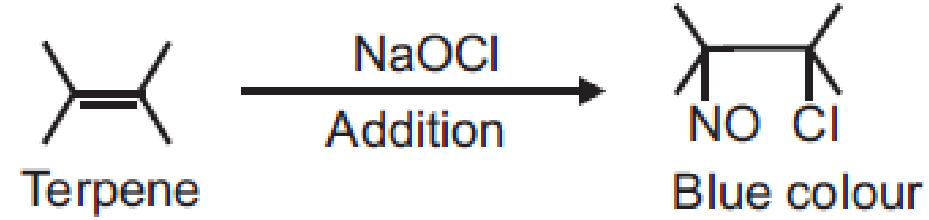
Examples :

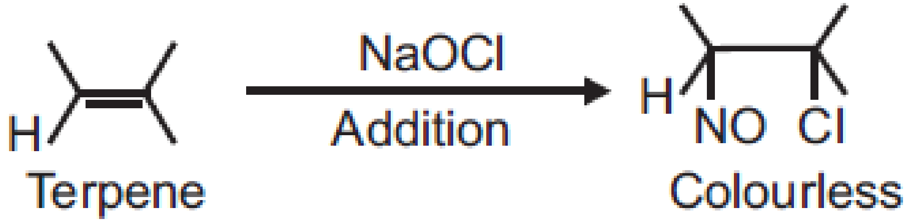
(i) **Bromination and hydrogenation :** From the amount of consumption of Br_2/H_2 molecule, the number of double bonds in a terpenoid can be estimated. These facts also tell the number of rings present in the structure.

(ii) **Epoxidation** : Epoxide formation with peracid also gives idea about double bonds present in the terpenoid molecule.



(iii) **Tilden's reagent :** Addition of nitrosyl chloride (NOCl) (Tilden's reagent) gives idea about substituent present on C=C bonds. When both C=C are tertiary it gives blue colour, while one is tertiary and other is secondary gives colourless complex.

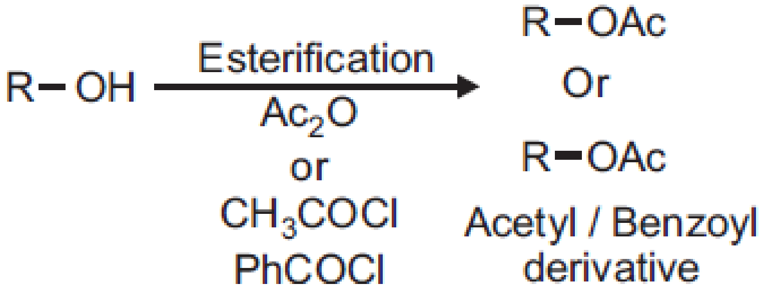




(C) Nature of oxygen atom present :

If oxygen is present in the molecule, it may be present in the form of –OH (hydroxyl), -CHO (aldehyde), -CO- (ketone), -COO- (acid derivatives), which can be determined by following methods.

(i) **Hydroxyl group (-OH) :** The presence of -OH group can be determined by the formation of acetate by the action of acetic anhydride, acetyl chloride or benzoyl chloride.



$$R-OH \xrightarrow[\substack{Ac_2O \\ \text{or} \\ CH_3COCl \\ PhCOCl}]{\text{Esterification}} \begin{matrix} R-OAc \\ \text{Or} \\ R-OAc \end{matrix}$$

Acetyl / Benzoyl derivative

(ii) If hydroxyl groups are present, then their number can also be estimated as follows ;

(a) Formation of monoacetyl derivative indicates the presence of one –OH group, while diacetyl and triacetyl derivative indicate the presence of two and three –OH groups respectively.

(b) Dehydration of alcohols using H_2SO_4 or H_3PO_4 (phosphoric acid) can be useful for distinguishing primary, secondary and tertiary alcohols.

(iii) **Carboxyl group (–COOH) :** The solubility of the compound in aqueous $NaHCO_3$, Na_2CO_3 or NH_3 indicates the presence of a carboxyl group, while titration with a standard alkali (NaOH) solution can give idea about number of –COOH groups in terpenoids.

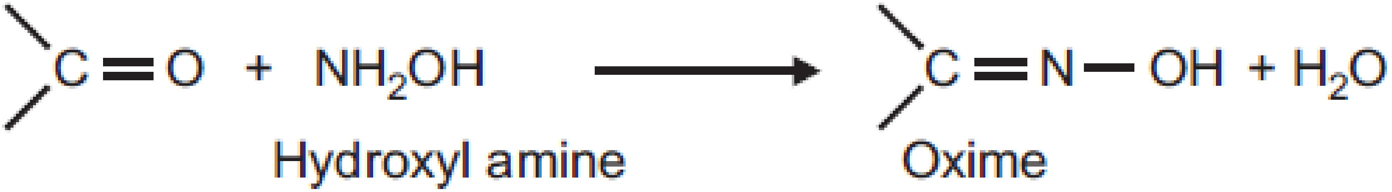
$$R{-}COOH + NaHCO_3 \longrightarrow R\text{ - }COONa + H_2O + CO_2\uparrow$$

Formation of esters also shows the presence of a carboxyl group.

$$\underset{\text{Terpene}}{R{-}COOH} + R'OH \xrightarrow{H^{\oplus}} R\text{ - }COOR' + H_2O$$

(iv) Carbonyl group (>C=O) :

(a) Terpenoids containing carbonyl functional group (C=O) form crystalline addition products like oxime, phenyl hydrazone and bisulphite.

1. 

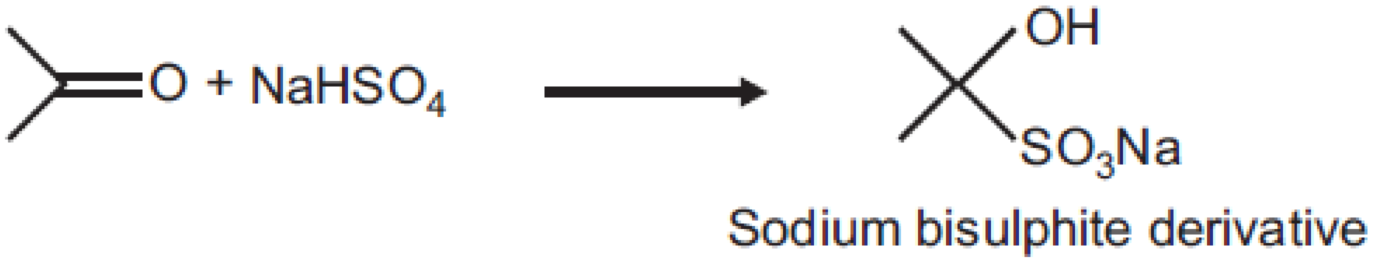
$$>C{=}O + NH_2OH \longrightarrow >C{=}N{-}OH + H_2O$$

2. 

$$>C{=}O + NH_2{-}NHC_6H_5 \longrightarrow >C{=}N{-}NHC_6H_5 + H_2O$$

3. 

$$>C{=}O + NH_2{-}NHCONH_2 \longrightarrow >C{=}N{-}NHCONH_2 + H_2O$$

4. 

$$>C{=}O + NaHSO_4 \longrightarrow >C(OH)(SO_3Na)$$

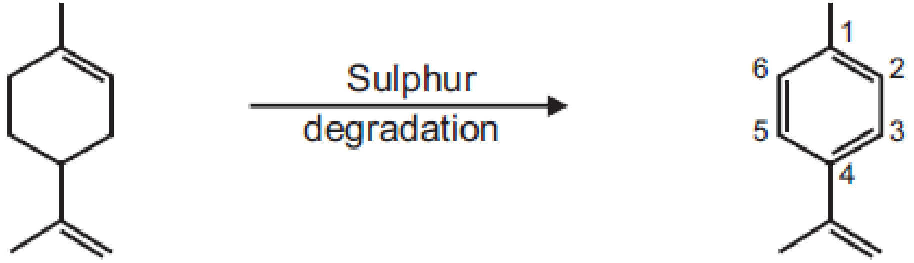
(b) Aldehydic group can be distinguished from other groups by silver mirror test with Tollen's reagent.

Aldehyde

Silver mirror

(c) Aldehydes on oxidation give carboxylic acids with the same number of carbon atoms, while ketones give less number of carbon atoms.

(v) Methyl ketone group ($-COCH_3$) : The presence of this group can be detected by iodoform test (iodine and sodium hydroxide or NaOI), in which a methyl ketone gives a yellow precipitate of iodoform.



Dipentene
Monocyclic monoterpenoid

p-Cymene
(Methyl and isopropyl groups are in 1, 4 positions)

(D) Nature of carbon skeleton and the relative position of substituents on rings (Dehydrogenation) :

The dehydrogenation of terpenoids with S, Se, Pt or Pd gives important information regarding the nature of carbon skeleton and the relative position of substituents on rings. The nature of carbon skeleton depends on the nature of product formed.

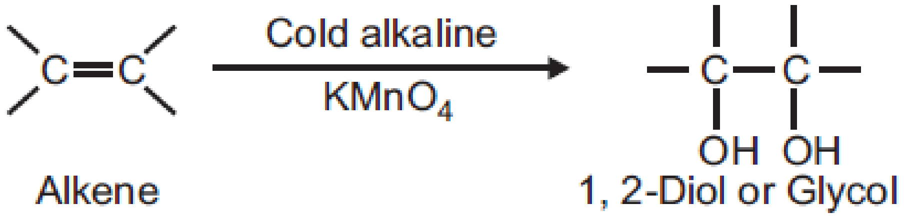
Example : α-terpineol on dehydrogenation by Se yields para-cymene, this indicates α-terpineol contains a six membered carbon skeleton.

(E) Oxidative degradation :

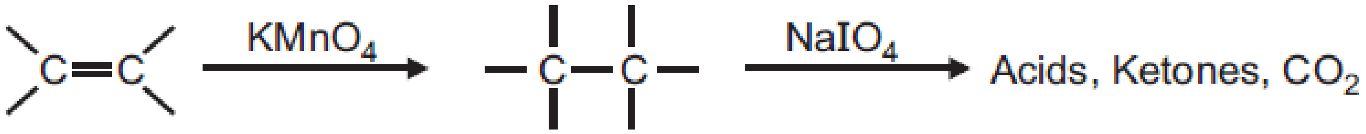
The oxidative degradation has been the parallel tool for elucidating the structure of terpenoids.

In this the terpenoid is oxidatively degraded into small fragments of known structure. The usual reagents used for this purpose are ozone (O_3), $KMnO_4$, CrO_3 , OsO_4, peroxy acids, etc. Since oxidizing agents are selective, depending on a particular group to be oxidized, the oxidizing agent is chosen.

(a) Alkaline $KMnO_4$: This reagent converts alkenes into 1, 2-diols or glycols.

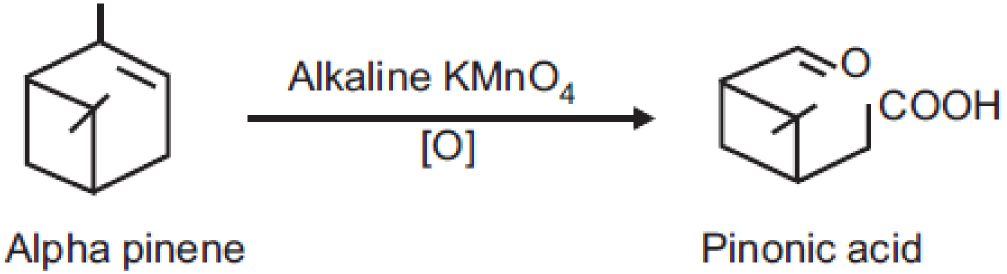


(i) The diols can be further cleaved by reagents like sodium periodate.



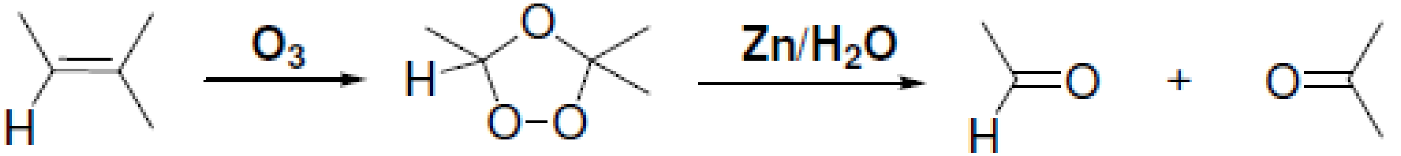
(ii) The formation of CO_2 indicates the presence of a terminal $=CH_2$ group.

$$CH_3-CH_2-CH=CH_2 \xrightarrow[\text{(ii) } NaIO_4]{\text{(i) } KMnO_4} CH_3-CH_2-COOH + CO_2\uparrow$$



If double bond is in ring, it forms ketoacids or dicarboxylic acids without loss of carbon.

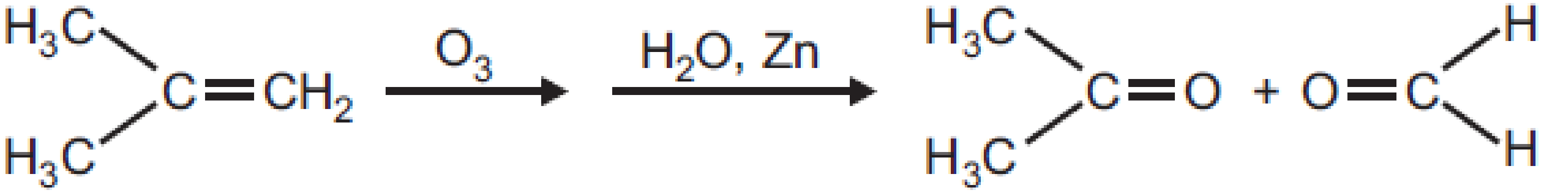
(b) **Ozonolysis (O_3) :** This is a very useful reagent for the cleavage of double bonds. The addition of ozone to the double bond forms an ozonide, which is then hydrolyzed to yield aldehydes and ketones.



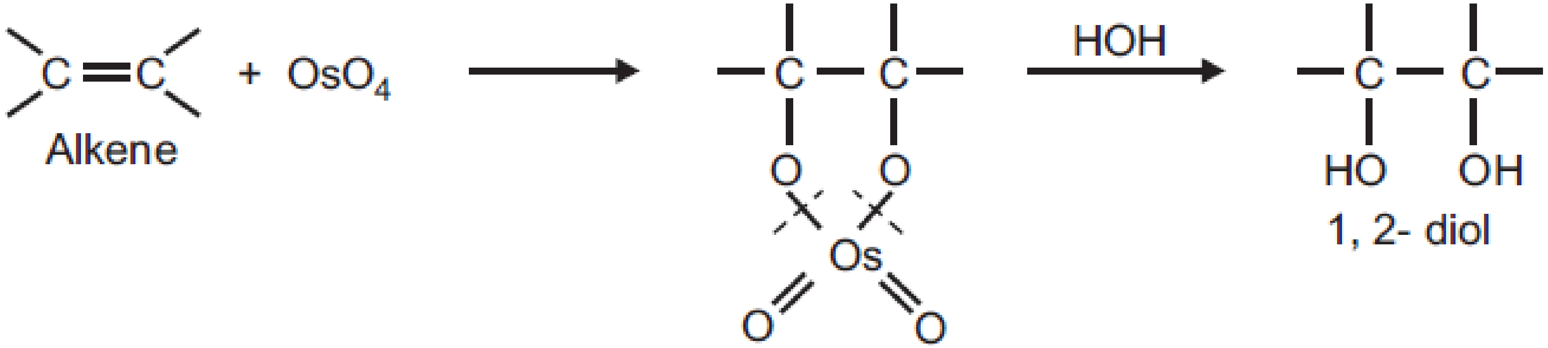
(i) Terminal alkenes give formaldehyde as one of the products.

