Alkaloids

Alkaloids are extremely difficult to define for they do not represent a homogeneous group of compounds either from the chemical, biochemical, or physiologic viewpoint. Consequently, Alkaloids are all organic nitrogenous compounds. Plants have been a rich source of alkaloids, but some are found in animals, fungi, and bacteria; practically all have been reproduced in the laboratory by chemical synthesis. Most possess basic properties, due to the presence of an amino nitrogen, and many possess marked physiologic activity. In spite of the difficulties attending a precise definition, the term is an extremely useful one, commonly applied to basic nitrogenous compounds of plant origin which are physiologically active.

Distribution:

1- angiosperms:-

Leguminosae, Papaveraceae, Ranunculaceae, Rubiaceae, Solanaceae, and Berberidaceae.

-The Labiatae and Rosaceae are almost free of them.

2- the gymnosperms only rarely contain them (Taxaceae).

3- the monocotyledons do not generally produce alkaloids, investigations indicate that the Amaryllidaceae and Liliaceae are two of the most promising families in which to search for alkaloid-yielding plants.

Alkaloids may occur in various parts of the plant:

- In seeds (nux vomica, areca),
- In fruits (black pepper, conium),
- In leaves (belladonna leaf, hyoscyamus),
- In underground stems (sanguinaria, corydalis),
- In roots (aconite, belladonna root),
- In rhizomes and roots (ipecac, hydrastis),
- In barks (cinchona, pomegranate).
- They are also found in the fungi (ergot, Amanita citrina).

The names of the alkaloids are obtained in various ways:

(1) from the generic name of the plant yielding them (hydrastine, atropine),
(2) from the specific name of the plant yielding them (cocaine, belladonnine),
(3) from the common name of the drug yielding them (ergotamine),
(4) from their physiologic activity (emetine, morphine),
(5) from the discoverer (pelletierine).

* By agreement, chemical rules designate that the names of all alkaloids should end in “ine.”

History of alkaloids:

Alkaloids are among the most important drugs in human history. The isolation of the alkaloid morphine by Friedrich in 1806 is regarded as the “formal” start of plant secondary metabolism. It is widely accepted that the main role of alkaloids in plants is toxicity against predators and pathogens. The same toxic properties observed in the plant defense scenario can often be used in prospection for new drugs. For example, a very specific toxicity may be used to fight certain tumor cell types, or also be used to control specific microorganisms or pests.

Toxicity to Humans and Other Vertebrates:

Animal intoxication by alkaloids is mostly caused by accidental ingestion of food contaminated with alkaloid-containing plants. Clearly, the amount of ingested alkaloid and the sensitivity of the target animal are key factors leading to intoxication.

. Some alkaloids can be extremely harmful to mammals, which is the case of the steroidal alkaloid cyclopamine in lambs, identified as the compound in Veratrum californicum (Liliaceae) responsible for teratogen effects.

The possible function of alkaloids in plants as:

(1) poisonous agents protecting the plant against insects and herbivores.

(2) end products of detoxification reactions representing a metabolic locking-up of compounds otherwise harmful to the plant.

(3) regulatory growth factors.

(4) reserve substances capable of supplying nitrogen or other necessary elements to the plant's economy.

The pharmacologic action of alkaloids varies widely:

1. some (morphine, codeine) are analgesics and narcotics while others (strychnine, brucine) are central stimulants.
2. Some (atropine, homatropine) are mydriatics whereas others (physostigmine, pilocarpine) are myotics.
3. Some (ephedrine) will cause a rise in blood pressure but others (reserpine) will produce a fall in excessive hypertension.

In fact, the alkaloids are capable of extensive physiologic activity.

PROPERTIES:

Most alkaloids are well-defined crystalline substances which unite with acids to form salts. In the plant they may exist in the free state, as salts or as N-oxides[N-oxides, also referred to as amine oxides, are organic compounds that contain the functional group N+-O-. Amine oxides are weak bases and highly polar molecules. Small amine oxides are found to be hydrophilic in nature and hence possess excellent water solubility]. ln addition to the elements carbon, hydrogen and nitrogen, most alkaloids contain oxygen, and an additional few, coniine, nicotine, and sparteine, which lack oxygen in their molecules, are liquids. Although colored alkaloids are relatively rare, they are not unknown; berberine for example is yellow and the salts of sanguinarine are copper-red.

Alkaloids usually contain one nitrogen atom, although some like ergotamine may contain up to five. The nitrogen may exist as a primary amine (RNH2), as a secondary amine (R2NH), or as a tertiary amine (R3N).

