ALKALOIDS

Alkaloids are naturally occurring organic substances, predominantly found in plant sources including marine algae and rarely in animals (e.g. in the toxic secretions of fire ants,ladybugs and toads). They occur mostly in seed-bearing plants mainly in berries, bark, fruits,roots and leaves. Alkaloids often contain at least one nitrogen atom in heterocyclic ring (Fig. 1).These are basic in nature and so referred the term alkaloid (alkali-like). Alkaloids possess remarkable physiological action on human and other animals. These are the active components of numerous medicinal plants or plant-derived drugs. Their structural diversity and different physiological activities are unique to any other group of natural products. Many drugs used by man for both medical and non medical purposes are produced in nature in the form of alkaloids

e.g. atropine, strychnine, caffeine, nicotine, morphine, codeine, cocaine etc. Naturally occurring receptors for many alkaloids have also been identified in human and other animals, suggesting an evolutionary role for the alkaloids in physiological processes. Alkaloids are relatively stable compounds that accumulate as end products of different biosynthetic pathways,

DISTRIBUTION/ OCCURRENCE

Alkaloids are generally occur in all parts of the plant but some times accumulated only in particular organ, whereas at the same time other organs are free from alkaloids e.g. the edible tubers of potato plant are devoid of alkaloids, whereas the green parts contain the poisonous alkaloid solanine. The organ in which alkaloids accumulated is not always the site of their synthesis, e.g. in tobacco, nicotine is produced in the roots and translocated to the leaves where it accumulates (Harborne and Herbert, 1995). After the isolation of first alkaloid narcotine by French apothecary Derosne in 1803 and morphine by Hanoverian apothecary Serturner in 1806, more than ten thousand alkaloids have been discovered from different sources (Evans, 2006). Alkaloids are commonly found in the orders Centrospermae, Magnoliales, Ranunculales, Papaverales, Rosales, Rutales, Gentiales,Tubiflorae and Campanulales. True alkaloids are rarely occur in lower plants. Among the Pteridophytes and Gymnosperms, the bioactive alkaloids lycopodium, ephedra and taxus are well known. Lysergic acid and sulphur containing alkaloid gliotoxin are best known examples isolated from fungi

Nearly 300 alkaloids belonging to more than 24 classes are found in the skin of amphibians along with other toxins (Evans, 2006). The poisonous neurotoxic alkaloids were isolated from the skin of frogs belonging to genus *Phyllobates*. Daly, (1993) isolated various antimicrobial alkaloids from the skin of reptilian. Some indole and isoquinoline alkaloids were isolated from mammals including mammalian morphine

EXTRACTION AND ISOLATION

1. Crystals of piperine extracted from black pepper.
2. Because of the structural diversity of alkaloids, there is no single method of their extraction from natural raw materials.[175] Most methods exploit the property of most alkaloids to be soluble in organic solvents but not in water, and the opposite tendency of their salts.
3. Most plants contain several alkaloids. Their mixture is extracted first and then individual alkaloids are separated.[176] Plants are thoroughly ground before extraction.[175][177] Most alkaloids are present in the raw plants in the form of salts of organic acids.[175] The extracted alkaloids may remain salts or change into bases.[176] Base extraction is achieved by processing the raw material with alkaline solutions and extracting the alkaloid bases with organic solvents, such as 1,2-dichloroethane, chloroform, diethyl ether or benzene. Then, the impurities are dissolved by weak acids; this converts alkaloid bases into salts that are washed away with water. If necessary, an aqueous solution of alkaloid salts is again made alkaline and treated with an organic solvent. The process is repeated until the desired purity is achieved.
4. In the acidic extraction, the raw plant material is processed by a weak acidic solution (*e.g.*, acetic acid in water, ethanol, or methanol). A base is then added to convert alkaloids to basic forms that are extracted with organic solvent (if the extraction was performed with alcohol, it is removed first, and the remainder is dissolved in water). The solution is purified as described above.[175][178]

Alkaloids are separated from their mixture using their different solubility in certain solvents and different reactivity with certain reagents or by distillation.[179]

The extraction of alkaloids is based on their basic character and solubility pattern. The general scheme for extraction is shown in Fig. 6. Extraction is usually served by one of the following general methods

1. The plants are defatted with petroleum ether, especially in case of seeds and leaves to remove the fat soluble constituents and then with polar solvents. The extract is concentrated under reduced pressure and treated with alkali so that the free bases convert in their salts and separated with organic solvents. This

process is known as Stas-Otto process. This method is frequently used in the extraction of ergotamine (Kokate et al., 2005) from ergot.

2. The powdered material is moistened with water and mixed with lime, which combines with acids, tannins and other phenolic substances and sets free the alkaloid salts. Extraction is then carried out with organic solvents such as ether or petroleum sprit. The concentrated organic liquid is then shaken with aqueous acid and allowed to separate. Alkaloid salts are now in aqueous liquid, while many impurities remain behind in the organic liquid.

3. The powdered material is extracted with polar solvents such as water or aqueous alcohol containing dilute acid. Pigments and other unwanted materials are removed by shaking with chloroform or other organic solvents. The free alkaloids are then precipitated by the addition of excess sodium bicarbonate or ammonia and then separated by filtration or by extraction with organic solvents.

4. The extract is treated with ammonia so as to convert the alkaloid salts into their free bases. Such liberated alkaloids in free base form are conveniently extracted with organic solvents like ether,benzene, chloroform etc. This method is not useful for the isolation of alkaloids of quaternary nitrogen.

5. The alkaloids present in the extract are converted into their reineckates by treating with $H[Cr(NH_3)_2(SCN)_4]$ (Reinecke's solution). The product is then dissolves in acetone and then passed this solution through an ion exchange column which afforded the alkaloids in a high state of purity.

Further purification of crude extract of alkaloids is done by following ways, which may,however vary for individual alkaloid

1. **Direct crystallization from solvent**: It is a simple method of isolation in which the alkaloids crystallise directly by fractionation process and may not be useful in case of complex mixtures
2. **Steam distillation:** This method is specially employed for volatile liquid alkaloids like coniine,sparteine and nicotine. However this method is not suitable for alkaloids of high molecular weights.In this method, the aqueous extract is made alkaline with caustic soda or sodium carbonate and then alkaloids are distilled off in steam.

Chromatographic techniques: Chromatography is an ideal method for separation of a vast number of alkaloids. The separation of alkaloids carried out by using stationary and mobile phase of different organic solvents. The different techniques of chromatography used for separation of individual alkaloid from complex mixture are as following

Classification of alkaloids along with some common examples and sources

S.No.	Class	Example	Biological sources	
1	Pyrrole and Pyrrolidine	Hygrine, nicotine, cuscohygrine, coca alkaloids	*Erythroxylum coca, Erythroxylum truxillense*	
2	Pyridine and Piperidine	Piperine, coniine, trigonelline, arecaidine, guvacine, pilocarpine, cytisine, nicotine, sparteine, pelletierine, lobeline, arecoline, anabasine	*Piper nigrum, Areca catechu, Lobelia nicotianefolia*	
3	Pyrrolizidine	Echimidine, senecionine, senesiphylline, symphitine	*Castanospermum australe, Senecio* sps.	
4	Tropane	Atropine, cocaine, ecgonine, scopolamine, hyoscine, meteloidine hyoscyamine, pseudo-pelletierine	*Atropa belladonna, Dhatura stramonium, Erythroxylon coca, Schizanthus porrigens*	
5	Quinoline	Quinine, quinidine, brucine, veratrine, dihydroquinine, dihydroquinidine, strychnine, cevadine, cinchonine, cupreine, cinchonidine, prenylated quinolin-2-one	*Cinchona officinalis, Cinchona calisaya, Almeidea rubra*	

6	Isoquinoline	Morphine, codeine, thebaine, papaverine, narcotine, sanguinarine, narceine, hydrastine, berberine, dtubocurarine, emetine, cephaeline, narcotine	*Papaver somniferum, Cephaelis ipecacuanha, Berberis aristata, Aristolochia elegans, Cocculus pendulus*	