(ii) Ozonolysis locate the position of double bonds in a molecule.

(iii) The formation of acetone and formaldehyde reveals the presence of isopropylidene and terminal double bond.



(c) **Osmium tetraoxide (OsO_4) :** Osmium tetraoxide is more selective for the conversion of olefins to cis-1,2-diols.



In general, oxidative degradation has been the most important tool for elucidating the structure of terpenoids.

II. **Physical methods :** It involves following methods.

(i) **Optical activity :** If terpenoids are optically active, its specific rotation is measured by means of polarimeter. It helps to distinguish two or more possible structures as in limonene and carvone.

(ii) **Refractive index :** Measurement of refractive index of the molecule gives us information about the nature of carbon skeleton.

(iii) **X-ray analysis :** X-ray analysis is many times very useful for elucidating the structure and stereochemistry of terpenoids.

(iv) **Spectroscopic methods :** These are the modern methods used for elucidating the structures of terpenoids.

(a) **Ultra violet (UV) spectroscopy :** It has been much used in terpenoid chemistry for the detection of conjugation.

For simple acyclic dienes, λ_{max} = 217-288 nm.

For heteroannular dienes (semicyclic), λ_{max} = 230-240 nm

For homoannular dienes, λ_{max} = 256-265 nm.

For α-β unsaturated carbonyl system, λ_{max} = 220-250 nm and 315-330 nm.

(b) **Infrared (IR) spectroscopy :** It is also very useful in terpenoid chemistry and is valuable in detecting the presence of a hydroxyl group –OH (~3400 cm^{-1}), a carbonyl group >C=O (~1700-1750 cm^{-1}) and α, β-unsaturated carbonyl group (~1660-1700 cm^{-1}).

(c) **Nuclear magnetic resonance spectroscopy (NMR) :** It is used to detect and identify the complete structure of compounds.

(d) **Mass spectroscopy (MS) :** It is frequently used to determine molecular weights, molecular formulae, nature of various functional groups in terpenoids.

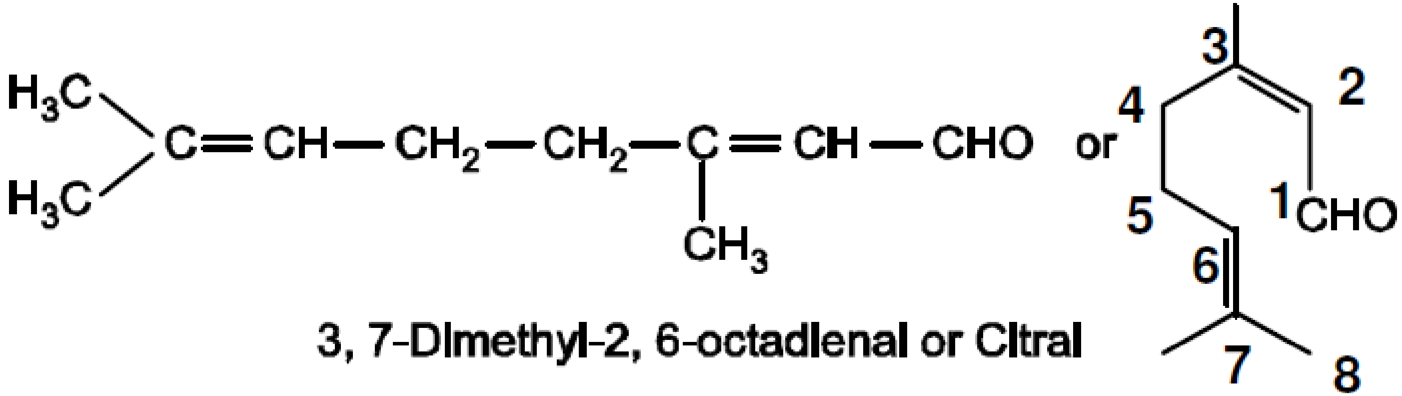
III. Synthesis : After arriving at the tentative structure from analytical evidence, the final proof of the structure depends on the synthesis.

4.2.8 Analytical Evidences and Synthesis of Citral

1. Introduction :

Citral is an oxygen containing acyclic monoterpenoid made up of two isoprene units linked with head-to-tail fashion (1-4 linkage) having aldehyde group.

It is an optically inactive colourless liquid having b.p. 229°C. Its molecular formula is $C_{10}H_{16}O$ having the following structure.



$$(H_3C)_2C{=}CH{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH{-}CHO$$

3, 7-Dimethyl-2, 6-octadienal or Citral

2. Occurrence :

Citral is a main component of citrus fruit's peel oil. It is especially found in orange peel. The peculiar smell of Lemon grass oil is due to citral. Citral is present in oils of several plants including

1. Lemon myrtle (90–98%),
2. Lemongrass (65–85%),
3. Lemon tea-tree (70–80%),
4. Lemon balm (11%),
5. Lime (6–9%),
6. Lemon (2–5%),
7. Orange.

3. Uses :

(i) Citral has a strong lemon (citrus) odour and widely used as an aroma compound in perfumery.

(ii) Citral is used as a flavor and for fortifying lemon oil.

(iii) It also has strong antimicrobial qualities and pheromonal effects in acari and insects.

(iv) Citral is used in the synthesis of vitamin A, lycopene, ionone, and methylionone, to mask the smell of smoke.

4. Isolation :

Citral containing lemongrass oil can be isolated by using stea distillation, while citral was obtained from lemongrass oil by simp column chromatography using silica gel as a stationary phase.

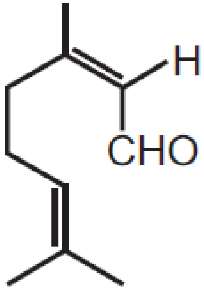
5. Determination of structure and synthesis of Citral :

Citral exists in two geometrical isomers in nature.

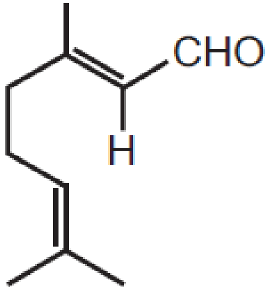
(i) **Cis-Citral (Z-form) :** The cis-isomer known as ‘Citral-b’ also called as ‘neral’.

(ii) **Trans-Citral (E-form) :** Trans-isomer known as ‘Citral-a’ also called as ‘geranial’.

Ordinary citral obtained from lemongrass oil is, infact, mixture of Citral-a (90%) and Citral-b (10%).



Cis-citral; citral-b;
Neral; Z-form



Trans-citral; citral-a;
Geranial; E-form

The following methods were used for the determination of structure of citral :

I. Chemical methods (Analytical evidences)
II. Physical methods
III. Synthesis

I. Analytical evidences (Constitution) :

A. Molecular formula : Molecular formula of citral is found to be $C_{10}H_{16}O$.

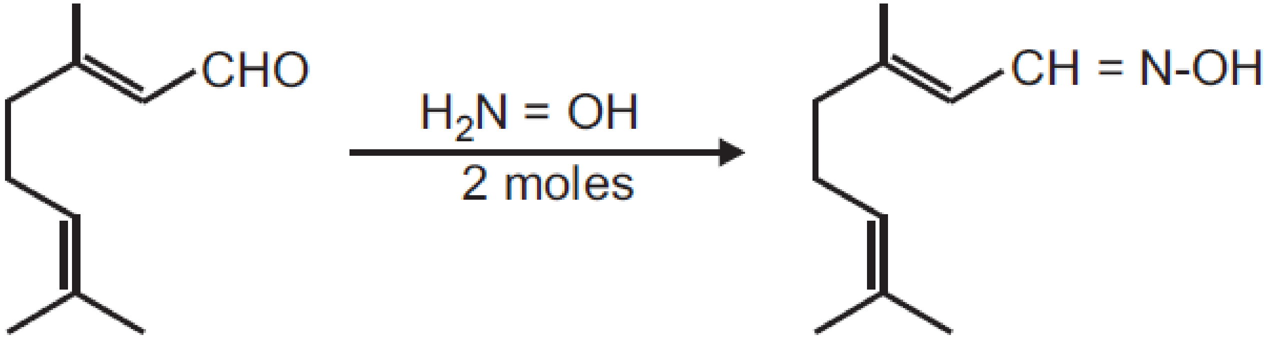
B. Presence of unsaturation : Citral on treatment with bromine gives tetrabromo derivative. Similarly, citral on catalytic hydrogenation forms a tetrahydro derivative.

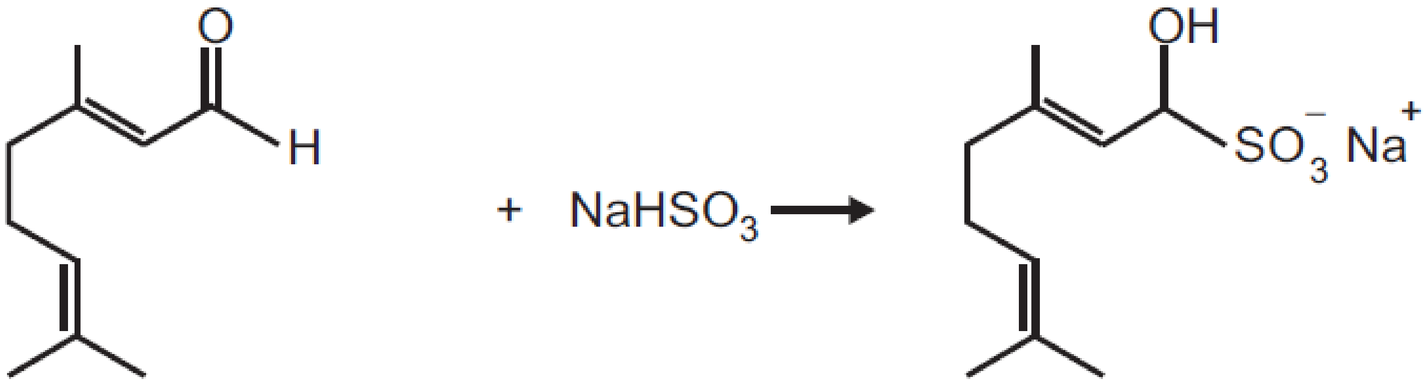
Both these reactions indicate the presence of two C=C double bonds in citral.

$$\underset{\text{Tetrabromo derivative}}{C_{10}H_{16}OBr_4} \xleftarrow{2Br_2} \underset{\text{Citral}}{C_{10}H_{16}O} \xrightarrow{2H_2} \underset{\text{Tetrahydro derivative}}{C_{10}H_{20}OH}$$

C. Nature of Oxygen :

(i) Presence of carbonyl group (aldehyde/ketone) : It forms oxime with hydroxylamine and gives bisulphite addition product with sodium bisulphite. Therefore, it must contain either an aldehyde or a ketone group (oxo group).



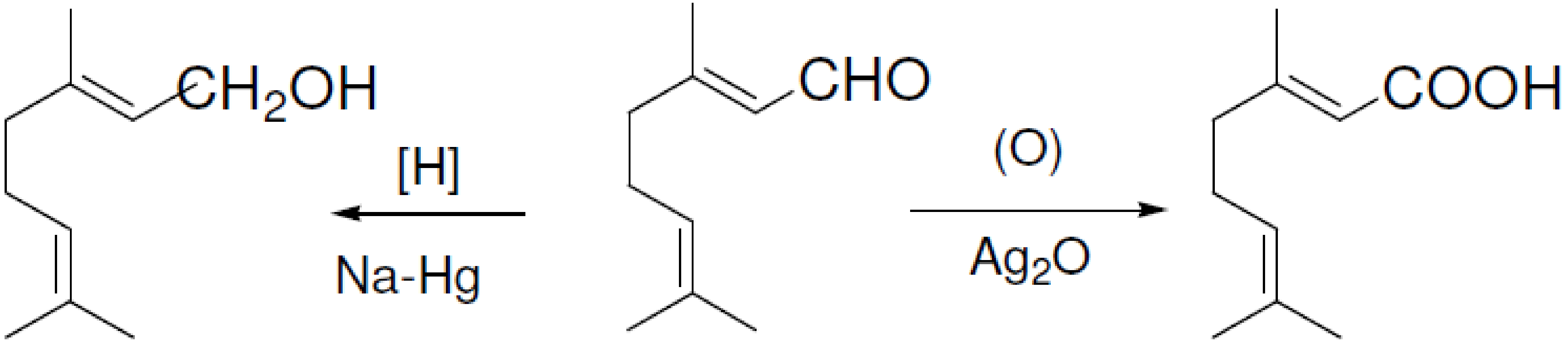


(ii) Presence of aldehyde group : The presence of aldehydic gro
is proved by following reactions.

(i) On mild oxidation with silver oxide (Tollens reagent), it gi
geranic acid with the same number of carbon atoms.

(ii) On reduction with sodium amalgam (Na-Hg) in dilute aci
forms primary alcohol called geraniol $C_{10}H_{18}O$.

Both these reactions indicate the presence of an aldehyde (−C
group in citral.



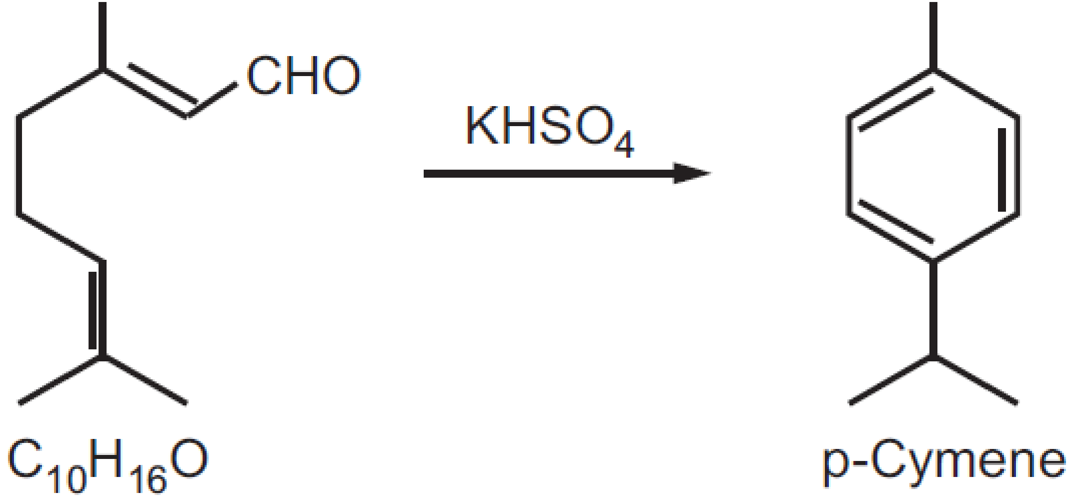
Geraniol **Citral** **Geranic acid**

D. Citral is acyclic terpenoid :

The molecular formula of citral is $C_{10}H_{16}O$. The formula of the parent hydrocarbon would be therefore $C_{10}H_{22}$. This agrees with a general formula of alkanes (C_nH_{2n+2}) and hence citral is acyclic terpenoid.