Since the nitrogen atom bears an unshared pair of electrons, such compounds are basic and resemble ammonia in chemical properties. The degree of basicity varies greatly depending upon the structure of the molecule and the presence and location of other functional groups.

Like ammonia, the alkaloids are converted into their salts by aqueous mineral acids, and when the salt of an alkaloid is treated with hydroxide ion, nitrogen gives up a hydrogen ion and the free amine is liberated. Quaternary ammonium compounds [R4N+ X-] such as tubocurarine chloride or muscarine chloride have

four organic groups covalently bonded to nitrogen, and the positive charge of this ion is balanced by some negative ion. The quaternary ammonium ion, having no proton to give up, is not affected by hydroxide ion; consequently, quaternary ammonium compounds have chemical properties quite different from those of the amines.

In spite of the difficulty in definitely characterizing alkaloids by definition, they do show a surprising number of physical and chemical properties. For the most part the alkaloids are insoluble or sparingly so in water but the salts formed upon reacting with acids are usually freely soluble. The free alkaloids are usually soluble in ether or chloroform or other relatively nonpolar, immiscible solvents in which, however, the alkaloidal salts are insoluble. This permits a ready means for the isolation and purification of the alkaloids as well as for their quantitative estimation.

Tests for alkaloids:

Most alkaloids are precipitated from neutral or slightly acid solution by :

- Mayer's reagent (potassium mercuric iodide solution),
- Wagner's reagent (solution of iodine in potassium iodide),
- Solution of tannic acid,
- Hager's reagent (a saturated solution of picric acid),
- Dragendorff's reagent (solution of potassium bismuth iodide).
- These precipitates may be amorphous or crystalline and are of various colors: cream (Mayer's), yellow (Hager's). reddish-brown (Wagner's and Dragendorff's).

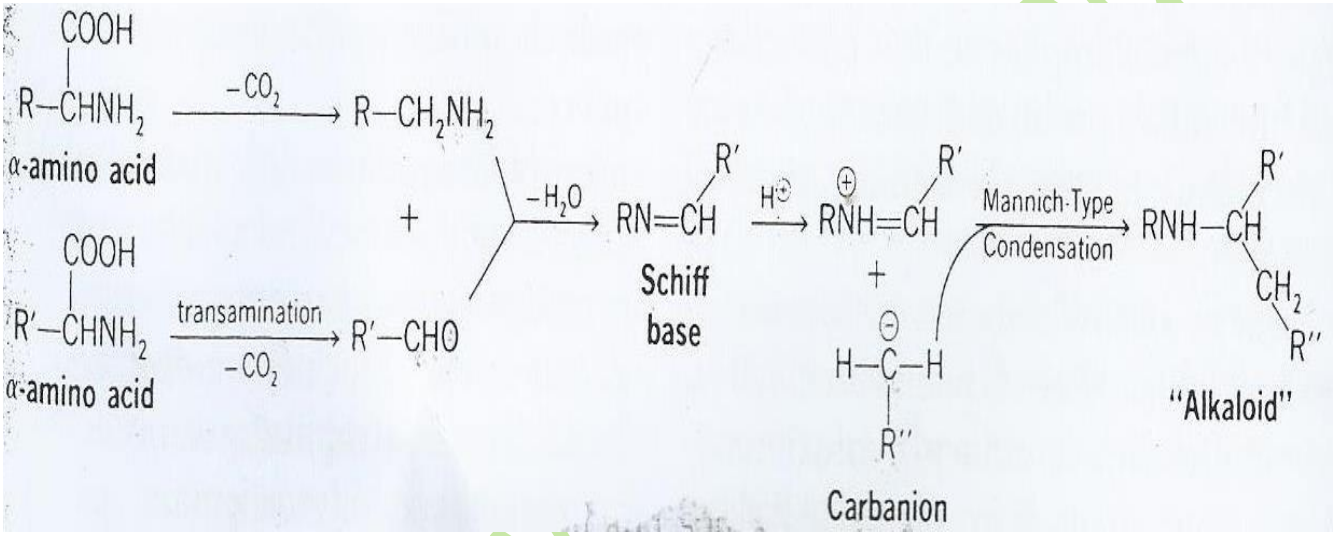
Care must be taken in the application of these alkaloidal tests:

1- the reagents also give precipitates with proteins. During the extraction of alkaloids from the plant and sub-sequent evaporation. Some proteins will not be extracted and others will be made insoluble (denatured) by the evaporation process and may be filtered out.