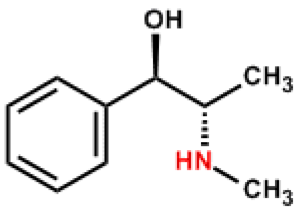
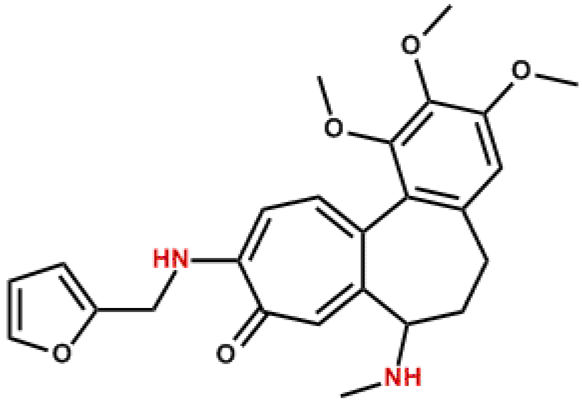
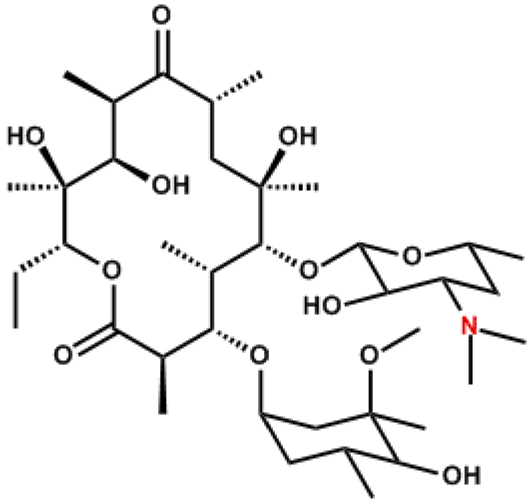
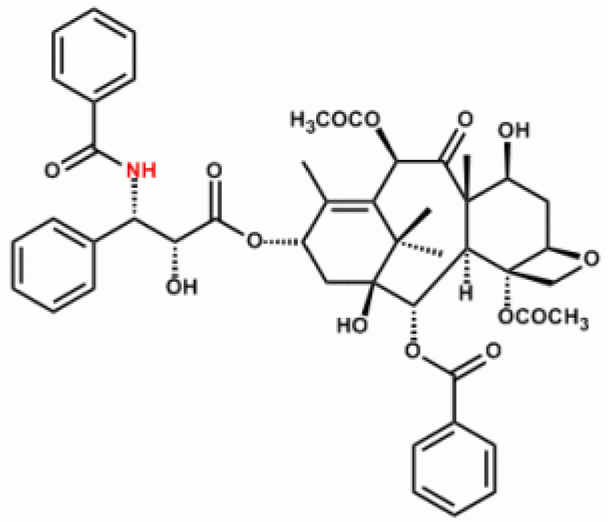
- Pyridine group: piperine, coniine, trigonelline, arecaidine, guvacine, pilocarpine, cytisine, nicotine, sparteine, pelletierine
- Pyrrolidine group: hygrine, cuscohygrine, nicotine
- Tropane group: atropine, cocaine, ecgonine, scopolamine, catuabine
- Quinoline group: quinine, quinidine, dihydroquinine, dihydroquinidine, strychnine, brucine, veratrine, cevadine

Alkaloids are basic nitrogen containing compounds. They are generally obtained from plants, animals and microorganisms and often demonstrate a marked physiological action. Alkaloids show greatly diverse structure and origins as well as pharmacological action. The only thing that unites all these natural compounds under the term ‘alkaloids’ (alkali-like) is the nitrogen atom which is present in all of them. According to pharmacognosy, alkaloids are broadly classified into two classes depending upon whether the nitrogen is a part of a ring or not.

1] Non-Heterocyclic Alkaloids or Atypical Alkaloids:

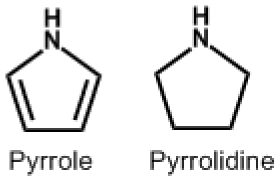
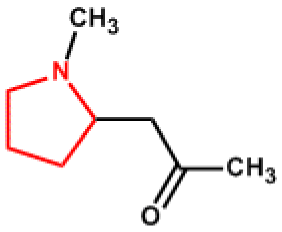
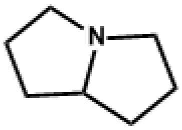
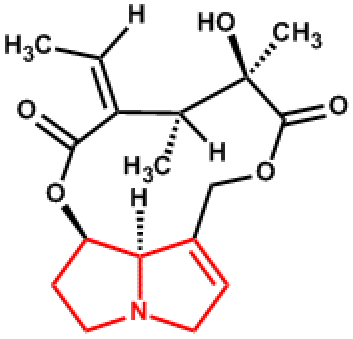
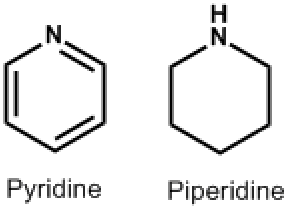
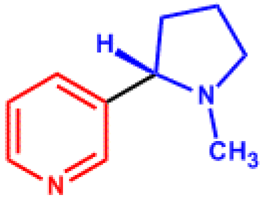
These are also sometimes called proto-alkaloids or biological amines. These are less commonly found in nature. These molecules have a nitrogen atom which is not a part of any ring system. Examples of these include ephedrine, colchicine, erythromycin and taxol etc. Table below shows the chemical structure and biological significance of these compounds:

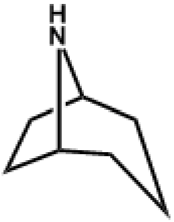
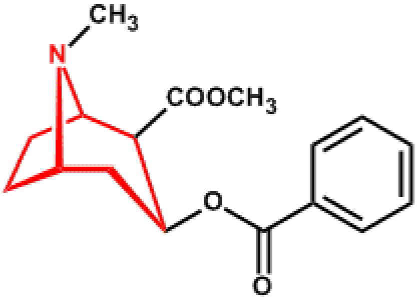
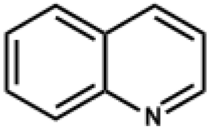
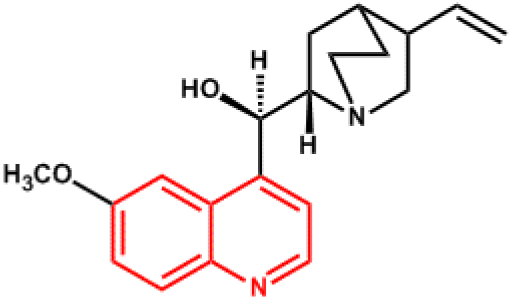
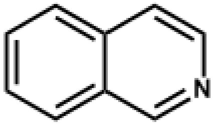
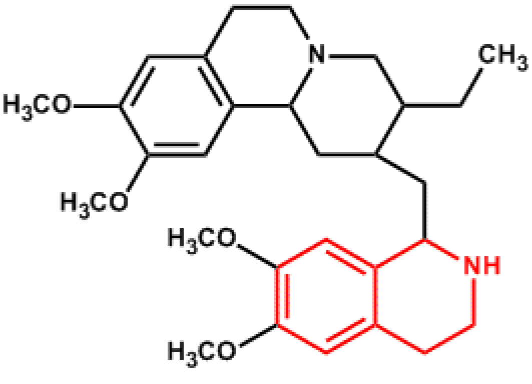
Name	Structure	Biological Significance

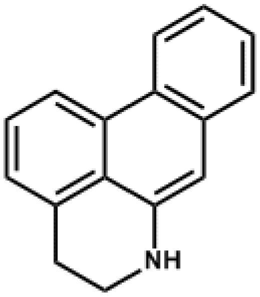
Ephedrine		Adrenergic agent-used for asthma and hay fever
Colchicine		Relieves gout
Erythromycin		Antibiotic
Taxol (Paclitaxel)		Used in the treatment of ovarian cancer, breast cancer and non-small cell lung cancer

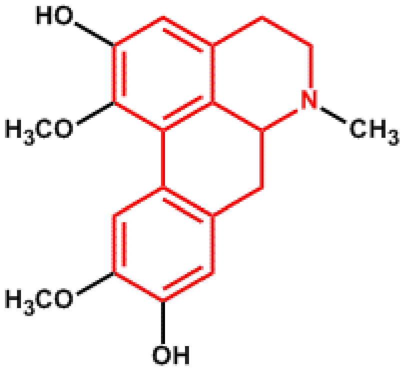
2] Heterocyclic Alkaloids or Typical Alkaloids:

Structurally these have the nitrogen as a part of a cyclic ring system. These are more commonly found in nature. Heterocyclic alkaloids are further subdivided into 14 groups based on the ring structure containing the nitrogen.