E. Presence of methyl $-CH_3$ and isopropyl group :

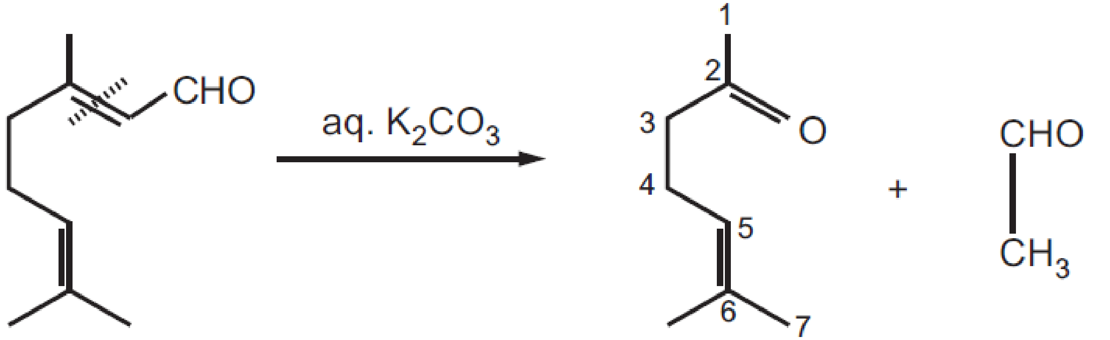
On treatment with $KHSO_4$, citral gives p-cymene. This indicates relative positions of methyl ($-CH_3$) and isopropyl group ($-CHMe_2$). This reaction also showed that citral molecule is acyclic in which two isoprene units are joined in head-to-tail manner.



F. Presence of α, β-unsaturated carbonyl system :

(i) U.V. spectrum of citral shows intense absorption band at λ_{max} 238 nm (ε = 13,500). This is the characteristic of an α, β-unsaturated carbonyl system. Hence, citral must be an α, β-unsaturated aldehyde

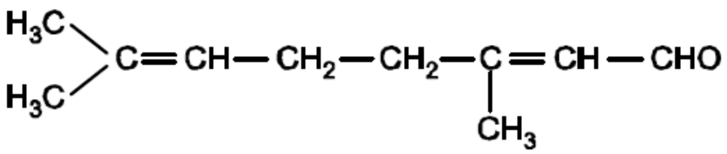
(ii) This is confirmed by the retro-aldol reaction; Citral when boiled with K_2CO_3 solution gives 6-methylhept-5-en-2-one (i.e. methyl heptenone) and acetaldehyde. This is a characteristic reaction of conjugated aldehyde.



6-Methylhept-5-en-2-one

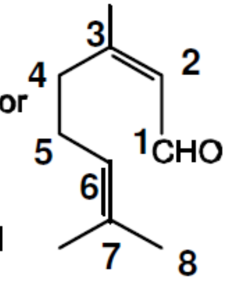
Acetaldehyde

All above evidences showed that citral has the following structure :



$$(H_3C)_2C{=}CH{-}CH_2{-}CH_2{-}\underset{CH_3}{\underset{|}{C}}{=}CH{-}CHO$$

or

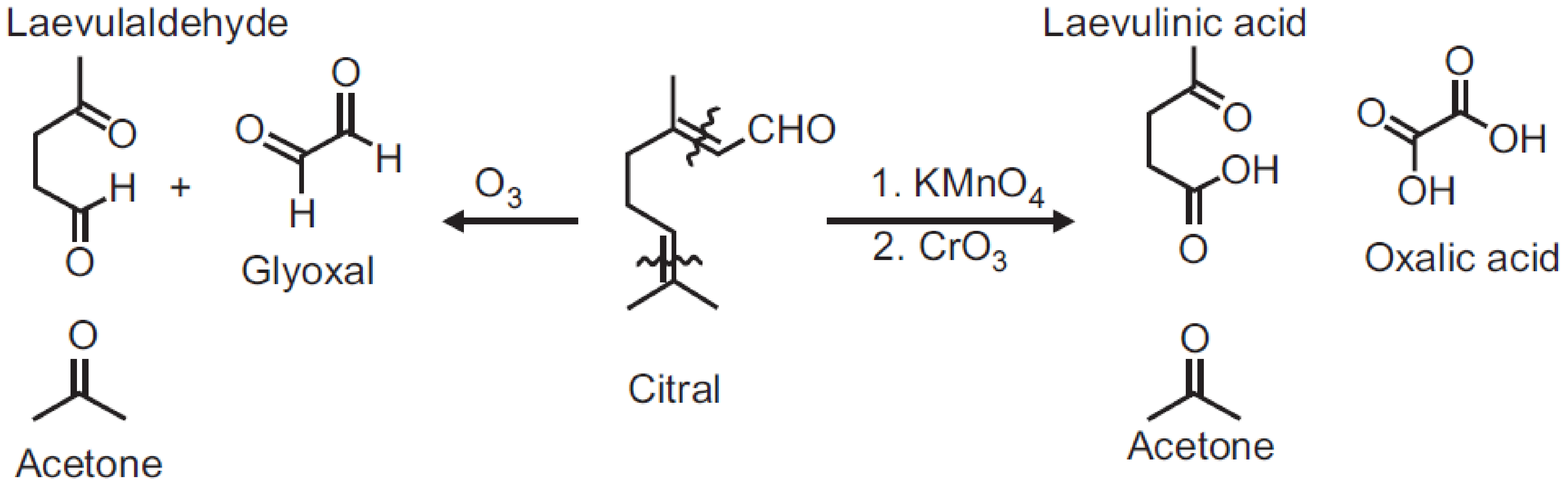


3, 7-Dimethyl-2, 6-octadienal or Citral

G. This structure is confirmed by following oxidative degradation reactions :

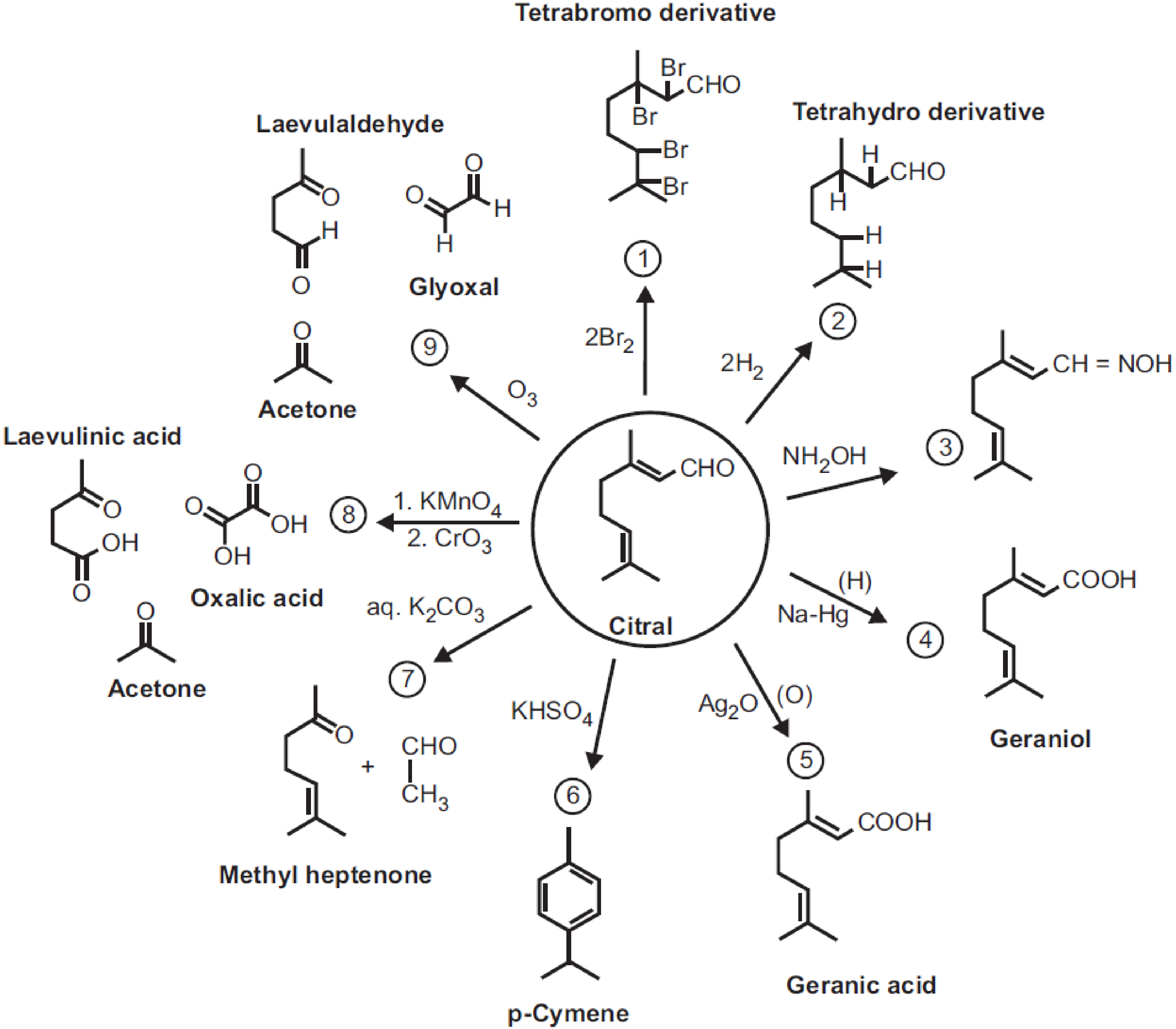
(i) **The oxidation with $KMnO_4$:** The oxidation of citral with alkaline $KMnO_4$, followed by chromic acid, gives acetone, levulinic acid and oxalic acid.

(ii) **Ozonolysis :** On ozonolysis citral gives acetone, laevulinic aldehyde and glyoxal.



This is accountable only if the position of double bonds is as shown in the above formula.

Summary of Reactions :

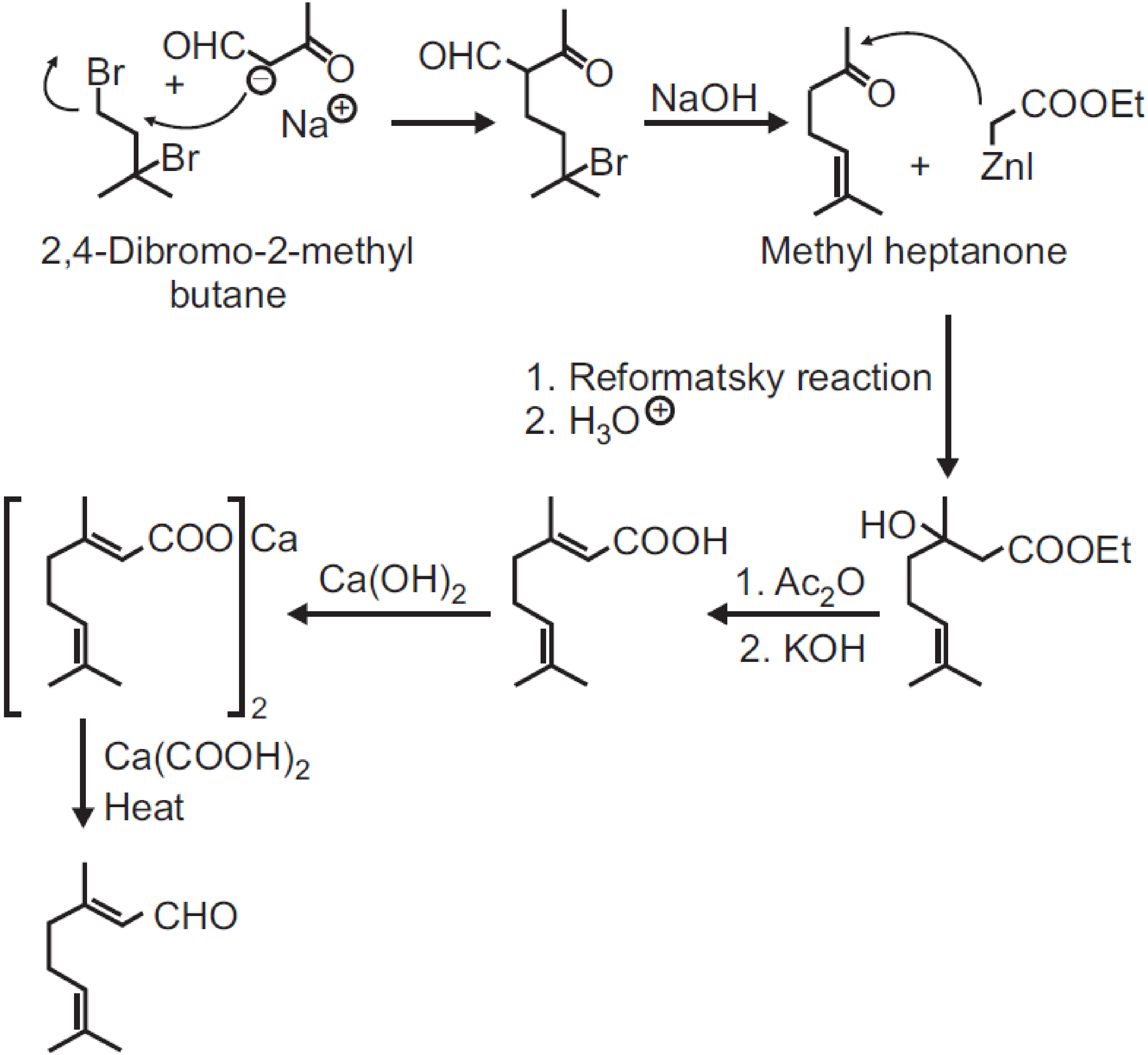


II. Synthesis of Citral :

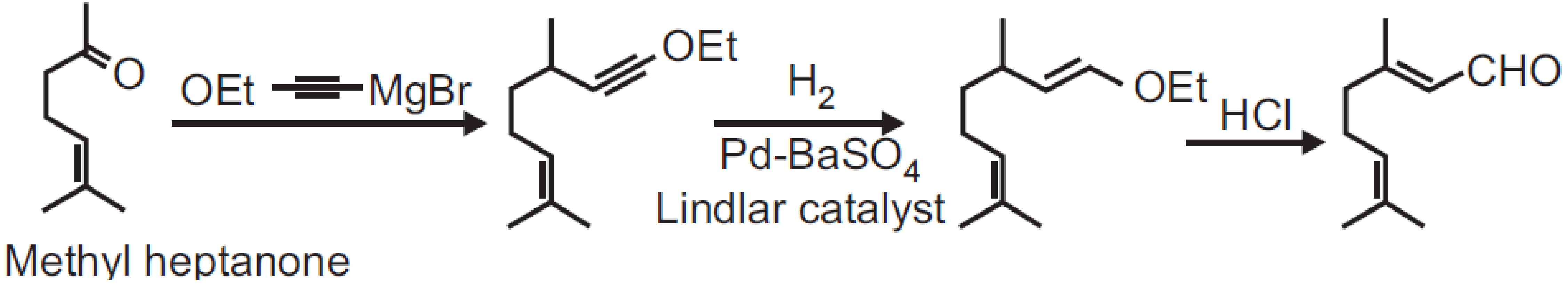
The structure of citral was confirmed by its synthesis.