2- caffeine, and other purine derivatives, does not precipitate like most alkaloids. It is usually detected by mixing with a very small amount of potassium chlorate and a drop of hydrochloric acid, evaporating to dryness and exposing the residue to ammonia vapor. A purple color is produced ,this is known as the murexide test.

Biosynthesis of alkaloids

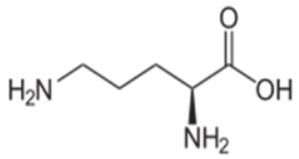
- The biosynthesis of many alkaloids' structures can be rationalized through simple chemical reactions that involve amino acids.
- The general reactions that are of particular importance include the decarboxylation & transamination of the amino acids to yield the corresponding amine or aldehyde respectively.
- These can react to form a Schiff base which in turn, can react with a carbanion in a Mannich type of condensation.



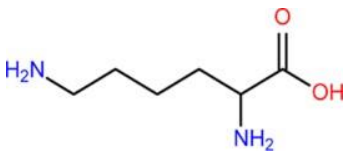
General reactions in alkaloid biosynthes

The major amino acids involved in the biosynthesis of alkaloids are

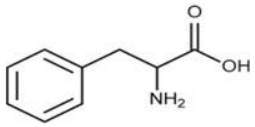
1. Ornithine



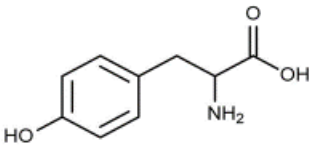
2. Lysine



3. Phenylalanine

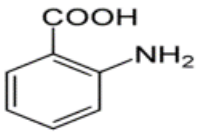


4. Tyrosine

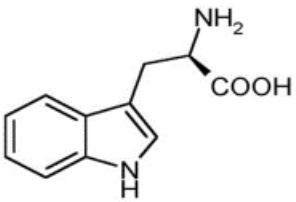


5. Anthranilic acid

It differs from other amino acids in that the COOH & NH_2 groups are not on the same carbon atom.



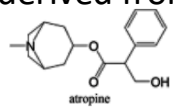
6. Tryptophan

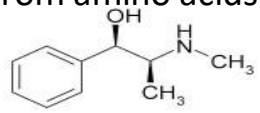


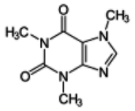
Classification:

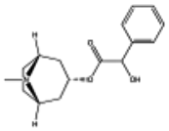
Various schemes for the classification of alkaloids have been suggested.

1. **Due to Hegnauer:**

True (Typical) alkaloids that are derived from amino acids and have nitrogen in a heterocyclic ring. e.g Atropine 

Protoalkaloids that are derived from amino acids and do not have nitrogen in a heterocyclic ring. e.g Ephedrine 

Pseudo alkaloids that are not derived from amino acids but have nitrogen in a heterocyclic ring. e.g Caffeine 

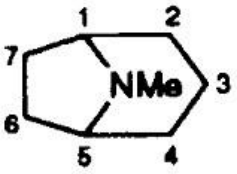
False alkaloids are non alkaloids give false positive reaction with alkaloidal reagents. e.g. homatropine. 

2. The following plan is based on the ring structure or nucleus of the chief alkaloid group in the plant drug:

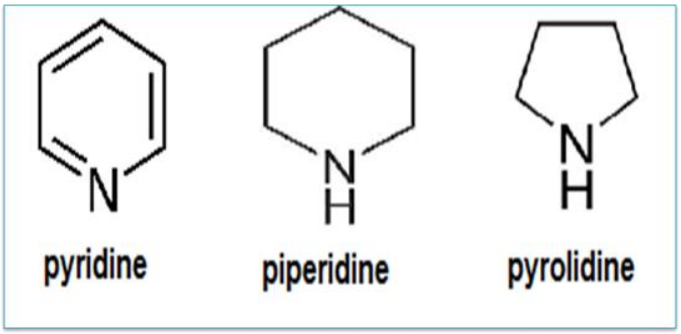
(1) pyridine-piperidine combined.
(2) tropane.
(3) quinoline.
(4) isoquinoline.
(5) indole.
(6) imidazole.
(7) steroid.
(8) lupinane.
(9) alkaloidal amine.
(10) purine.

3.Alkaloids that classified according to the nature of the basic chemical structures from which they derive:

1. Arecoline, pelletierine, lobeline, coniine, and nicotine are derivatives of pyridine and piperidine.
2. atropine, hyoscyamine, and hyoscine are derived from tropane, a condensation product of pyrrolidine and piperidine.