No.	Heterocycle	Example
1.	**Pyrrole and Pyrrolidine**  	Hygrine, Stachydrine  **Hygrine**
2.	**Pyrrolizidine** 	Senecionine, Symphitine, Echimidine, Seneciphylline  **Senecionine**
3.	**Pyridine and Piperidine**  	Lobeline, Nicotine, Piperine, Conine, Trigonelline  **Nicotine** **(Pyridine + Pyrrolidine)**
4.	**Tropane (piperidine/N-methyl-pyrrolidine)**	Cocaine, Atropine, Hyoscyamine, Hyoscine

		 Cocaine
5.	**Quinoline** 	Quinine, Quinidine, Cinchonine, Cinchonidine  Quinine
6.	**Isoquinoline** 	Morphine, Emetine, Papaverine, Narcotine, Tubocurarine, Codeine  Emetine
7.	**Aporphine (reduced isoquinoline/naphthalene)**	Boldine

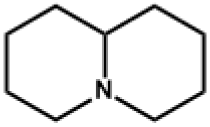


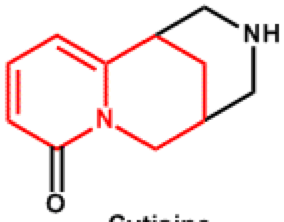


Boldine

Lupanine, Cytisine, Laburnine, Sparteine

8. **Quinolizidine**

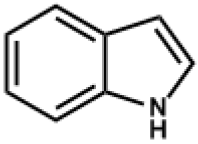


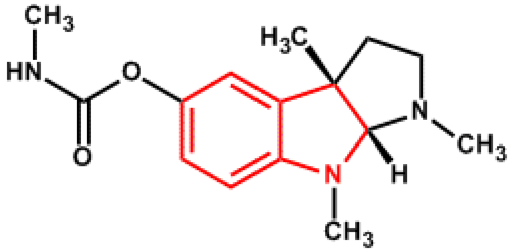


Cytisine

Ergometrine, Vinblastine, Vincristine, Strychnine, Brucine, Ergotamine, Yohimbine, Reserpine, Serpentine, Physostigmine

9. **Indole or Benzopyrole**

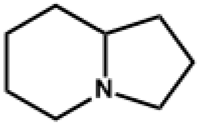


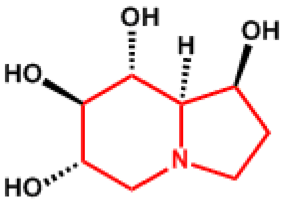


Physostigmine

Castanospermine, Swainsonine

10. **Indolizidine**

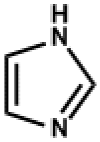
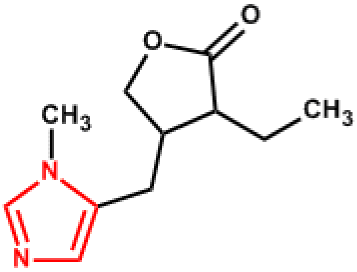
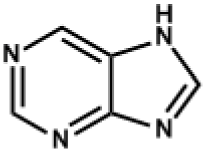
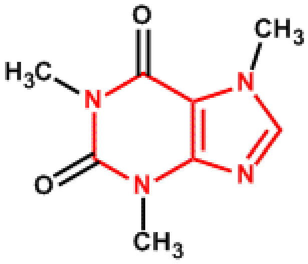
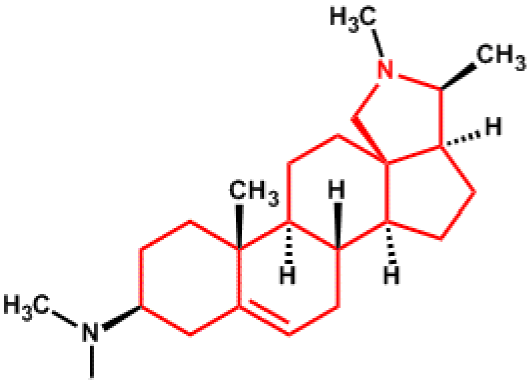


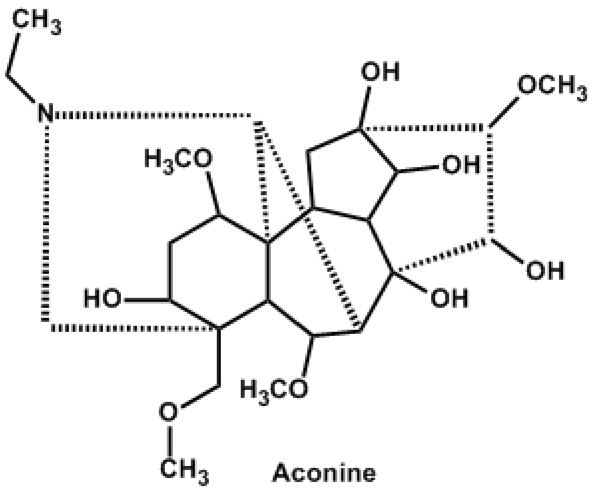


Castanospermine

11. **Imidazole or glyoxaline**

Pilocarpine, Pilosine

		 Pilocarpine
12.	**Purine (pyrimidine/imidazole)** 	Caffeine, Theobromine  Caffeine
13.	**Steroidal (some combined as glycosides)***	Conessine, Solanidine  Conessine
14.	**Terpenoid***	Aconitine, lycaconitine, Aconine



Aconine

**Note- Steroidal and terpenoid classes are also treated as separate classes or along with glycosides.*

Properties of alkaloids

Physical Properties

1- Most alkaloids contain oxygen; those compounds are usually colorless crystals at ambient conditions.

2- Oxygen-free alkaloids, such as nicotine[146] or coniine,[22] are typically volatile, colorless, oily liquids.[147]

3- Some alkaloids are colored, like berberine (yellow) and sanguinarine (orange).[147]

4- Most alkaloids have a bitter taste. It is believed that plants evolved the ability to produce these bitter substances, many of which are poisonous, in order to protect themselves from animals; however, animals in turn evolved the ability to detoxify alkaloids.

- Their molecular weight ranges from 100 to 900 daltons.
- Those without oxygen atoms in their structure are usually liquid at ordinary temperature. Examples are nicotine, sparteine, and coniine.
- Those with oxygen atoms are crystalline, such as berberine.

Chemical Properties

1- Most alkaloids are weak bases, but some are amphoteric, for example theobromine and theophylline.[148]

2- Most alkaloids are poorly soluble in water but readily dissolve in organic solvents, such as diethyl ether, chloroform and 1,2-dichloroethane. However, caffeine dissolves well in boiling water.[148]

3- With acids, alkaloids form salts of various strengths. Those salts are usually soluble in water and alcohol and poorly soluble in most organic solvents. Exceptions include scopolamine hydrobromide, which is soluble in organic solvents and water-soluble quinine sulfate.

Some alkaloids can produce developmental defects in the offspring of animals that consume them but cannot detoxify them. A characteristic example is the alkaloid cyclopamine, which is present in the leaves of corn lily. During the 1950s, up to 25% lambs born by sheep that had grazed on corn lily suffered serious facial defects. Those defects ranged from deformed jaws to cyclopia (see picture). After decades of research, in 1980s, the substance that was responsible for the deformities was identified as the alkaloid 11-deoxyjervine, which was renamed cyclopamine.

- Most alkaloids are optically active, except for those from the purine group.
- Basicity depends on the availability of lone pairs of electrons on the N atom and the type of heterocycle and substituents in the molecule.
- Alkaloids have the ability to form salts with mineral acids (such as with HCl, H_2SO_4, HNO_3) or organic acids (such as with tartaric acid and sulfamic acid).

DETERMINATION OF THE CHEMICAL CONSTITUTION OF THE ALKALOIDS

The chemical tests used for detection of alkaloids depend on their character to precipitate with organic acids in the form of their salts. These are also precipitated by the reaction of compounds of heavy metals like mercury, gold, platinum etc. Caffeine and some other alkaloids which are highly water soluble, do not give the tests with usual reagents. Some common reagents,used to the detection of alkaloids are summarized in Table 2.

S.No	Name of reagent	Chemical composition	Colour obtained
1	Mayer's reagent	Potassium mercuric iodide solution	Cream
2	Wagner's eagent	Solution of iodine in potassium iodide	Reddish-brown
3	Dragendorff's reagent	Potassium bismuth iodide solution	Reddish-brown
4	Hager's reagent	Saturated solution of picric acid	Yellow
5	Picrolonic acid	Solution of picrolonic acid	Yellow
6	Tannic acid	Solution of tannic acid	
7	Murexide test	*Potassium chlorate+HCl+NH_3	Purple
8	Mineral acids	Phosphotungstic acid, phosphomolybdic acid	Yellow
9	Acidic p-methylaminobenzaldehyde	p-Methyl-aminobenzaldehyde and sulphuric acid	Bluish-violet to red
10	Nitric acid	Dilute nitric acid	Orange-red

FUNCTIONAL GROUP ANALYSIS

IR spectrometric studies have proved a very important analytical tool for establishing the presence of certain functional groups in alkaloids. IR spectroscopy is the study of the reflected,absorbed or transmitted radiant energy in region from 0.8 to 500 μ m. A more commonly used measurement for IR spectroscopy is the frequency, expressed in wave number. The quantitative analysis of alkaloids, quinine and strychnine (6.20 and 6.06 μ) is also possible. FTIR is a new method of spectroscopy which has come into use more recently. It is especially useful for examining small samples and for taking the spectrum of compounds produced in the out flow of a chromatograph. The regions in which functional groups absorb are summarized in Table 4.