(a) **Barbier-Bouveault-Tiemann's synthesis :** It involves following steps :

- (i) **Synthesis of methylheptanone :** 2,4-Dibromo-2-methyl butane on reaction with Na-salt of acetyl acetone followed by reaction with NaOH yields methyl heptenone.
- (ii) **Conversion of methylheptenone to geranic ester :** Methylheptenone is converted to geranic ester by Reformatsky's reaction.
- (iii) **Conversion of geranic ester to citral :** Geranic ester is then converted to citral by distilling a mixture of calcium salts of geranic acid.


Br
OHC
+
O
Na⊕
Br
2,4-Dibromo-2-methyl butane
OHC
O
Br
NaOH
O
COOEt
+
ZnI
Methyl heptanone
1. Reformatsky reaction
2. $H_3O^{\oplus}$
HO
COOEt
1. Ac_2O
2. KOH
COOH
$Ca(OH)_2$
COO
Ca
2
$Ca(COOH)_2$
Heat
CHO

(b) Arne's synthesis : It involves following steps :



4.3 Alkaloids

4.3.1 Introduction

The term alkaloid means alkali like i.e. the compounds having properties similar to alkalis. Hence, the name alkaloid is given to all organic bases isolated from plants and contains at least one nitrogen atom as a part of heterocyclic ring.

In general, alkaloids are very poisonous, but if used in very small quantities, they act as medicines. Many such alkaloids are in use from earlier days e.g. Morphine is used to get relief from pain, quinine in the treatment of malarial fever, ephedrine as a bronchodialator in the treatment of bronchial asthma, etc. Thus, basic properties, complex structures, physiological action and plant origin are the main features of alkaloids.

4.3.2 Occurrence

Alkaloids were established to be present in the plant kingdom and in animals, including humans, marine organisms, fungi and other microorganisms. Alkaloids are mainly found in seeds, roots, leaves and bark of the plant and generally occur as salts of various plant acids like acetic, oxalic, citric, maleic, tartaric, etc.

4.3.3 Isolation

The alkaloids can be isolated in two steps :

Step I : Isolation of residue containing a mixture of alkaloids :

It involves solvent extraction as a main step.

Step II : Separation of alkaloid from residue :

The residue obtained from above steps generally contains many alkaloids and these are separated by chromatographic methods.

General method for isolation of alkaloids is as follows :

(i) The plant material is dried, then finely powdered and extracted with boiling methanol.

(ii) The solvent is distilled off and the residue is treated with inorganic acids to form water soluble salts.

(iii) The free bases are liberated by the addition of Na_2CO_3 to the aqueous solution of salts and extraction with various solvents like ether, chloroform, etc.

(iv) After evaporation of solvent, the residue obtained contains a mixture of alkaloids. This mixture is then separated into individual compounds by using different techniques like preparative thin layer chromatography, column chromatography, recrystallization etc.

4.3.4 Classification

Today, we know thousands of alkaloids which are isolated from plants. But still there is no rational classification of alkaloids because of the diverse nature of carbon skeleton in them. Alkaloids are often divided into following classes based on

1. The pharmacological action (biological activity).
2. The biochemical origin (biosynthetic pathway of production in the plant).
3. Taxonomic character : This is based on texon.
4. The chemical structure.

(1) **Classification based on pharmacological action (biological activity) :** These are of following types :

   (i) Analgesic and narcotic e.g. Morphine and strychnine.
   (ii) CNS stimulants e.g. Caffeine.
   (iii) Anti-asthmatics e.g. Ephedrine.
   (iv) Anti-hypertensives e.g. Reserpine.
   (v) Smooth muscle relaxants e.g. Papaverine.

(2) **Classification based on biochemical origin (biosynthetic pathway of production in the plant) :** These are of following types :

   (i) Indole alkaloids: derived from tryptophan.
   (ii) Piperidine: derived from lycine.
   (iii) Ptrrolidine: derived from ornithine.
   (iv) Imidazole: derived from histidine.

(3) **Classification based on taxonomic character :** This is based on texon.

   (i) Cannabinaceous alkaloid e.g. Hemp.

   (ii) Rapacious alkaloids e.g. Quinine.

   (iii) Solanaceous alkaloids e.g. Tree Tobacco, Ashwagandha.

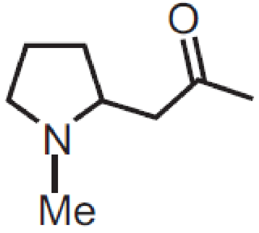
(4) **Classification based on chemical structure (type of nitrogen, heterocyclic or non-heterocyclic and type of ring structure) :** Broadly they are of following types.

   (i) True alkaloids : These contain nitrogen in the heterocycle and originate from amino acids e.g. Atropine, nicotine, and morphine.

   (ii) Protoalkaloids : Which contain nitrogen (but not the nitrogen heterocycle) and also originate from amino acids. e.g. Adrenaline and ephedrine.

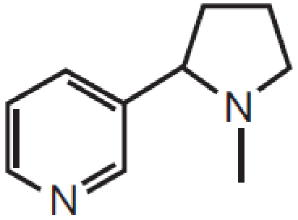
   (iii) Pseudoalkaloids : Alkaloid-like compounds that do not originate from amino acids and do not originate from amino acids e.g. Caffeine, theobromine, In general, alkaloids are grouped into following types based on the structure of carbon-nitrogen cycle present in the molecule.

1. **Pyrrolidine derivatives :** They contain pyrrole in their structure. e.g. Hygrine.



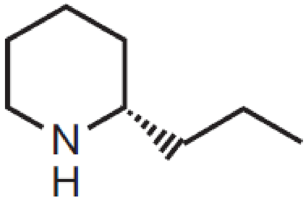
Hygrine

2. **Pyridine-Pyrrolidine derivatives :** They contain both pyridine-pyrrolidine in their structure. e.g. Nicotine.



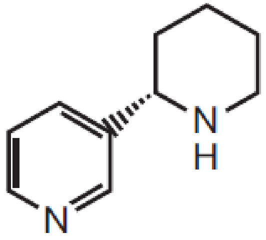
Nicotine

3. **Piperidine derivatives :** They contain piperidine in their structure. e.g. Conine.



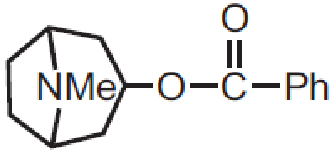
Coniine

4. **Pyridine-piperidine derivatives :** They contain both pyridine and piperidine in their structure. e.g. Anabasine.



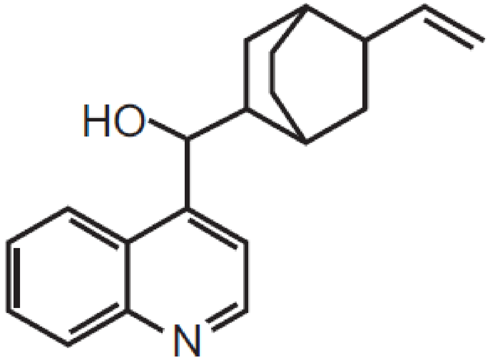
Anabasine

5. **Tropane (Piperidine / N-methylpyrrolidine) derivatives :** They contain both piperidine / N-methylpyrrolidine. e.g. Atropine.



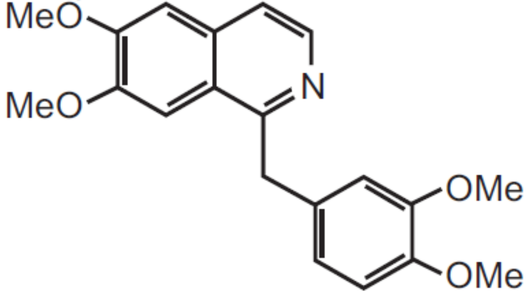
Atropine

6. **Quinoline derivatives :** They contain quinoline. e.g. Cinchonine.



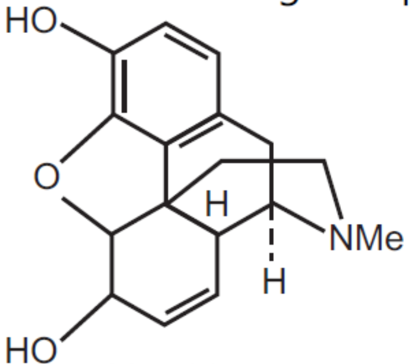
Cinchonine

7. **Isoquinoline derivatives :** They contain isoquinoline in their structure. e.g. Papaverine.



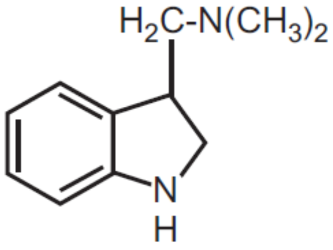
Papaverine

8. **Phenanthrene derivatives :** These contain phenanthrene framework in their structure. e.g. Morphine.



Morphine

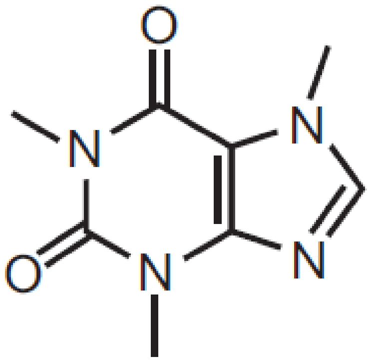
9. **Indole derivatives :** These are indole derivatives. e.g. Gramine.



Gramine

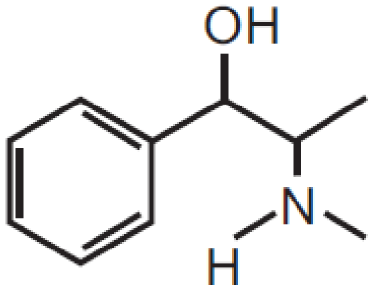
Gramine

10. Purine derivatives : These are purine derivatives. e.g. Caffeine.



Caffeine

11. Phenylethylamine group : These contain phenylethylamine framework in their structure. e.g. Ephedrine.



Ephedrine

4.2.5 General Properties of Alkaloids

1. **Physical properties** :
   - **(i)** The alkaloids are usually colourless, crystalline, non-volatile solids. Some alkaloids like coniine and nicotine are liquids and few alkaloids are coloured (e.g. berberine is yellow).
   - **(ii)** Solid alkaloids are insoluble in water but are soluble in ethanol, ether, chloroform etc. Liquid alkaloids like coniine and nicotine are soluble in water.
   - **(iii)** Most alkaloids have a bitter taste and are optically active (laevorotatory). Optically active alkaloids are very useful for resolving racemic acids (e.g. they are used for resolution of acids).

2. Chemical properties :

(i) Alkaloids are basic in nature due to presence of N. In the tertiary state nitrogen is usually part of a ring system.

Examples : Primary (R-NH_2) : Norephedrine
Secondary (R_2-NH) : Ephedrine
Tertiary (R_3N) : Nicotine

(ii) Basicity of alkaloid depends on the nature of amine (N) present in alkaloids.

$R_2NH > RNH_2 > R_3N$

(iii) Some alkaloids also contain an oxygen atom.

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(iii) Some alkaloids also contain an oxygen atom.

(iv) Tests for detection and identification : Chemical tests commonly performed for detection of alkaloids are of two types :

(i) **Precipitation reactions** : Most alkaloids are precipitated from neutral or slightly acidic medium. Many of these precipitates have definite crystalline shapes and may be useful in identification of alkaloids.

Examples :

(a) Dragondorff's reagent : Solution of potassium bismuth iodide gave orange coloured ppt.

(b) Hander's reagent : Picric acid gave yellow ppt.

(c) Mayer's reagent : Potassium mercury iodide gave cream coloured ppt.

(d) Wagner's reagent : I_2 in KI gave red-brown ppt.

(ii) Colour reactions : These reactions are usually performed by the addition of colour reagents to free bases not to their salts to produce characteristic coloured solutions. The reagents contain concentrated sulfuric acid and an oxidizing agent.

4.2.6 General Methods for Determination of Structure of Alkaloids

The following methods were used for determination of structure of alkaloids :

I. Chemical methods
II. Physical methods
III. Synthesis

I. Chemical methods (Analytical evidences) :

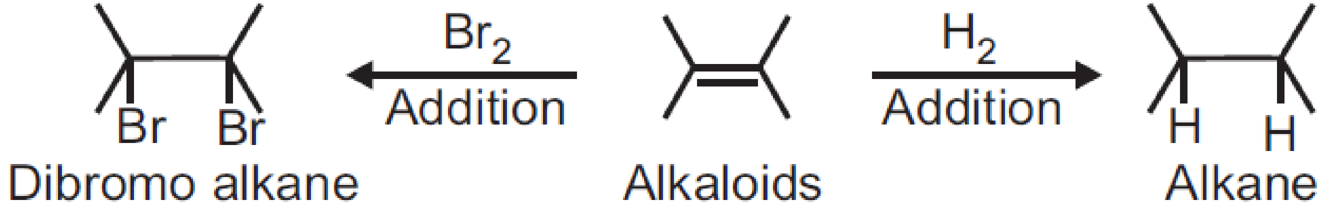
A. Molecular formula : The first step in structure elucidation is determination of molecular formula.

i) The molecular formula of pure compound is determined by usual qualitative and quantitative elemental analysis. Elemental analysis of the sample estimates the percentage of different elements from which empirical and molecular formula is determined.

ii) Molecular formula and its molecular weight is also obtained by mass spectrometry.

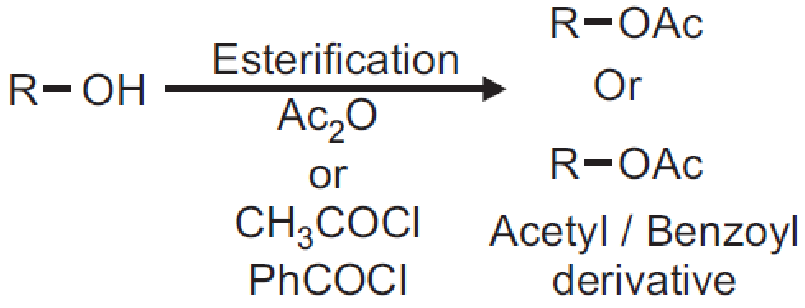
B. Detection of unsaturation : The presence of unsaturation (qualitative) as well as number of unsaturation (quantitative) is ascertained by addition reaction e.g. Bromination and hydrogenation.