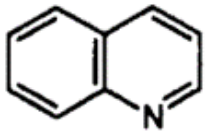


Tropane

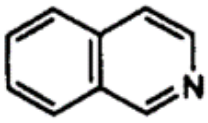


pyridine piperidine pyrolidine

3. The Cinchona alkaloids; quinine, quinidine, cinchonine, and cinchonidine contain quinoline as the principal nucleus; hydrastine, d-tubocurarine, emetine, and certain of the Opium alkaloids are characterized by the isoquinoline nucleus.

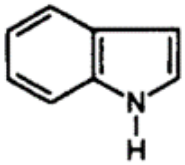


Quinoline



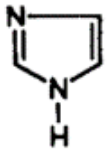
Isoquinoline

4. ergonovine, reserpine, and strychnine which derive from the indole ring.



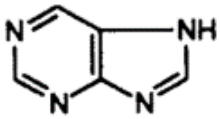
Indole

5. pilocarpine having the imidazole ring.



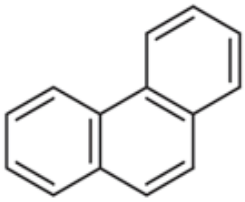
Imidazole

6. caffeine and theobromine which are purine bases.

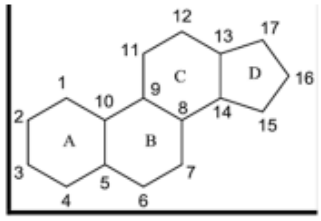


Purine

7. morphine and codeine possessing the phenanthrene ring, and aconitine and protoveratrine which contains a steroidal structure.



phenanthrene



cyclopentanoperhydrophenanthrene

Extraction of alkaloids:

-The extraction by fractional extraction (From less Polar to more Polar).

1-Defeating by non-polar solvent (Petroleum Ether, benzene, alkane,….) To get rid of Chlorophyll, Wax, Volatile oil, Fixed oil.

2-Filtration, for marc use methanol or ethanol 95% Evaporate by rotary evaporator (to Concentrate).

3-Add Tartaric acid 2% and Ethyl acetate will separate into two layers:

-Organic layer (For week or neutral alkaloids)

-Aqueous layer (acidic layer, Tartaric acid) which have alkaloidal salt.

To break the salt, add NH3 or Sodium bicarbonate. then add ethyl acetate again so will it separate into two layers again:

- Aqueous layer (Quaternary alkaloids 4º)

- Organic layer (For basic alkaloid 1^0,2º,3º).

- Large-scale extractions based on the above principles and the crude mixtures of alkaloids afterwards sent to a factory for separation and purification. This has been done for both cinchona and coca alkaloids by fractional precipitation or by fractional crystallization of salts such as oxalates, tartarates or picrates.

Purification of the extract:

- Direct crystallization:

The simplest procedure, but it seldom success when a crude mixture is involved.

The extract is evaporated to dryness & the residue is dissolved in a crystallizing solvent, which may be either a single organic solvent or a mixture of two solvents.

In a general order of increasing solubility of most alkaloids is as follows:

- Hexane , benzene, ether, ethyl acetate, methanol, acetone, chloroform & dioxane.

. Steam distillation:

It is used in rare cases, for liquid alkaloids, e.g. coniine, nicotine & sparteine.

. Crystallization of sparingly soluble salts:

The choice of acid is unlimited, but HCl, HBr, oxalic, picric, perchloric, sulfuric, maleic, tartaric acids are among the widely used acids.