S. No	Functional groups	Appearance of band (cm$_{-1}$)
1	*C-H (str.)	3300-2800
2	O-H (str.)	3700-3350
3	C-O (str.)	1280-1000
4	C=O (str.)	1950-1640
5	#N-H (str.)	3500-3300
6	C-N (aliphatic) C-N (aromatic)	1210-1200 1350-1250
7	C≡C, C≡N (str.)	2350-2000
8	C=C, C=N, N=O (str.) and N-H (bend.)	1640-1500
9	Double bond (bend.) Other str., bend. and combination bands	950-750 1400-400 (finger print region)

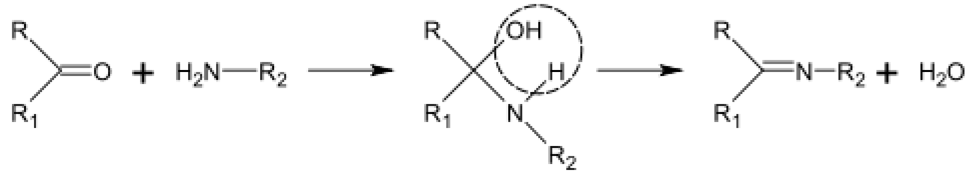
DEGRADATION AND SYNTHESIS OF ALKALOIDS

Biological precursors of most alkaloids are amino acids, such as ornithine, lysine, phenylalanine, tyrosine, tryptophan, histidine, aspartic acid, and anthranilic acid.[180] Nicotinic acid can be synthesized from tryptophan or aspartic acid. Ways of alkaloid biosynthesis are too numerous and cannot be easily classified.[82] However, there are a few typical reactions involved in the biosynthesis of various classes of alkaloids, including synthesis of Schiff bases and Mannich reaction.[180]

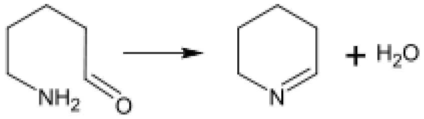
Synthesis of Schiff bases

Main article: Schiff base

Schiff bases can be obtained by reacting amines with ketones or aldehydes.[181] These reactions are a common method of producing C=N bonds.[182]



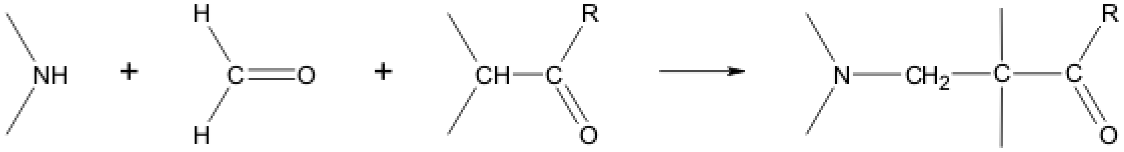
In the biosynthesis of alkaloids, such reactions may take place within a molecule,[180] such as in the synthesis of piperidine:[38]



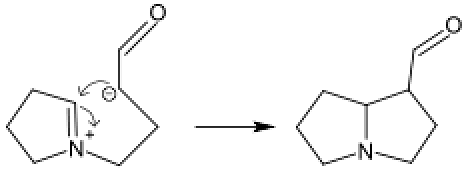
Mannich reaction

Main article: Mannich reaction

An integral component of the Mannich reaction, in addition to an amine and a carbonyl compound, is a carbanion, which plays the role of the nucleophile in the nucleophilic addition to the ion formed by the reaction of the amine and the carbonyl.[182]



The Mannich reaction can proceed both intermolecularly and intramolecularly:[183][184]



S

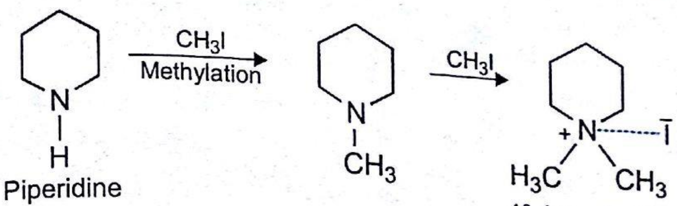
(1) **Formation of Salts.** Like amines they form salts both with inorganic and organic acids. These salts when treated with a base (NaOH, Na_2CO_3) are decomposed to liberate free alkaloid.

$$(Alk)NH + HCl \longrightarrow (Alk)\overset{+}{N}H_2\overset{-}{Cl} \xrightarrow{NaOH} (Alk)NH$$

This reaction is valuable in isolation of alkaloids from plant materials.

(2) **Exhaustive Methylation.** This is a composite reaction of an alkaloid (heterocyclic amine), involving the following steps :

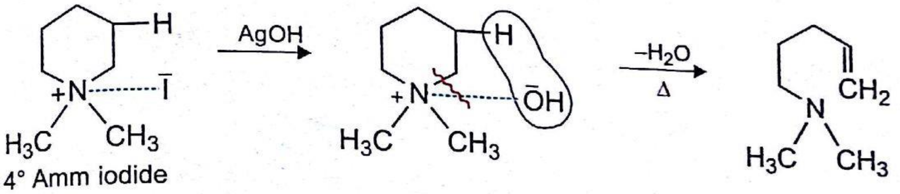
(*i*) The alkaloid (after hydrogenation, if unsaturated) is treated with excess of CH_3I to form 4° ammonium iodide. For example,



Piperidine

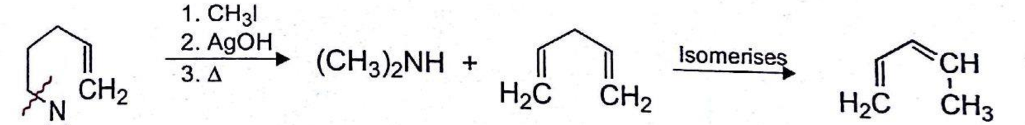
4° Amm iodide

(*ii*) 4° Ammonium iodide is converted to the hydroxide and heated. The OH of hydroxide extracts a H atom from β position and eliminates a water molecule. Also, the ring is cleaved at the N atom to give an open-chain 3° amine.



4° Amm iodide

(*iii*) The steps (*i*) and (*ii*) are repeated when a second cleavage at the N atom gives an unsaturated hydrocarbon which isomerizes to a conjugated diene.



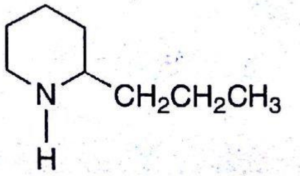
Conjugated diene

The exhaustive methylation of an alkaloid is an important method which tells us the nature of the carbon skeleton in the heterocyclic system.

IMPORTANT ALKALOIDS

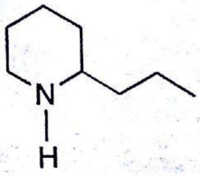
CONIINE, $C_8H_{17}N$

As already shown, coniine is one of the simplest alkaloids belonging to 'piperidine group'. Its structural formula can be written as



Coniine
(2-*n*-Propylpiperidine)

or



Line formula

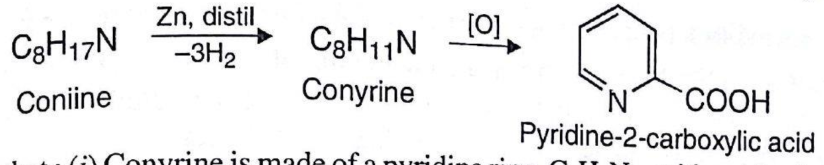
Coniine occurs in seeds and other parts of the hemlock herb (*conium maculatum*). It is one of *history's most poisonous alkaloids*. Socrates, the great Greek philosopher, was executed in 400 BC by *drinking a cup of hemlock*.

Isolation. The powdered hemlock seeds are distilled with sodium hydroxide solution. The distillate is extracted with ether. The ethereal extract is evaporated and the oily residue is carefully fractionated. The fraction distilling at 167°C is coniine.