From number of consumption of Br_2/H_2 molecule, the number of double bonds can be estimated. This fact also tells the number of rings present in the structure.



C. Nature of oxygen atom present : If oxygen is present in the molecule, it may be in the form of –OH (hydroxyl), –CHO (aldehyde), –CO– (ketone), –COO– (acid derivative), which can be determined by following methods.

i) **Hydroxyl group (–OH) :** The presence of -OH group can be determined by the formation of acetate by the action of acetic anhydride, acetyl chloride or benzoyl chloride.



$$R{-}OH \xrightarrow[\substack{Ac_2O \\ \text{or} \\ CH_3COCl \\ PhCOCl}]{\text{Esterification}} \begin{matrix} R{-}OAc \\ \text{Or} \\ R{-}OAc \\ \text{Acetyl / Benzoyl} \\ \text{derivative} \end{matrix}$$

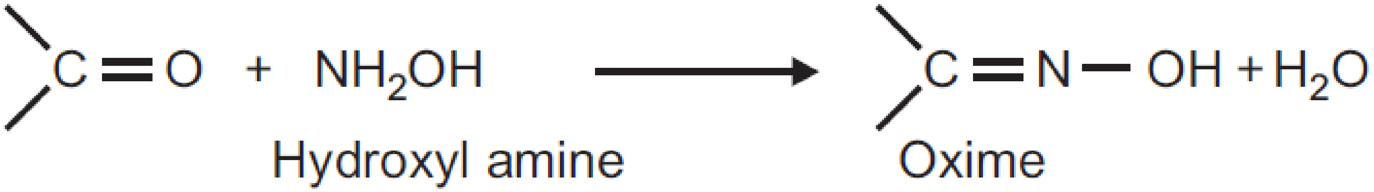
If hydroxyl groups are present, then their number can also be estimated by adding excess of acetic anhydride hydrolyzing and titrating against standard alkali (if the 'N' present in the alkaloid is primary or secondary), this is also affected by acylation.

(a) Formation of monoacetyl derivative indicates the presence of one –OH group, while diacetyl and triacetyl derivatives indicate the presence of two and three –OH groups respectively.

(b) Phenolic –OH group : If the alkaloid is soluble in alkali and can be reprecipitated by carbon dioxide and gives colour reaction with ferric chloride then the group is phenolic.

ii) **Carbonyl group (>C=O) :** Terpenoids containing carbonyl functional group (C=O) form crystalline addition products like oxime, phenyl hydrazone and bisulphite.

1.



2.

3.

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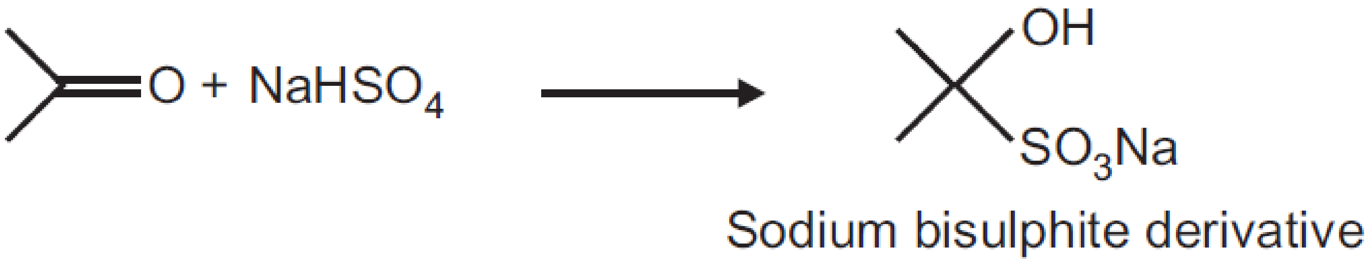
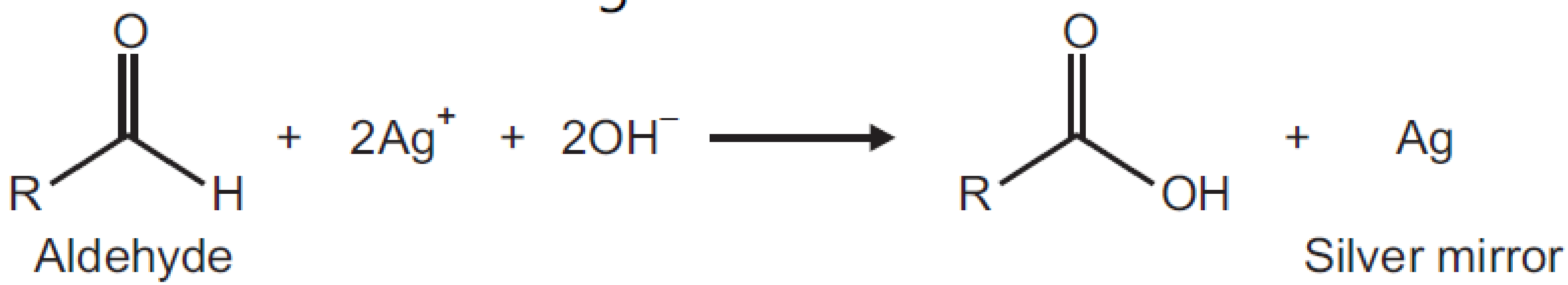
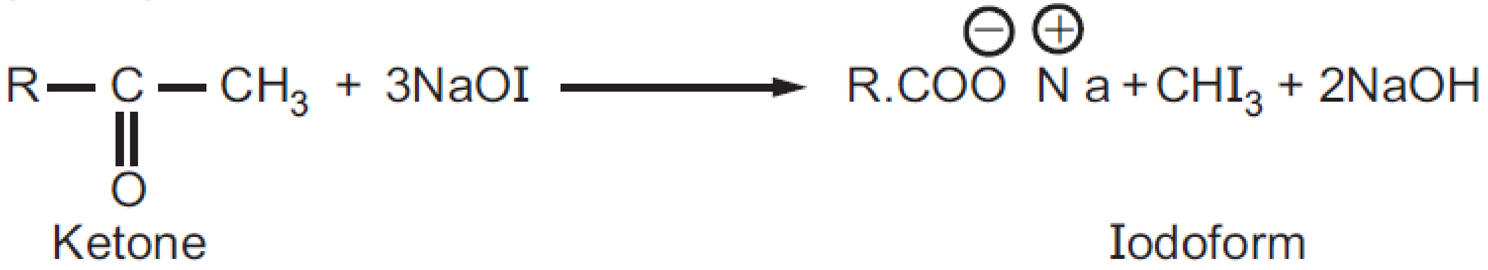


(i) Aldehydic group can be confirmed by silver mirror test with Tollen's reagent.



(ii) Aldehydes on oxidation give carboxylic acids with the same number of carbon atoms, while ketones give less number of carbon atoms.

iii) Methyl ketone group ($-COCH_3$) : The presence of this group can be detected by iodoform test (iodine and sodium hydroxide or NaOI), in which a methyl ketone gives a yellow precipitate of iodoform.



$$\underset{\text{Ketone}}{R-\underset{\underset{O}{\|}}{C}-CH_3} + 3NaOI \longrightarrow R.COO^{\ominus}\,Na^{\oplus} + \underset{\text{Iodoform}}{CHI_3} + 2NaOH$$

iv) **Carboxyl group (–COOH) :** The solubility of alkaloids in aqueous $NaHCO_3$, Na_2CO_3 or NH_3 indicates the presence of a carboxyl group, while titration with a standard alkali (NaOH) solution give idea about the number of –COOH groups.

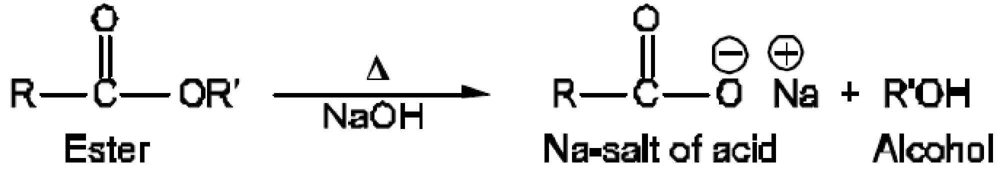
$$R-COOH + NaHCO_3 \longrightarrow R-COONa + H_2O + CO_2\uparrow$$

Formation of esters also shows the presence of a carboxyl group.

$$\underset{\text{Alkaloid}}{R-COOH} + R'OH \xrightarrow{H^{\oplus}} R-COOR' + H_2O$$

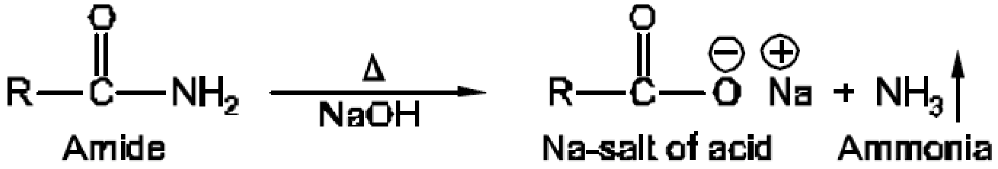
v) **Ester, lactone, amide, lactum :** The presence of all these groups can be determined by hydrolyzing alkaloid and examining the products obtained.

1.



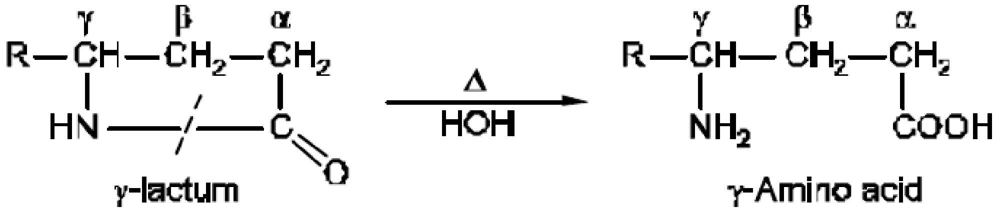
$$\underset{\text{Ester}}{R-\overset{O}{\overset{\|}{C}}-OR'} \xrightarrow[NaOH]{\Delta} \underset{\text{Na-salt of acid}}{R-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{O}\ \overset{\oplus}{Na}} + \underset{\text{Alcohol}}{R'OH}$$

2.



$$\underset{\text{Amide}}{R-\overset{O}{\overset{\|}{C}}-NH_2} \xrightarrow[NaOH]{\Delta} \underset{\text{Na-salt of acid}}{R-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{O}\ \overset{\oplus}{Na}} + \underset{\text{Ammonia}}{NH_3\uparrow}$$

3.

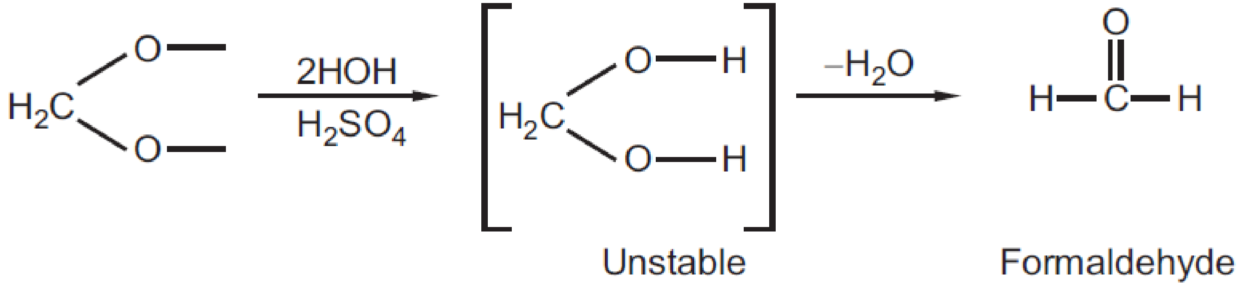


vi) **Methoxy group ($-OCH_3$) (Zeisel method) :** The presence of methoxy group is detected and estimated by Zeisel method. The alkaloid is heated with conc. HI at its boiling point (126°C) and convert methoxy group ino methyl iodide, which react with $AgNO_3$ to form the precipitate of AgI. From the weight of silver iodide obtained, it is possible to determine the number of $-OCH_3$ groups.

$$R-O-CH_3 + HI \xrightarrow{\Delta} R-OH + \underset{\text{Methyl iodide}}{CH_3I}$$

$$CH_3I + \underset{\text{(alcoholic)}}{AgNO_3} \xrightarrow{126^\circ C} AgI\downarrow + CH_3NO_3$$

vii) **Methylene dioxy group ($-O-CH_2-O-$) :** This group is detected and estimated by heating the alkaloid with conc. HCl or H_2SO_4 and determining the amount of formaldehyde formed.

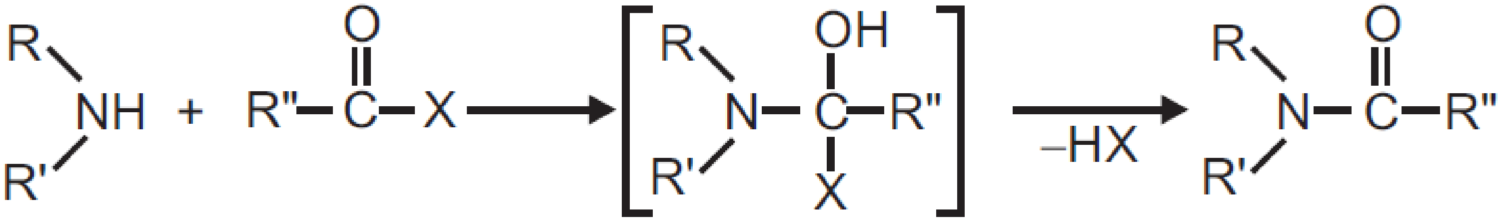


D. Nature of Nitrogen : All alkaloids contain mostly tertiary amino group which is present in the form of >N−CH_3 group.

(a) Distinction between primary, secondary and tertiary amines : All alkaloids must contain N atom and most of the times it is basic in nature. In the majority of alkaloids, N is present as a part of a heterocyclic system. Therefore, it must be either a secondary (=NH) or tertiary (=N–CH_3 or =N–).

Primary, secondary and tertiary of nitrogen may be distinguished by following reactions like reaction with acetic anhydride/methyl iodide/nitrous acid/30% H_2O_2.

(i) Reaction with acetic anhydride (acylation) : Amines react with acetic anhydride to form amides. Secondary amines are more reactive than primary amines, while tertiary amines cannot be acylated.