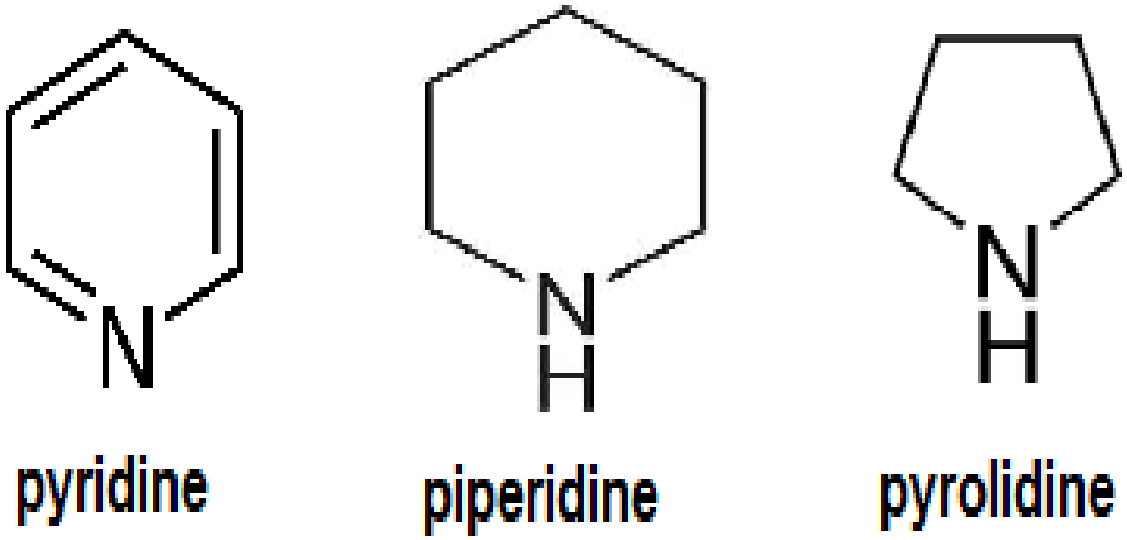
The general procedure for hydro halides involves dissolving the crude base in methanol or acetone & adding an ethereal solution of the acid.

Oxalates, picrates & perchlorates are usually formed by mixing methanolic solutions of the base & the acid.

Distribution between immiscible solvents:

The alkaloids are taken up in a dilute acid solution. From this it may be possible to recover the alkaloids by the addition of ammonium hydroxide solution & extract with water immiscible organic solvent. The choice of organic solvent for this method is usually limited to benzene, chloroform or ether.