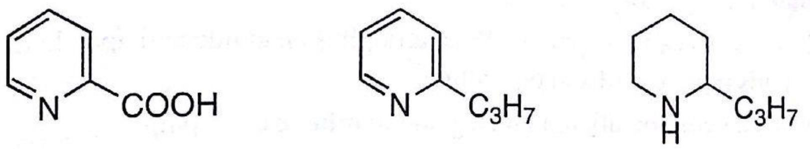
Properties. Coniine is a colourless unpleasant smelling liquid, bp 167°C. It is sparingly soluble in water but fairly soluble in organic solvents, readily soluble in ethanol. The natural alkaloid is dextrorotatory, $[\alpha]_D = +15.6$. It is strongly basic and forms salts with acids such as hydrochloric acid and hydrobromic acid. Both coniine and its salts are highly toxic to humans causing paralysis, convulsions and death.

Structure. (1) Molecular formula of coniine is found to be $C_8H_{17}N$.

(2) **Coniine contains piperidine ring with 2-side chain.** When distilled with zinc dust, coniine gives conyrine ($C_8H_{11}N$) which on oxidation with $KMnO_4$ gives pyridine-2-carboxylic acid.

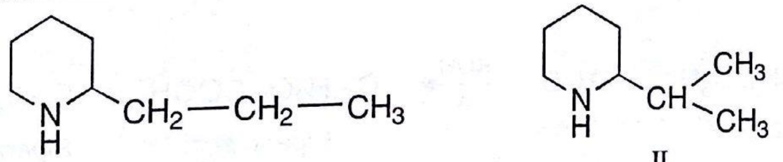


This shows that : (*i*) Conyrine is made of a pyridine ring, C_5H_4N–, with a side-chain in 2-position ; (*ii*) The side-chain is C_3H_7 ($C_8H_{11}N - C_5H_4N$) ; (*iii*) Coniine is hexahydroconyrine. Thus the structural formulas of conyrine and coniine may be written as :



Pyridine-2-carboxylic acid Conyrine Coniine

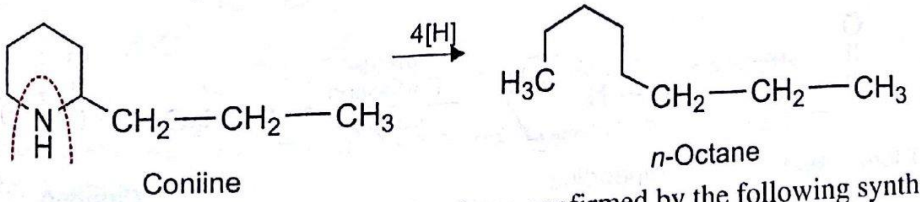
(3) **Two possible structures of side-chain.** The side-chain –C_3H_7 could be *normal* or *iso*, so that the two possible structures for coniine are :



I (*normal* side-chain)

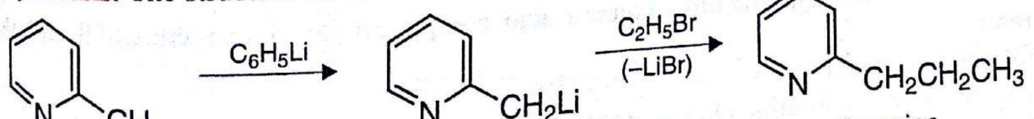
II (*iso* side-chain)

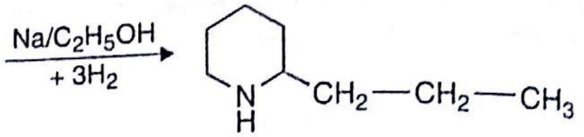
(4) **HI reduces coniine to *n*-octane.** The structure I is actually shown to be correct as the natural alkaloid when heated with hydriodic acid at 300°C is reduced to give *n*-octane.



Coniine *n*-Octane

(5) **Synthesis.** The structure of coniine has been confirmed by the following synthesis :



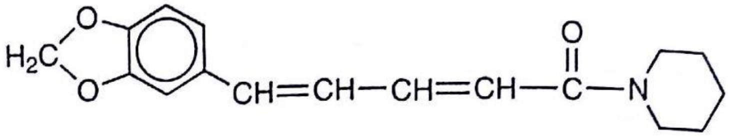


(±)-Coniine

The racemic coniine is resolved by means of (+)-tartaric acid. The (+)-coniine so obtained is identical with the natural alkaloid.

PIPERINE, $C_{17}H_{19}O_3N$

It is a piperidine alkaloid having the structural formula



Piperine occurs in black pepper (*Piper nigrum*) to the extent of 5 to 10 percent.

Isolation. Powdered black peppers are heated with milk of lime, $Ca(OH)_2$. The resulting mass is evaporated to dryness. The residue is extracted with ether. The ether solution is evaporated and the residue is crystallized from ethanol to give pure piperine.

Properties. Piperine forms beautiful colourless monoclinic crystals mp 129.5°C, having the characteristic sharp flavor of black pepper. It is sparingly soluble in water but dissolves easily in ethanol and ether. It is optically inactive.

Piperine is a very weak base, practically neutral. It is an amide and upon hydrolysis with aqueous base (or acid) yields piperic acid and piperidine.

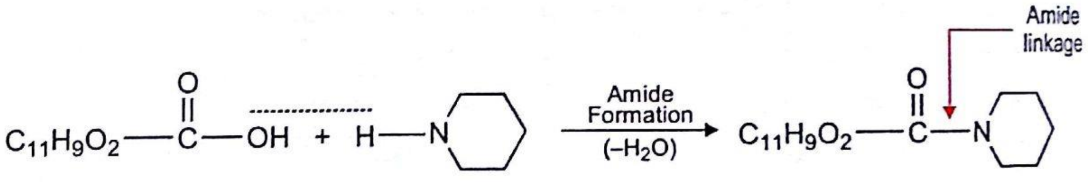
Piperine is used occasionally in favoring and to relieve colic pain.

Structure. (1) As shown by elemental analysis and molecular weight determination, the molecular formula of piperine is $C_{17}H_{19}O_3N$.

(2) **Amide Structure.** On hydrolysis with alkali it gives piperic acid and a secondary base, piperidine.

$$\underset{\text{Piperine}}{C_{17}H_{19}O_3N} + H_2O \xrightarrow[\Delta]{KOH} \underset{\text{Piperic acid}}{C_{11}H_9O_2.COOH} + \underset{\text{Piperidine}}{C_5H_{10}NH}$$

This reaction indicates that piperine is the piperidine-amide of piperic acid and its structure could be derived as



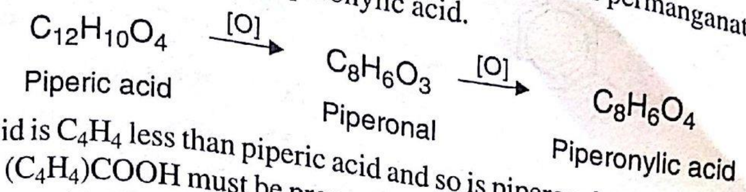
Piperic acid Piperidine Piperine

If we can now find the structure of piperic acid, complete molecular structure of the alkaloid could be written.

(3) **Structure of Piperic Acid ($C_{12}H_{10}O_4$) :**

(*i*) As shown by routine chemical tests, it contains one COOH group and two ethylene double bonds.

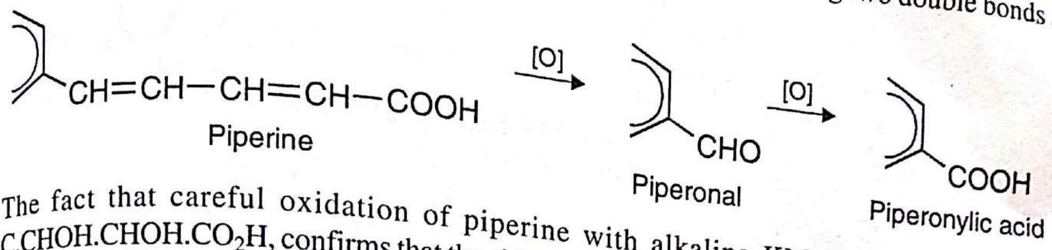
(*ii*) **Structure of Side-chain.** When oxidized with potassium permanganate, piperic acid first forms an aldehyde, piperonal, and then piperonylic acid.



$$C_{12}H_{10}O_4 \xrightarrow{[O]} C_8H_6O_3 \xrightarrow{[O]} C_8H_6O_4$$

Piperic acid — Piperonal — Piperonylic acid

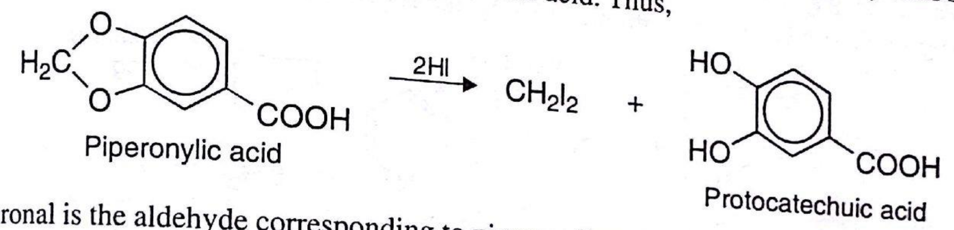
Piperonylic acid is C_4H_4 less than piperic acid and so is piperonal. Since piperonal shows negative test for COOH, the $(C_4H_4)COOH$ must be present as side-chain of the aromatic moiety in piperic acid. To explain the above oxidation reactions we construct the side-chain having two double bonds and a COOH group as below.