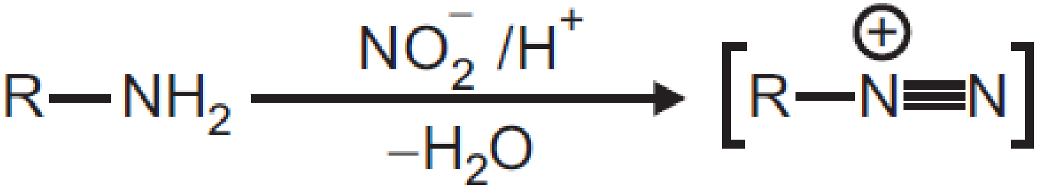


(ii) **Reaction with nitrous acid (HNO_2) :** Primary aliphatic/aromatic amine reacts with nitrous acid (HNO_2) to form highly unstable diazonium salts.

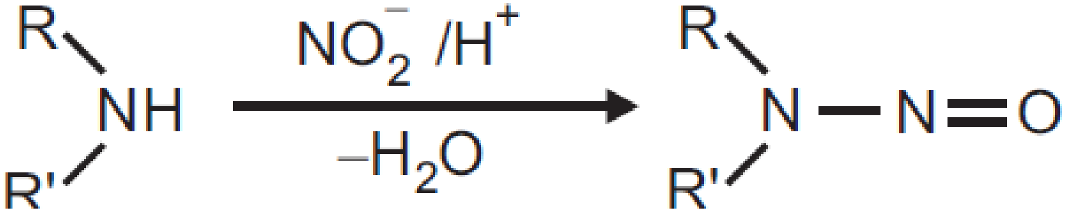
i) Secondary aliphatic and aromatic amines react with nitrous acid to yield N-nitrosoamines,

ii) Tertiary aliphatic amines form salts with nitrous acid.

iii) Tertiary aromatic amines form nitroso-substituted derivatives.



$$R{-}NH_2 \xrightarrow[-H_2O]{NO_2^-/H^+} \left[R{-}\overset{\oplus}{N}{\equiv}N\right]$$

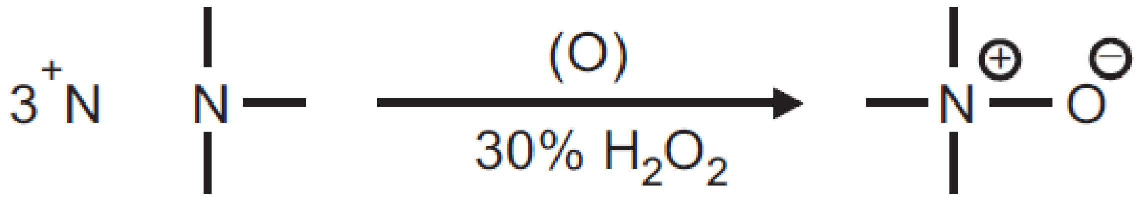


(iii) Reaction with methyl iodide : If the alkaloid reacts with one mole of methyl iodide, it forms an N-methyl derivative, indicating the presence of a secondary nitrogen atom.

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

$$N\leqq(C_{10}H_{14})\geqq N + 2CH_3I \longrightarrow {}^{-}ICH_3-\overset{+}{N}\leqq(C_{10}H_{14})\geqq\overset{+}{N}CH_3I^{-}$$

(iv) Reaction with 30%H_2O_2 : If all above tests are negative then N is probably tertiary which reacts with 30 % H_2O_2 to form amine oxide.

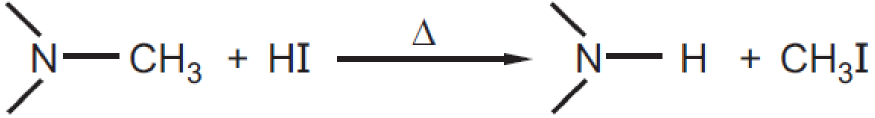


$$3\overset{+}{}N \quad -\overset{|}{\underset{|}{N}}- \xrightarrow[30\%\ H_2O_2]{(O)} -\overset{|}{\underset{|}{N}}{}^{\oplus}-O^{\ominus}$$

(b) The nature and number of alkyl groups attached to nitrogen (N-methyl group : >N-CH_3) : It can be determined by following methods :

(i) Distillation of an alkaloid with aqueous KOH : When alkaloid is reacted with aqueous KOH then the formation of methylamine (CH_3NH_2), dimethylamine $(CH_3)_2NH$ or trimethylamine $(CH_3)_3N$ indicate the attachment of one, two or three methyl groups to a nitrogen atom respectively.

(ii) Herzig-Meyer method : When the alkaloid is heated with hydriodic acid (HI) at 150-300°C under pressure, then N-methyl groups are converted into methyl iodide.



$$CH_3I + \underset{\text{(alcoholic)}}{AgNO_3} \xrightarrow{126^\circ C} AgI\downarrow + CH_3NO_3$$

The methyl iodide formed can be reacted with ethanolic $AgNO_3$ to form AgI precipitates (as in Zeisel's method). From the weight of precipitated AgI, the number of N-methyl groups can be found out.

(c) Nature of heterocyclic system present in the alkaloid :

The relationship between nitrogen atom and the carbon framework of the alkaloid is found out by following different degradation methods.

(i) Hoffmann’s exhaustive methylation method
(ii) Emde’s degradation
(iii) Von-Braun’s method for amines
(iv) Zinc dust distillation
(v) Alkali fusion
(vi) Reductive degradation
(vii) Oxidation
(viii) Dehydrogenation

(i) **Hoffmann's exhaustive methylation method :** This method was applied by Willstater in 1870 and was further developed by Hoffmann. In this method, the heterocyclic ring present in an alkaloid can be opened totally eliminating the nitrogen atom giving rise to aliphatic compounds.

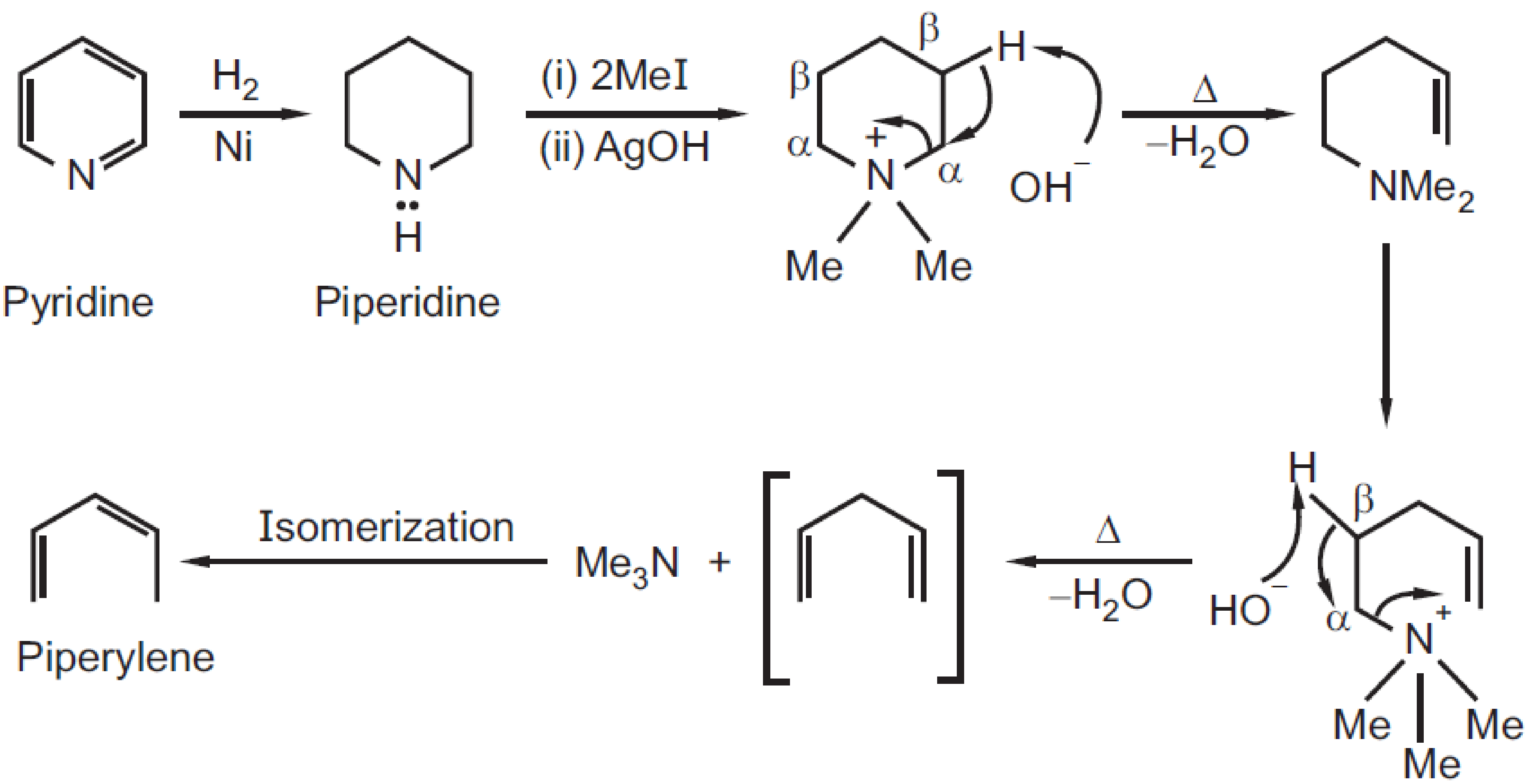
In general, exhaustive methylation involves heating the quaternary hydroxide at about 200°C and involves following steps :

(a) Hydogenation of heterocyclic ring (if it is unsaturated).

(b) Conversion of the saturated compound to the quaternary methyl ammonium hydroxide.

(c) Heating quaternary methyl ammonium hydroxide that eliminate water molecule from β-hydrogen and –OH.

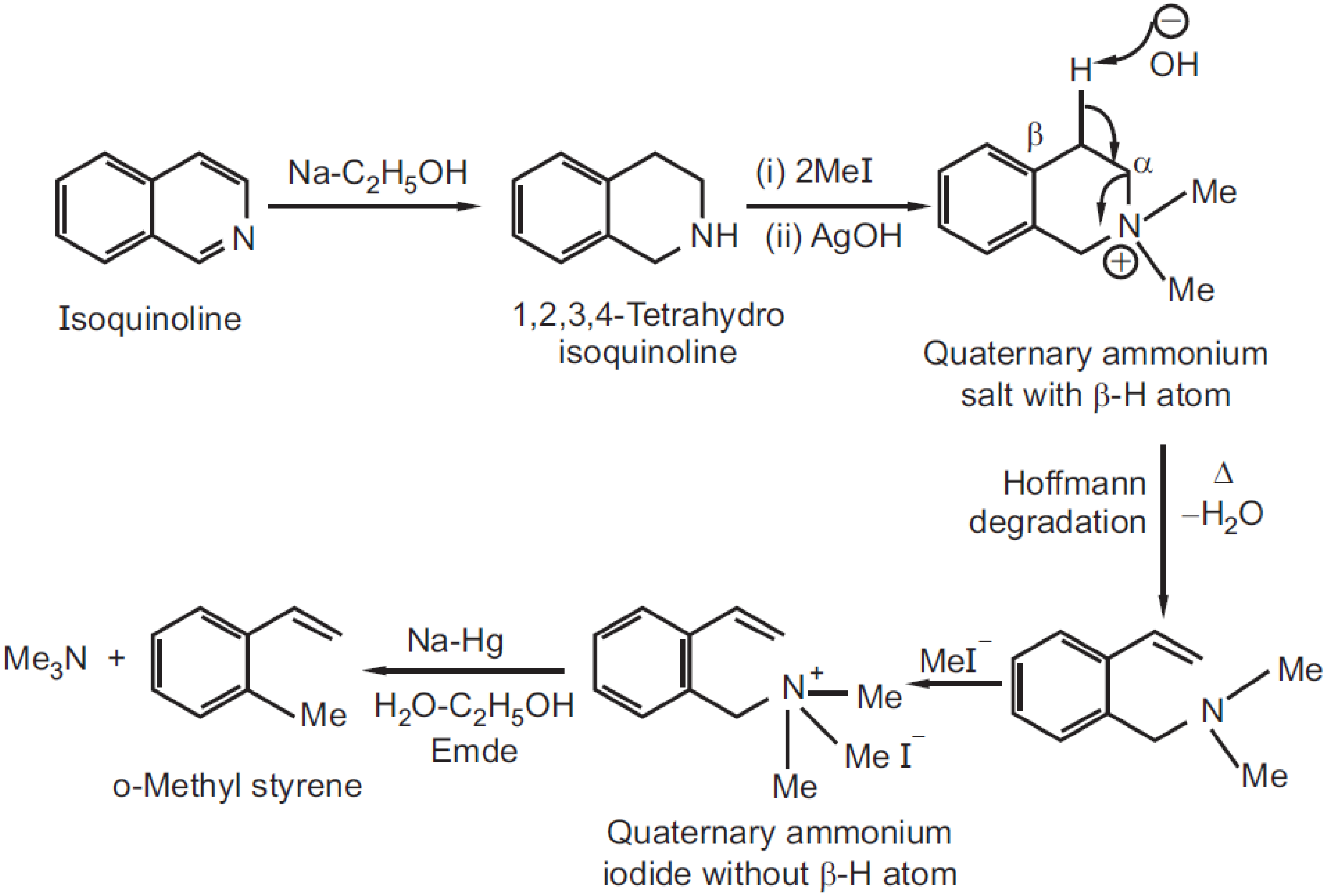
(d) Steps (b) and (c) are repeated until the complete removal of N atom from the molecule, leaving an unsaturated hydrocarbon, which is isomerized to conjugated diene.



Formation of 1, 3-pentadiene indicates that nitrogen atom must be present in a six membered ring.

(ii) Emde's method : If the alkaloid does not contain a β-hydrogen atom, then Hoffmann's exhaustive methylation method fails. In such cases, Emde's method may be employed.

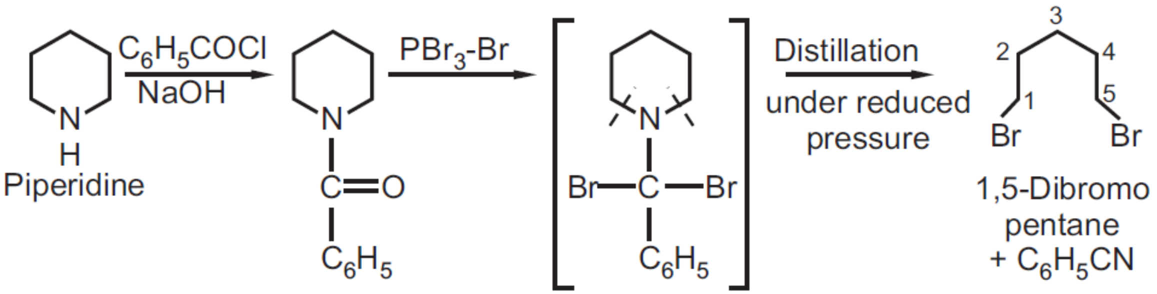
This method is similar to HEM with only change in the last step, the quaternary ammonium halide is reduced with Na-Hg in aqueous ethanol or with sodium in liquid ammonia or is catalytically hydrogenated.