Pyridine –piperidine-pyrolidine alkaloids

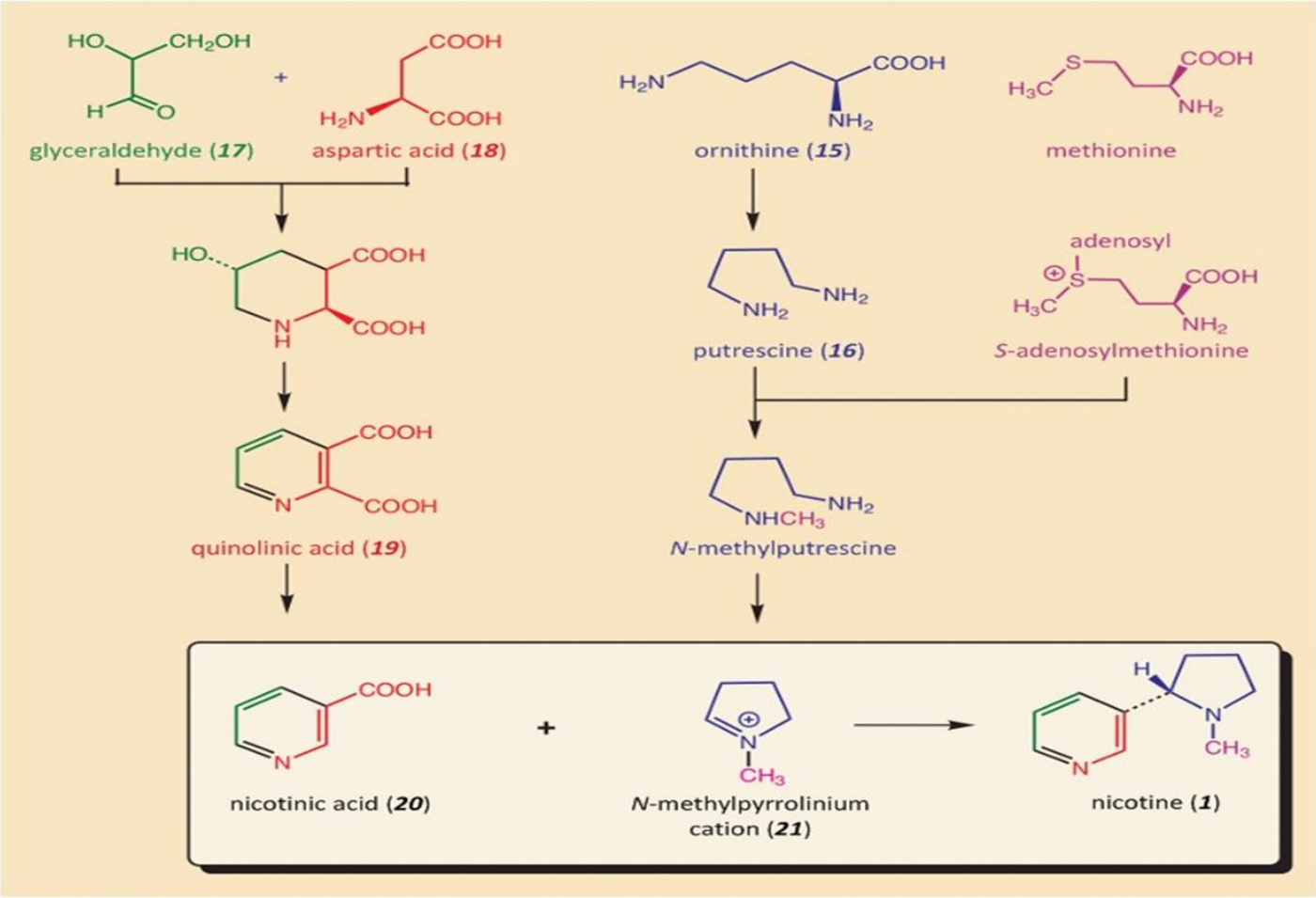


- **Upon reduction, the tertiary base, pyridine is converted into the secondary base piperidine.**
- **These two nuclei form the basis for this group which sometimes is divided into three groups:**
- **Derivatives of piperidine e.g. lobeline from lobelia.**
- **Derivatives of nicotinic acid e.g. arecoline from areca.**
- **Derivatives of both pyridine-pyrolidine e.g. nicotine from tobacco.**

BIOSYNTHESIS OF PYRIDINE- PIPERIDINE ALKALOIDS:

Nicotine: The biosynthetic pathway leading to this compound is summarized as follows:

. Ornithine is incorporated into nicotine by tobacco plants. This incorporation result in a symmetric labeling pattern of nicotine. .Putrescine, N- methylputrescine, and N-methyl-aminobutanal are all incorporated.The N-methylpyrrolinium ion is the key intermediate which, through electrophilic aromatic substitution attached to C-3 of the pyridine ring of nicotinic acid.

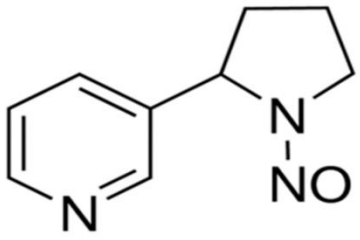


Drugs containing pyridine-piperidine alkaloids:

Tobacco

- **It is the dried leaves of Nicotiana tobacco F: Solanaceae.**
- **It is cultivated for smoking, it contains alkaloids from 0.6-0.9%, the main one is nicotine which is an oily liquid alkaloid, it is colorless liquid but when oxidized convert to yellow color.**
- **nicotine has pronounced effects on the cardio vascular system, where peripheral vasoconstriction, atrial tachycardia & an increase in both systolic & diastolic blood pressure are observed.**
- **It is worth noting that 50% of all smokers die of heart disease & 20% of lung cancer.**

- **The carcinogenicity of tobacco is probably not due to nicotine but rather to a far more potent carcinogen (N-nitroso nor nicotine)**
- **It is found in cigarettes, cigars & chewing tobacco at levels in the range of 2-90pp, parts per billion concentrations of N-nitrosamines are considered hazardous to health.**

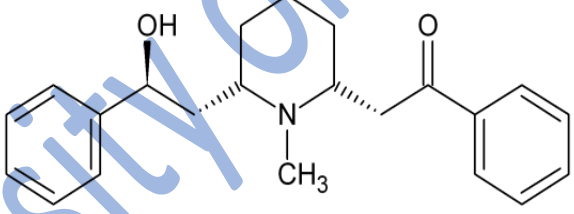


N-nitroso nor nicotine

Lobelia or (Indian tobacco)

It is the dried leaves & tops of *Lobelia inflate* F: Lobeliaceae (Campanulaceae).

The drug contains 14 alkaloids, of which lobeline is the major & most important.



Lobeline

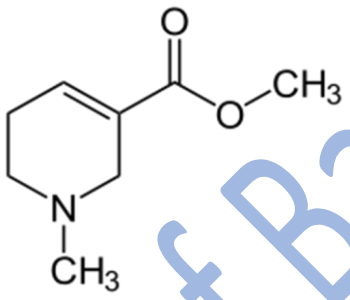
Lobeline occurs in colorless crystals very slightly soluble in water, but readily soluble in hot alcohol.