Piperine — Piperonal — Piperonylic acid

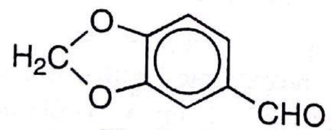
The fact that careful oxidation of piperine with alkaline $KMnO_4$ gives tartaric acid, $HO_2C.CHOH.CHOH.CO_2H$, confirms that the side-chain in piperic acid is a straight chain with carbon-carbon double bonds in alternate positions.

(*iii*) **Structure of Piperonal.** When boiled with concentrated hydriodic acid, piperonylic acid gives methylene iodide (CH_2I_2) and protocatechuic acid (3,4-dihydroxybenzoic acid). This shows that piperonylic acid is methylene ether of protocatechuic acid. Thus,

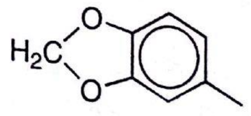


Piperonylic acid — Protocatechuic acid

Piperonal is the aldehyde corresponding to piperonylic acid and its structure can be written as :

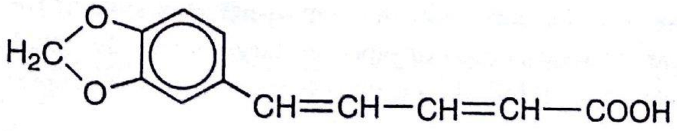


Piperonal

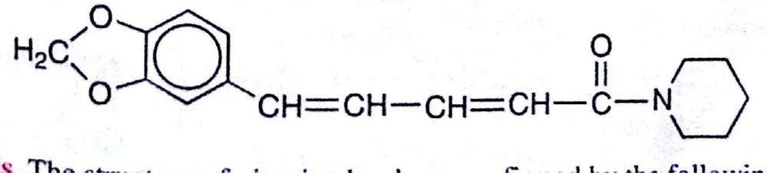


Aromatic moiety in piperic acid

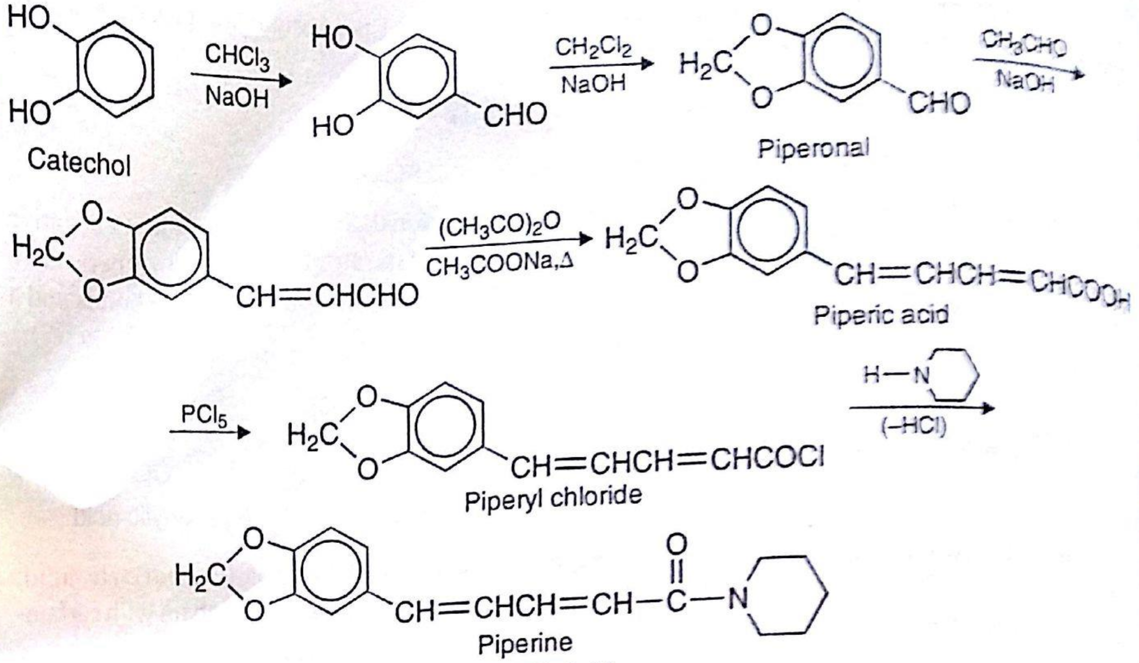
(*iv*) Knowing the structure of the side-chain from (*ii*), we can construct the possible structural formula of piperic acid.



(4) **Alkaloid Structure.** The structure of piperine is obtained by joining piperic acid and piperidine through an amide linkage (*See 2*).



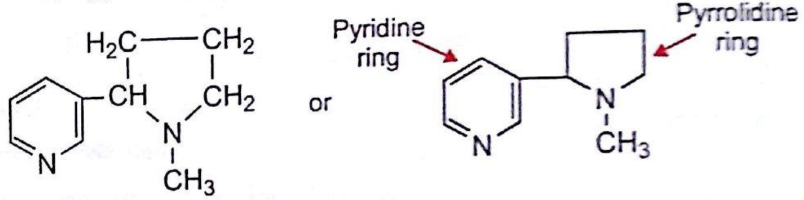
(5) **Synthesis.**



The product is identical with the natural alkaloid.

NICOTINE, $C_{10}H_{14}N_2$

It is a pyridine (or pyridine-pyrrolidine) alkaloid having the structural formula



Nicotine occurs to the extent of 2-8 per cent in dried leaves of the tobacco plant (*Nicotiana tabacum*).

Isolation. Dry tobacco leaves are finely powdered and extracted with dilute acid solution. To the acid extract is added NaOH solution, and steam distilled. The oily layer so obtained is crude nicotine which is purified by fractional distillation in vacuum.

Properties. Nicotine is a colourless liquid, bp 245.5°C. It has tobacco-like smell and a burning 'alkali taste'. It is soluble in water and also in organic solvents. The natural alkaloid is dextrorotatory. $[\alpha]_D = +163.2°$.

In very small doses nicotine stimulates the central nervous system for a while. That is why smokers crave for it *via* cigarettes, cigars or pipes. In large doses, the alkaloid causes depression, respiratory paralysis, and death. It kills insects on contact and is used in sprays against leaf-sucking pests.

Structure. (1) The molecular formula of nicotine has been found to be $C_{10}H_{14}N_2$.

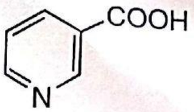
(2) **Presence of Two 3° N-atoms.** When treated with methyl iodide, it forms dimethiodide showing that both the N-atoms of nicotine are tertiary in character.

$$\underset{\text{Nicotine}}{C_{10}H_{14}N_2} + 2CH_3I \longrightarrow C_{10}H_{14}\left(-\overset{+}{N}\overset{-}{I} \atop \underset{CH_3}{|}\right)_2$$

Dimethiodide

(3) **Presence of a Pyridine ring.** On oxidation with chromic acid or nitric acid, nicotine gives nicotinic acid (pyridine-3-carboxylic acid).

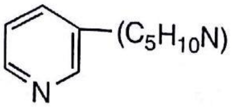
$$\underset{\text{Nicotine}}{C_{10}H_{14}N_2} \xrightarrow{[O]} \underset{\text{Nicotinic acid}}{(C_5H_4N)COOH} \quad \text{or}$$



This shows that the alkaloid contains a pyridine ring (C_5H_4N) with a side-chain.