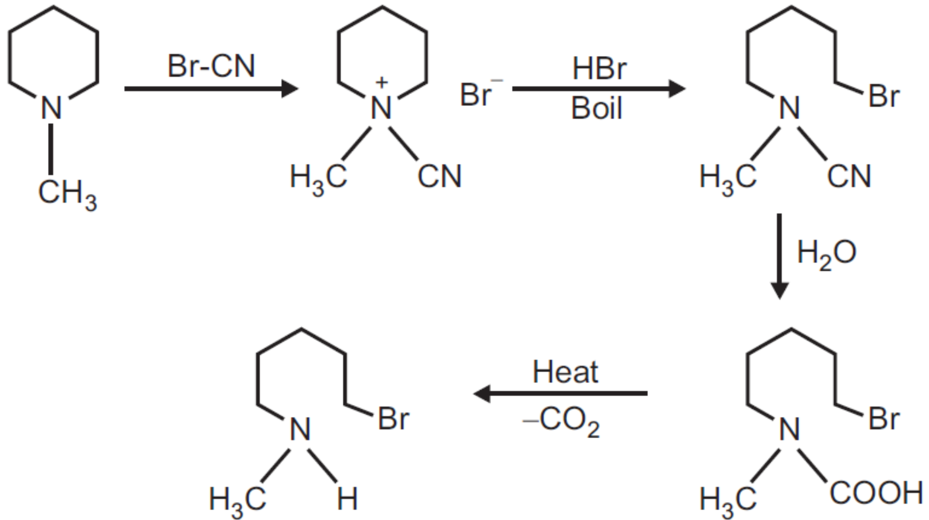
(iii) Von-Braun's method : If alkaloid contains secondary/tertiary cyclic amines then Von-Braun's method is used.

(a) Von-Braun's method for secondary cyclic amines : In this secondary cyclic amines are treated with benzoyl chloride in the presence of NaOH that yields benzoyl derivatives, which on reaction with PBr_3-Br_2 followed by distillation under reduced pressure yields dibromo compound.

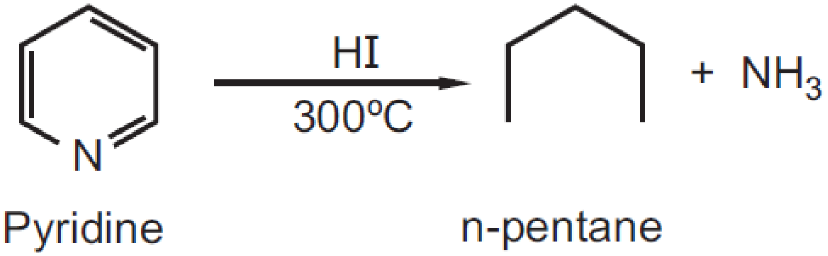
Formation of 1, 5-dibromopentane indicates that nitrogen atom is present in a six membered ring.



(b) Von-Braun's method for tertiary cyclic amines : Here the reagent used is cyanogen bromide (BrCN). Repetition of this process can lead to 1, 5-dibromopentane.



(iv) Reductive degradation : In many cases, the ring is opened by heating the alkaloid with hydriodic acid (HI) at 300°C.



(v) Fusion with KOH : Fusion of alkaloid with solid KOH gives simple fragments from which nature of alkaloid can be determined.

$$\text{Papavearine} \xrightarrow{\text{Fusion with KOH}} \text{Substituted Isoquinoline}$$

This reaction indicates that papaverine contains isoquinoline ring.

(vi) Zinc dust distillation : Distillation of alkaloid over Zn-dust degrades it into stable aromatic derivative. This usually gives same products as like (v) except that when the alkaloid contains 'O', the oxygen is removed.

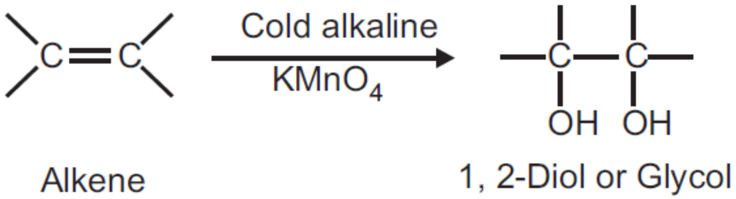
(vii) Oxidation (Oxidative degradation) : This is one of the efficient tools in determining the fundamental structure in which alkaloids can be degraded into various simple products by using various oxidizing agents.

Since oxidizing agents are selective, depending on the particular group to be oxidized, the oxidizing agent is chosen.

In order to carry out mild oxidation, H_2O_2, I_2/EtOH, or alkaline potassium ferricyanide are usually used. In order to carry out moderate oxidation, acid or alkaline $KMnO_4$ is used.

(a) Alkaline $KMnO_4$: This reagent converts alkenes into 1, 2-diols or glycols. The diols can be further cleaved by reagents like sodium periodate.

1.



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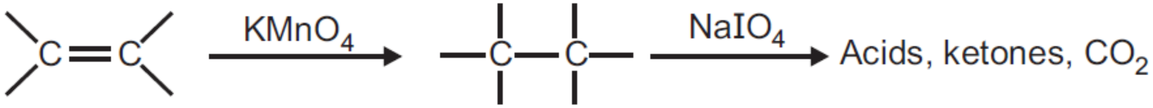
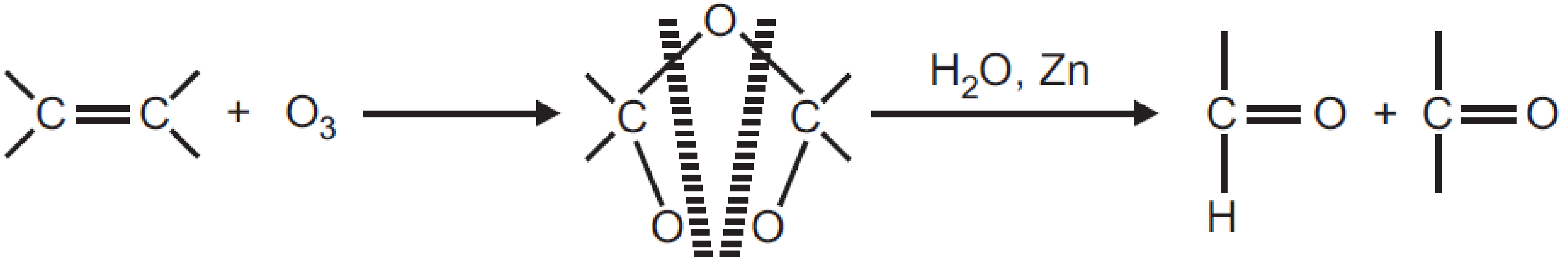


(i) The formation of CO_2 indicates the presence of a terminal $=CH_2$ group.

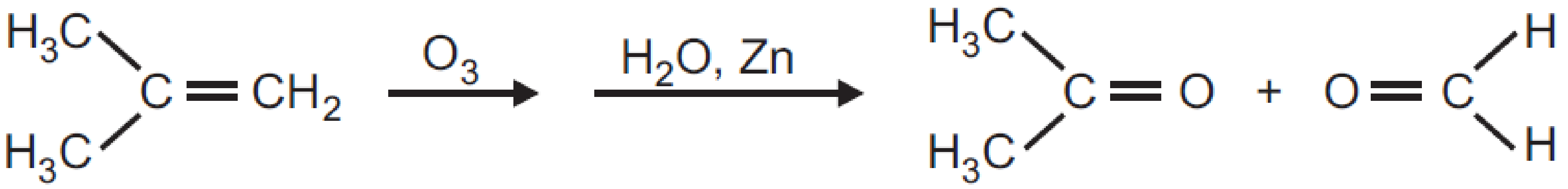
$$CH_3-CH_2-CH=CH_2 \xrightarrow[\text{(ii) } NaIO_4]{\text{(i) } KMnO_4} CH_3-CH_2-COOH + CO_2\uparrow$$

(ii) If double bond is in ring, it forms keto acids or dicarboxylic acid without loss of carbon.

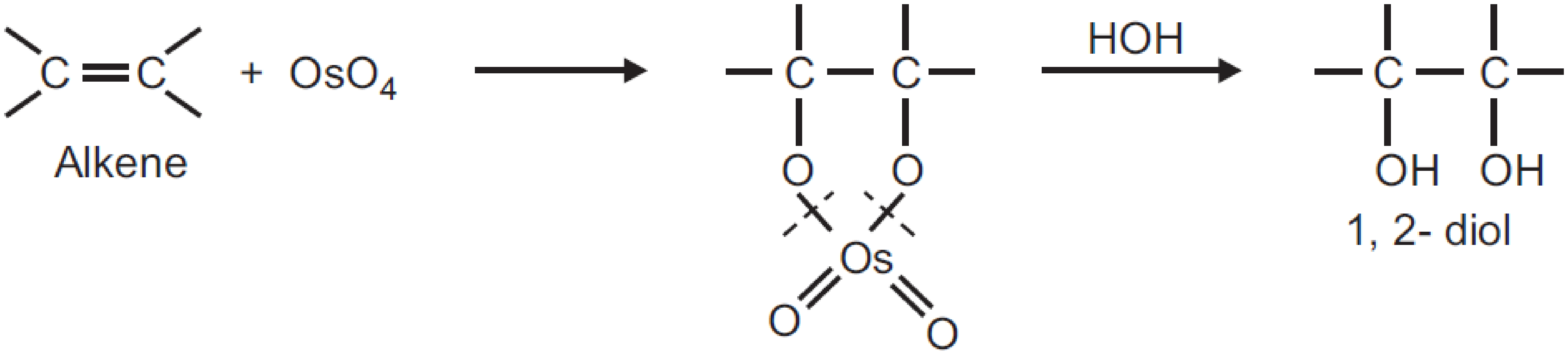
(b) Ozonolysis (O_3) : This is a very useful reagent for the cleavage of double bonds. The addition of ozone to the double bond forms an ozonide, which is then hydrolyzed to yield cleavage products. The products are aldehydes and ketones.



Terminal alkenes give formaldehyde as one of the products. Ozonolysis locate the position of double bonds in a molecule. The formation of acetone and formaldehyde reveal the presence of isopropylidene and terminal double bond.



(c) **Osmium tetraoxide (OsO_4) :** OsO_4 is superior to $KMnO_4$ for selective conversion of olefins to cis-1,2-diols in high yield but at the same time it is very toxic and expensive.



In general, oxidative degradation has been the most important tool for elucidating the structures of alkaloids.

4.2.7 Structure and Synthesis of Nicotine

1. Introduction :

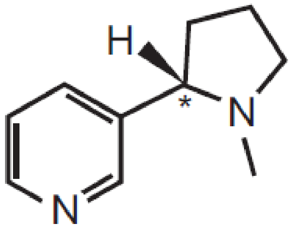
Nicotine is also called as 1-methyl, 2-β-pyridylpyrrolidine. The alkaloid was named after the Frenchman NICOT who introduced tobacco in France in 1560. It is highly poisonous compound (a crude tobacco extract is used as an insecticide due to this reason).

2. Occurrence and Isolation of Nicotine :

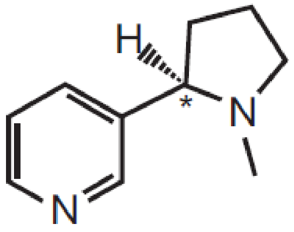
Nicotine is the principal alkaloid of the plant '*Nicotiana tabaccum*' and first isolated in 1828 by Posselt and Reimann. It occurs as maleic or citric salt in the dry leaves of the plant. It is a colourless laevorotatory oily alkaloid (B.P 246°C) with tobacco smell and soluble in water and organic solvents.

3. Structure of Nicotine :

It is a bicyclic compound with pyridine and pyrrolidone rings. The molecule possesses an asymmetric carbon and so exists in two enantiomeric forms.



(S)-Nicotine



(R)-Nicotine

The following methods are used for determination of structure of Nicotine :

I. Chemical methods (Analytical evidences)
II. Physical methods
III. Synthesis

I. Analytical Evidences :

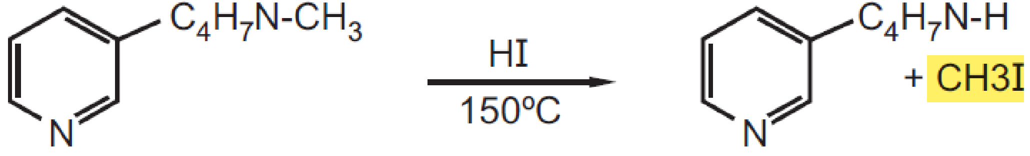
A. Molecular formula : Molecular weight determination and elemental analysis, shows that the molecular formula of nicotine is $C_{10}H_{14}N_2$.

B. Nature of nitrogen atom :

(a) Ditertiary base : It does not form benzoyl derivative, but on treatment with CH_3I it forms two isomeric methiodide addition products. This shows that it contains two tertiary N atoms. So it is a ditertiary base.

$$\underset{\text{Nicotine}}{C_{10}H_{14}N_2} + 2CH_3I \longrightarrow \underset{\text{Dimethiodide of nicotine}}{[C_{10}H_{14}N_2 \cdot 2CH_3]^{++}\ 2I^{-}}$$

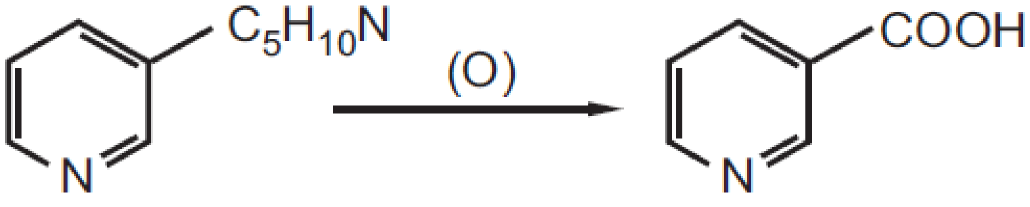
(b) Presence of >N−CH$_3$ group (Herzig-Meyer method) : When nicotine is heated with conc. HI at 150°C (Herzig-Meyer), it gave methyl iodide confirming the presence of >N−CH_3 group.



Nicotine

C. Presence of pyridine nucleus :

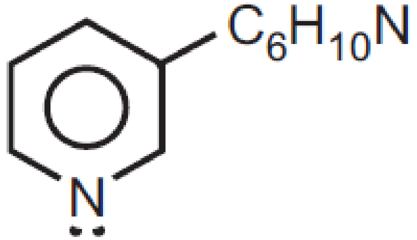
Oxidation of nicotine with chromic acid or nitric acid or $KMnO_4$ gives nicotinic acid (pyridine-3-carboxylic acid) a compound of known structure.