Uses and Dose. Galenical preparations of Lobelia were formerly used for expectorant purposes. Lobeline is a respiratory stimulant, but its action is somewhat unreliable and of brief duration. Other effects resemble those of nicotine. For this reason, 0.5 to 1.5 mg doses of lobeline sulfate are incorporated in tablets or lozenges which are intended to aid in breaking the tobacco habit.

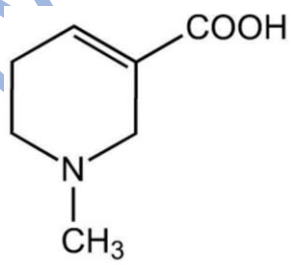
Areca

- Is the dried, ripe seed of *Areca catechu* (Fam. Palmae). Areca contains several alkaloids which are reduced pyridine derivatives. Among them are arecoline (arecaidine methyl ester), arecaidine (N- methyl guvacine), guvacine (tetrahydronicotinic acid), and guvacoline (guvacine methyl ester). The content of total alkaloids ranges up to 0.45%.

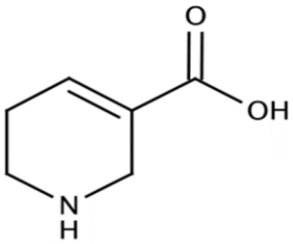
Uses. Arecoline Hydrobromide is used in veterinary medicine as an anthelmintic drug against parasitic worms especially tenea.



Arecoline



Arecaidine:



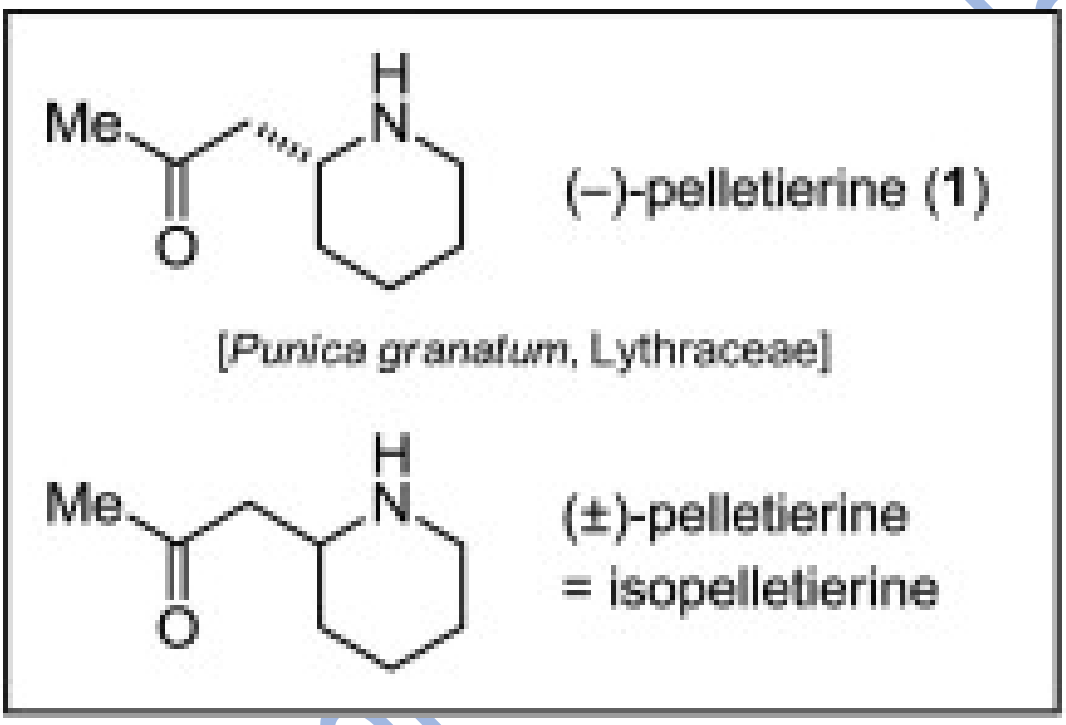
Guvacine (tetra hydro nicotinic acid)

POMEGRANATE:

Pomegranate Root and Stem Bark or Granatum is derived from *Punica granatum* (Fam. Punicaceae). They contain about 0.5–0.9% of volatile liquid alkaloids,

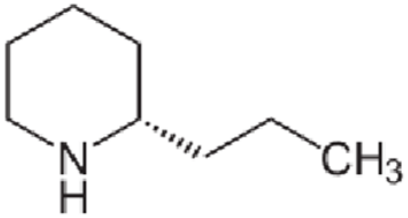
the chief of which are pelletierine and pseudopelletierine, together with about 22% of tannin.