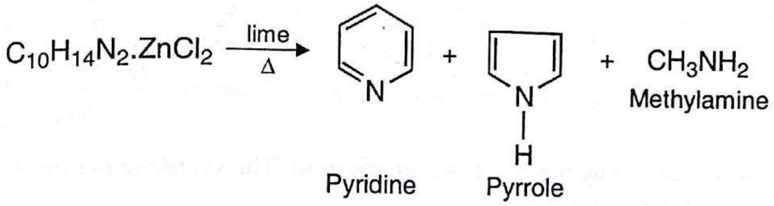
$$\underset{\text{Nicotine}}{C_{10}H_{14}N_2} - C_5H_4N = \underset{\text{side-chain}}{C_5H_{10}N}$$

The formula of nicotine may be written as



(4) **Structure of the Side-chain :**

(*i*) Nicotine zinc chloride complex on distillation with lime gives (*a*) pyridine ; (*b*) pyrrole ; and (*c*) methylamine.

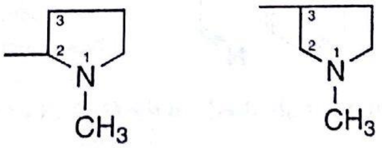


This indicates that the side-chain is a pyrrole derivative.

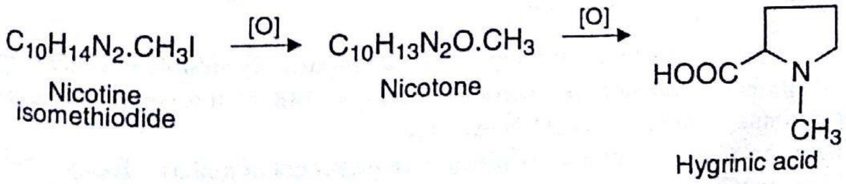
(*ii*) When heated with concentrated hydriodic acid at 200-300°C, nicotine forms methyl iodide. This proves that CH_3 group in the side-chain is attached to N-atom.

$$\underset{3^\circ\text{nitrogen}}{>N-CH_3} + HI \xrightarrow{\Delta} >N-H + CH_3I$$

(*iii*) To account for the side-chain, (C_4H_7)N–CH_3, it may be written as *N*-methylpyrrolidine group.

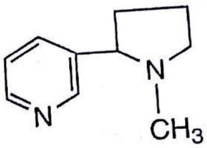


(*iv*) Nicotine hydriodide when treated with methyl iodide, forms nicotine isomethiodide which on oxidation with potassium ferricyanide yields *nicotone*. Nicotone on oxidation with chromium trioxide produces *hygrinic acid*.

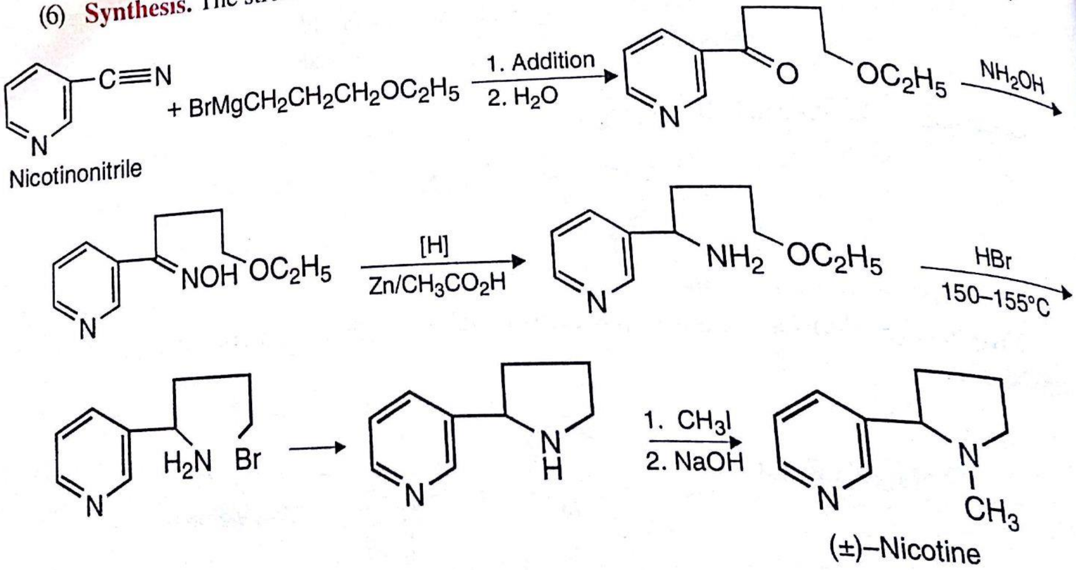


Therefore, the pyrrolidine ring is bonded to pyridine ring through 2-position.

(5) **Structural formula.** From (3) and (4), the structural formula of nicotine may be constructed as



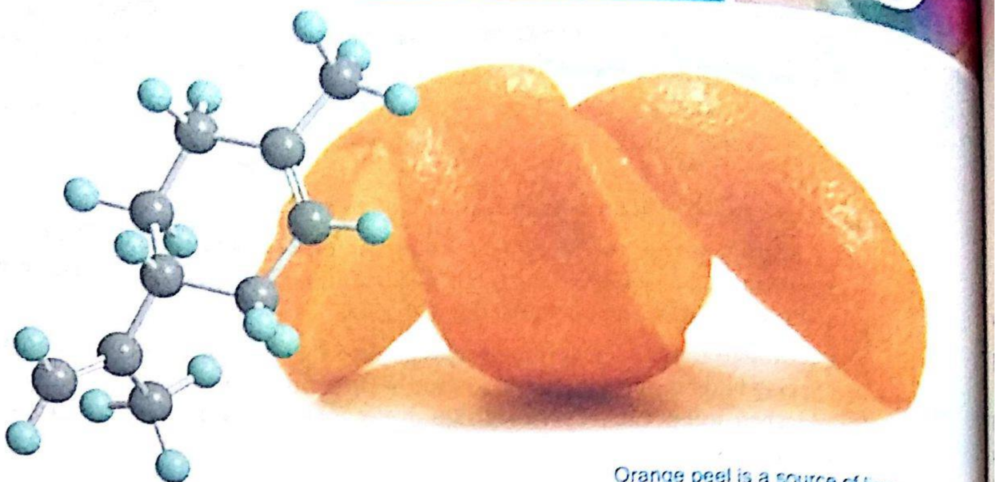
(6) **Synthesis.** The structure of nicotine has been confirmed by the following synthesis :



The product was resolved by means of (+)-tartaric acid. The synthetic (–)-nicotine was found to be identical with the natural alkaloid.

Terpenes

48



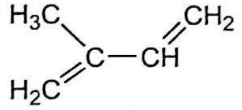
Orange peel is a source of limonene.

Terpenes are a class of compounds that give plants their odor, flavor, and in some cases color. They occur widely in the leaves and fruits of higher plants as conifers, citrus, and eucalyptus. *When the plant source is distilled with steam, the oily materials so obtained are called* **Essential Oils** (essential parts of plants).

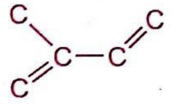
The essential oils are generally composed of mixture of either the hydrocarbons (*polyenes*) having general formula $(C_5H_8)_n$, or their oxygen derivatives (alcohols, aldehydes, ketones). This class of compounds are designated as **Terpenes** or **Terpenoids.**

ISOPRENE RULE

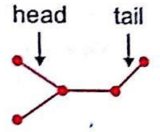
From a study of the molecular structure of a large number of the then known terpenes, Otto Wallach (Noble Prize 1910) gave the so-called **Isoprene Rule**. It states that : **The molecules of all terpenes are constructed of two or more isoprene (iso-C_5) units, usually joined in a head-to-tail fashion.** Isoprene is 2-methyl-1,3-butadiene and may be represented as :



Isoprene

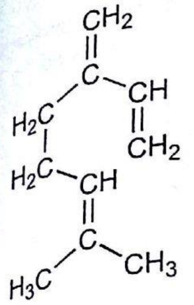


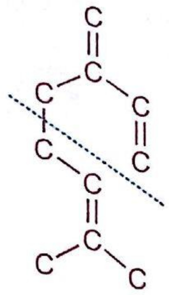
Condensed formula

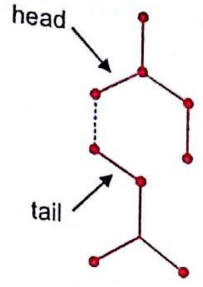


Isoprene skeleton

In applying Isoprene rule, we look only for the skeletal unit iso-C_5, neglecting the number and position of double bonds. Thus the terpene known as *myrcene* could be dissected by the dashed line into two isoprene units that are joined 'head-to-tail'.


Myrcene


Condensed formula

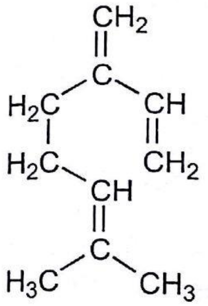


Carbon skeleton
(dotted bond shows head-to-tail arrangement)

Isoprene rule although generally valid, is not universal. However, it has proved of great help in deriving the structure of terpenes.