Nicotine

Nicotinic acid

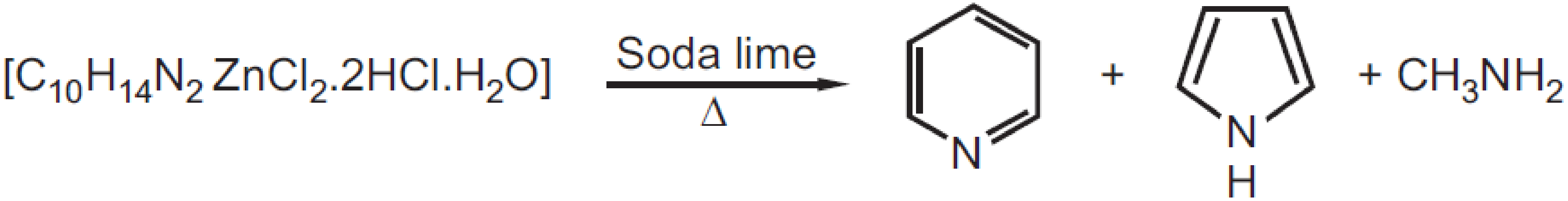
This shows that the alkaloid contains a pyridine nucleus with a side chain at 3-position. Hence the partial structure of nicotine may be written as



D. Nature and position of the side chain :

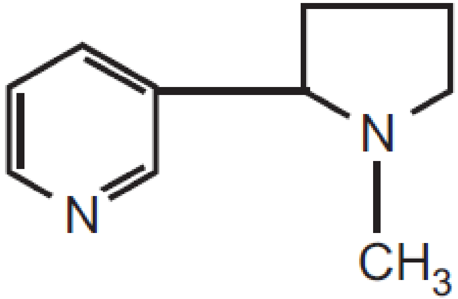
(i) Presence of pyrrole-type ring (Distillation with $ZnCl_2$) :

When nicotine is treated with $ZnCl_2$/HCl, it forms nicotine zinc chloride, which on distillation with soda lime decomposes into pyridine, pyrrole and methylamine. This suggests that the side chain $C_5H_{10}N$ is a pyrrole derivative.

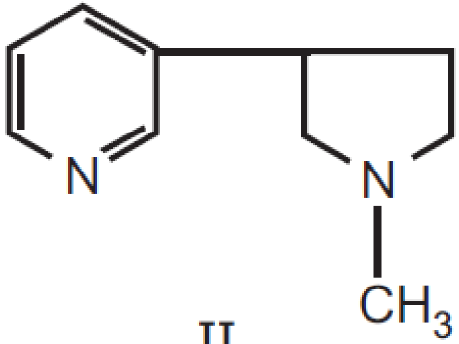


Nicotine zincichloride Pyridine Pyrrole

(ii) **Presence of N-methyl pyrrolidone :** Nicotine on complete hydrogenation requires $3H_2$ molecules, indicating that the side chain is fully saturated and confirms the presence of N-methyl pyrrolidone. There are only two positions through which pyrrolidine ring may be attached to pyridine to give two probable structures (**I** and **II**).

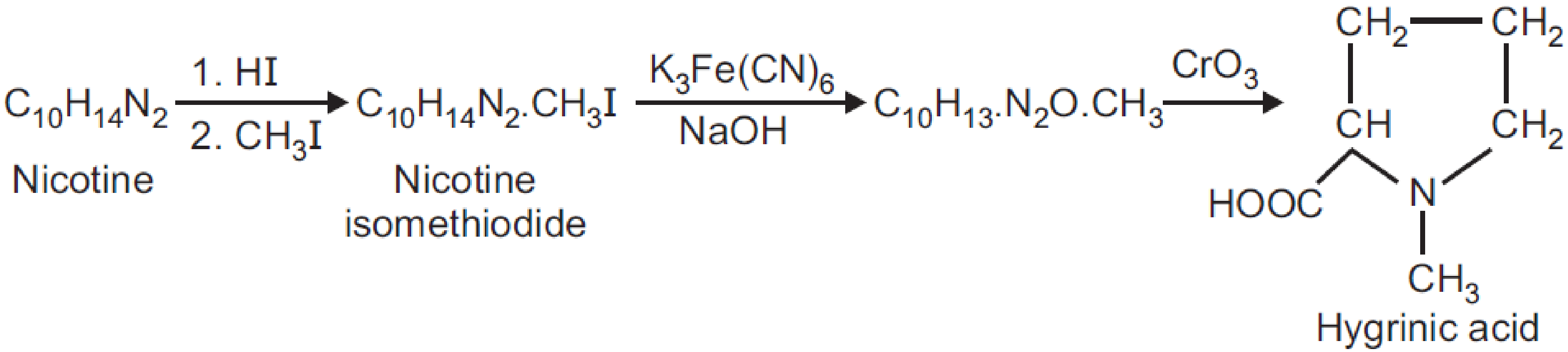


I



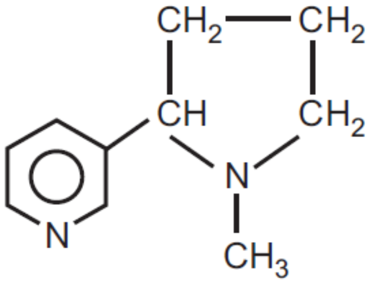
II

(iii) **Nicotine was found to have structure I :** Nicotine on reaction with HI and CH_3I, forms nicotine isomethiodide which on oxidation with potassium ferricyanide yields nicotone. This on further oxidation with chromium trioxide produces hygrinic acid.



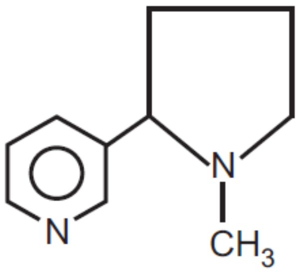
The formation of hygrinic acid proves N-methylpyrrolidine is attached to the pyridine nucleus through C2.

From the above considerations the structural of nicotine may be written as,



(N-methylpyrrolidine-2-pyridine)

or

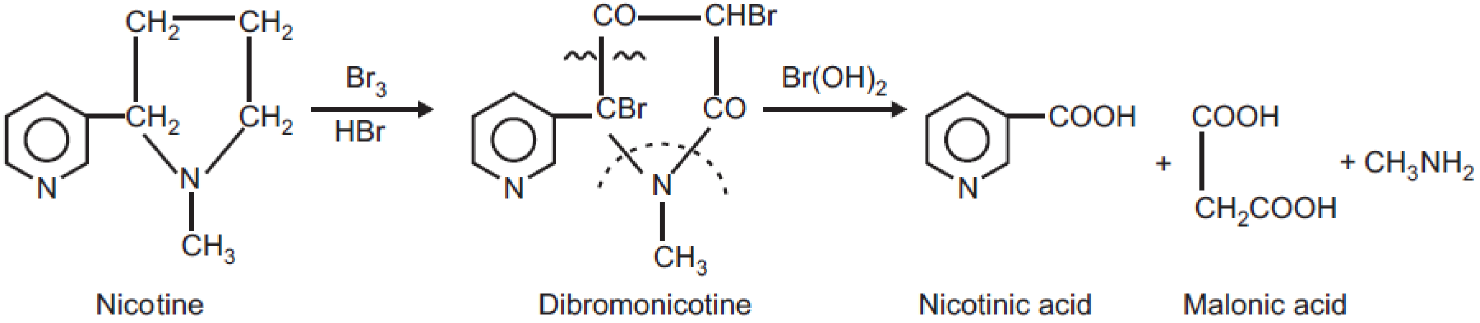


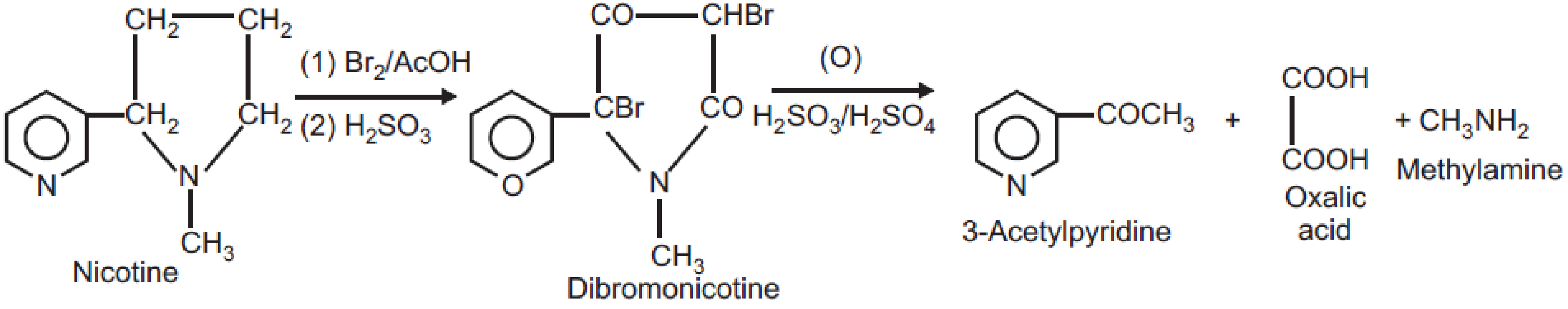
E. Confirmation of above structure :

The evidence for above structure has been given by Pinner (1893) on the basis of following points.

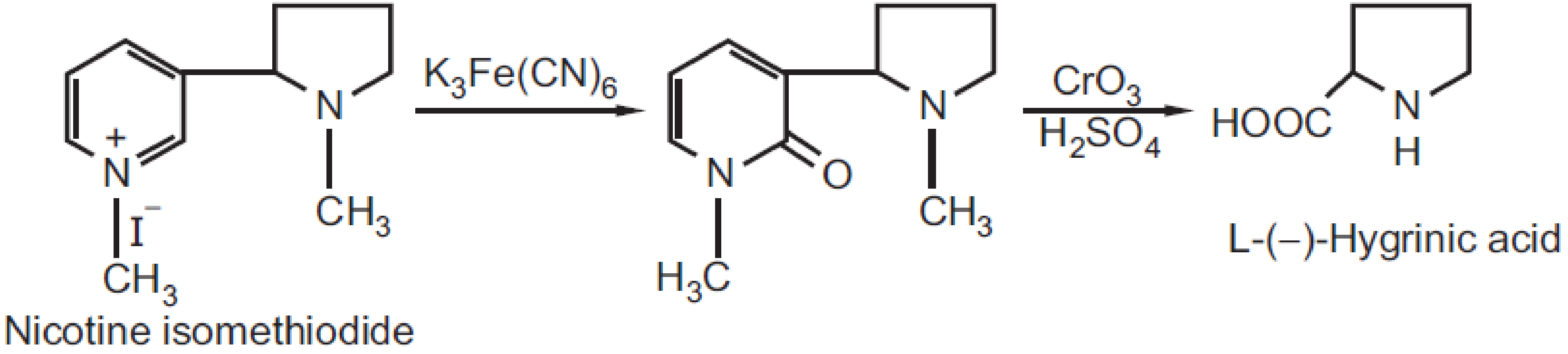
Reaction of nicotine with bromine in the presence of hydrobromic acid gives dibromonicotine having molecular formula $C_{10}H_8Br_2N_2O_2$ which further decomposes on heating with barium hydroxide give nicotinic acid, malonic acid and methylamine.

These products can only be explained if nicotine has carbon skeleton of structure I.



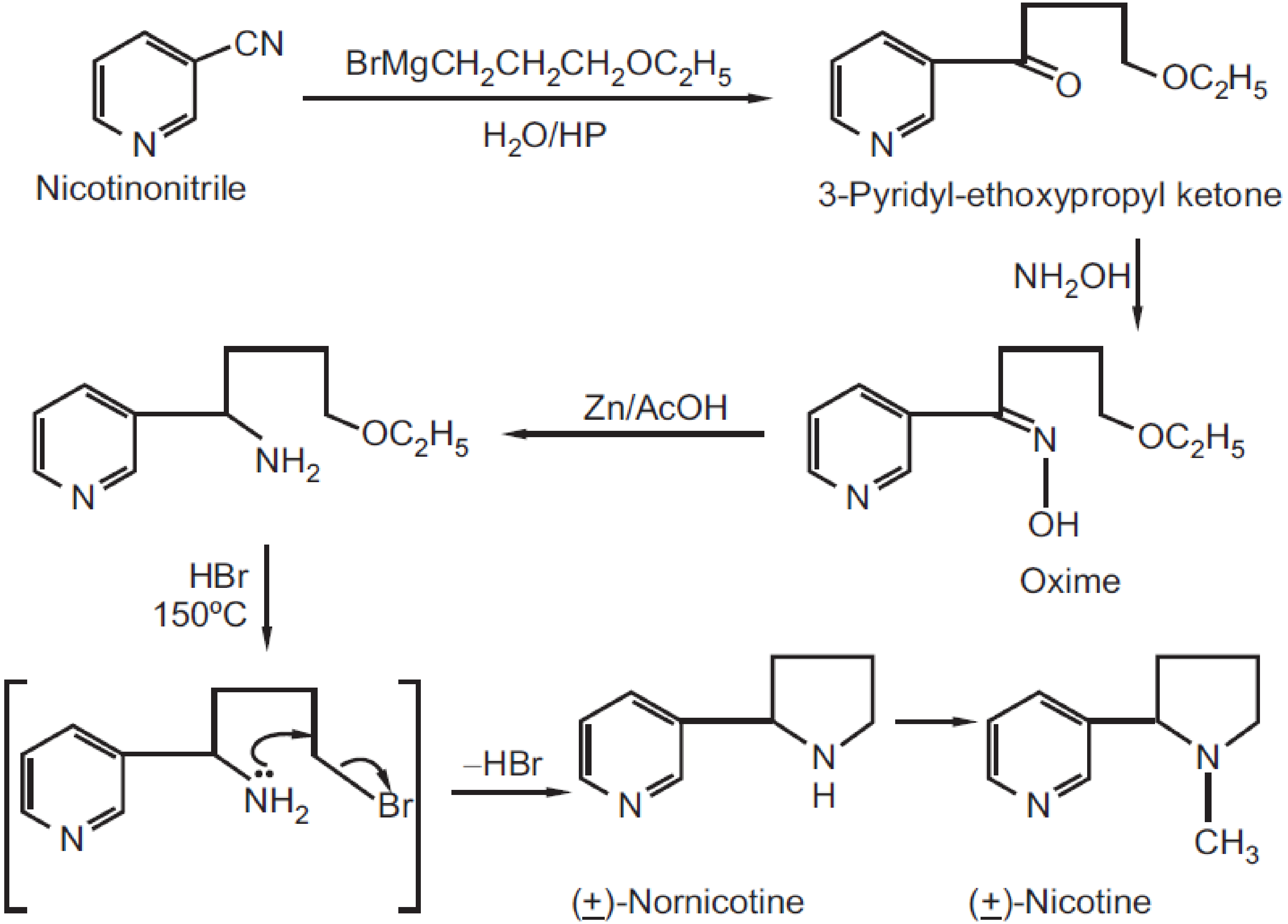


Direct evidence for the presence of pyrrolidine ring and its linkage to pyridine nucleus in nicotine was given by Karrev (1925). Oxidation of nicotine isomethiodide with potassium ferricyanide gave nicotine, which on further oxidation with chromium trioxide gives L (–) hygrinic acid, a compound of known structure.



B. Synthesis of Nicotine :

1. Craig Synthesis (1933) : It involves following steps :



2. Sugasava (1954) :