LINE FORMULAS OF TERPENES

The structures are frequently written with line formulas. The carbon-carbon bonds are represented by lines. The carbon atoms with appropriate number of hydrogens are understood to be present at corners or junctions, and the ends of lines. Thus the line formulas of *myrcene* and *menthol* may be written as


Myrcene

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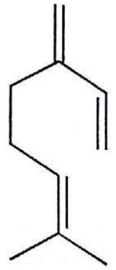
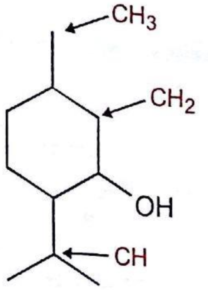

Line formula



Menthol

CLASSIFICATION OF TERPENES

Terpenes are classified according to the number of isoprene units (C_5) in the molecule. The simplest terpenes have two isoprene units (ten carbons) and are called **Monoterpenes**. In fact, the designation **Terpenes** is by custom specifically reserved for the C_{10} compounds. Other classes are listed below :

Monoterpenes	Two isoprene units	C_{10}
Sesquiterpenes	Three isoprene units	C_{15}
Diterpenes	Four isoprene units	C_{20}
Triterpenes	Six isoprene units	C_{30}
Tetraterpenes	Eight isoprene units	C_{40}

The above classes of terpenes are further subdivided according to the number of rings in the molecule :

Acyclic	No rings (Straight chain)
Monocyclic	One ring
Bicyclic	Two rings
Tricyclic	Three rings, and so on.

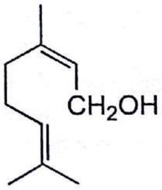
Then terpenes are classified on the basis whether they are pure hydrocarbons or oxygen derivatives (aldehydes, ketones, alcohols or ethers). The classification of terpenes can be illustrated by the following examples :

Acyclic monoterpenes :

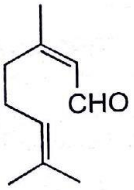
Ocimene
(basil oil)

Myrcene
(bayberry oil)

Acyclic oxygenated monoterpenes :

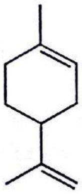


Geraniol
(rose oil)

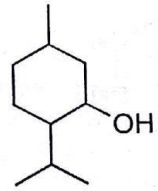


Citral
(lemon oil)

Monocyclic monoterpenes :

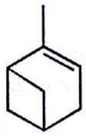


Limonene
(lemon and orange oil)

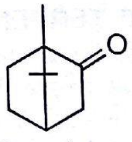


Menthol
(mint oil)

Bicyclic monoterpenes :



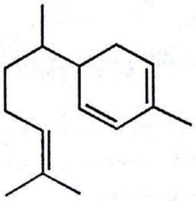
α-Pinene
(turpentine oil)



Camphor
(camphor oil)

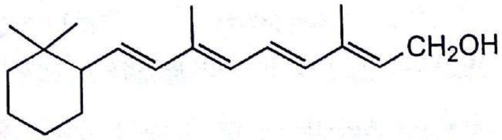
The discussion of *sesqui-*, *di-*, *tri-*, and *tetraterpenes* is beyond the scope of this book.

Sesquiterpenes

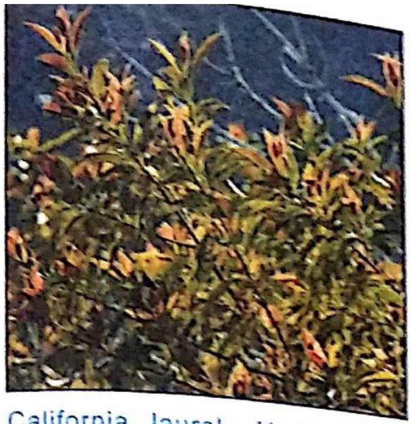


Zingiberene
(ginger oil)

Diterpene



Vitamin A



California laurel, *Umbellularia californica*, is a source of myrcene.

A camphor tree, *Cinnamomum camphora*.

ISOLATION OF TERPENES

Essential oils are first extracted from the plant source (leaves, flowers, stem or root) mainly by three methods :

(1) **Steam Distillation.** The mascerated plant material is steam distilled. The oil, if any, is collected separately. The aqueous steam distillate is saturated with salt and extracted with a purified solvent as light petroleum or benzene. The combined oil and the solvent extract are dried. The solvent is then removed by evaporation under reduced pressure to give the essential oil.

(2) **Direct Solvent Extraction.** If a particular terpene is decomposed under the conditions of steam distillation, the plant material is directly extracted with *light petroleum* or *ether* at room temperature. The extract is filtered and the solvent removed by evaporation under *vacuo* to recover the essential oil.

(3) **By Fat Adsorption (*Enfleurage Process*).** The flower petals are spread over a molten layer of fat (tallow and lard) for several days. The fat enriched with adsorbed essential oil from petals, is stirred with pure ethanol. The ethanol extract is then evaporated at 0°C in vacuum to give the essential oil.

The essential oils obtained as above are usually mixture of many terpenes. These are separated by fractional distillation or vapor-phase chromatography. Chemical methods are also used where possible.

GENERAL PROPERTIES OF TERPENES

(*Physical*). (1) Most terpenes are colourless, fragrant liquids having high refractive indices. A few of them e.g., camphor, are solids.

(2) They are lighter than water and readily volatile in steam.

(3) They are soluble in organic solvents (light petroleum, ether, benzene) but usually not in water.

(4) They are optically active and a number of them possess antiseptic properties.

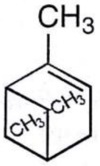
(*Chemical*). (1) They give the usual addition reactions of the carbon-carbon double bonds (*e.g.*, with HBr, Br_2, H_2, $HOCl$, O_3) and the aliphatic rings.

(2) They also show reactions characteristic of the functional groups such as $-CHO$, $>CO$, and $-OH$, when present in the molecule.

cigarettes ;

α-PINENE, $C_{10}H_{16}$

It is a *bicyclic monoterpene* and has the structure :



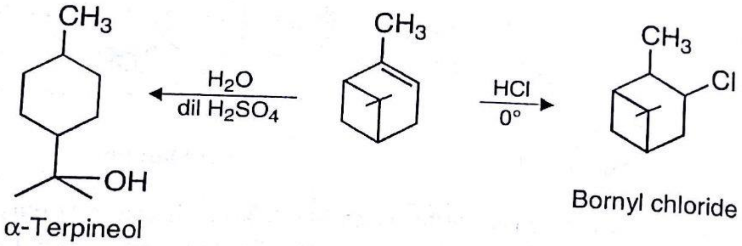
or

α-Pinene is the chief component of turpentine oil obtained from the pine tree.

Preparation. It is isolated from turpentine oil by steam distillation followed by fractional distillation. It is purified by conversion into nitrosyl chloride which upon treatment with aniline liberates α-pinene.

Properties. α-Pinene is a colourless liquid, bp 156°C. It has a characteristic odor and is optically active, $[\alpha]_D = 48.8°$.

(1) **Reaction with HCl.** It reacts with dry hydrogen chloride at 0°C to form bornyl chloride, mp 131°C, with a faint camphor odor ('artificial camphor').



α-Terpineol

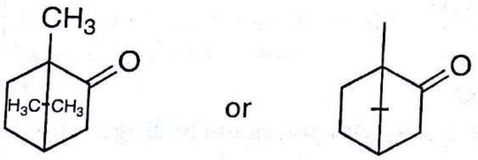
Bornyl chloride

(2) **Reaction with H_2SO_4.** When treated with dilute H_2SO_4, the 4-carbon ring in terpene cleaves to form α-Terpineol.

Uses. Turpentine oil which is mainly α-pinene is used as a thinner for paints and for the commercial synthesis of camphor.

CAMPHOR, $C_{10}H_{16}O$

It is a well-known bicyclic terpene ketone



Preparation. It is prepared by chilling *Camphor oil* obtained by steam distillation of wood and leaves of the camphor tree which grows in Formosa. Now it is mostly produced by a synthetic method starting from α-pinene.

Properties. Camphor is a colourless crystalline solid, sp gr 0.999, mp 179°C, bp 209.1°C. It sublimes at room temperature and its vapor have a strong characteristic smell. Natural camphor is dextrorotatory, $[\alpha]_D = +44°$. Chemically it behaves as a ketone. It forms an oxime and on reduction forms a secondary alcohol, *Borneol*.

Uses. Camphor is used as : (*i*) a medicinal, incense ; (*ii*) plasticizer ; (*iii*) moth repeller ; and (*iv*) in embalming fluids.