Pelletierine tannate, a mixture of the tannates of the alkaloids, was included in the BP 1948 and was used as an anthelminthic with a specific action on tapeworms.

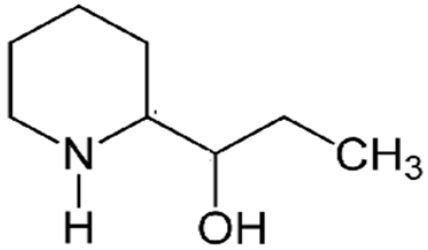


Conium (poison hemlock):

- It is the full grown but unripe fruit of *Conium maculatum* F: Umbellifareae.
- It contains number of alkaloids the important of which is coniine & conhydrine.

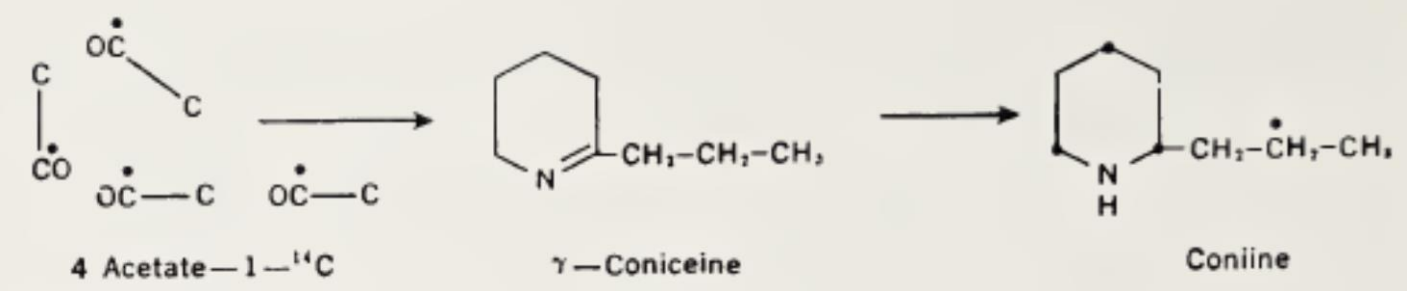


coniine



conhydrine

It is used as anti spasmodic.



Biosynthesis of coniine.

Piper

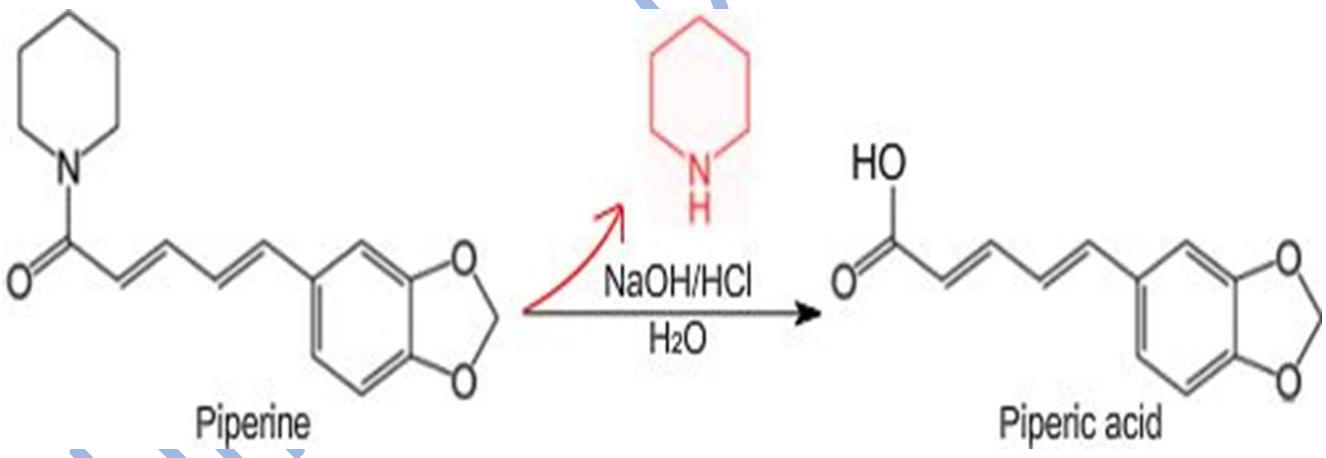
It is the dried full grown unripe fruit of *Piper nigrum* F: Piperaceae.

It contains up to 4.5-8% of piperine.

Mainly used as a condiment.

It has an irritant, stimulant & febrifuge activity (decrease body temperature).

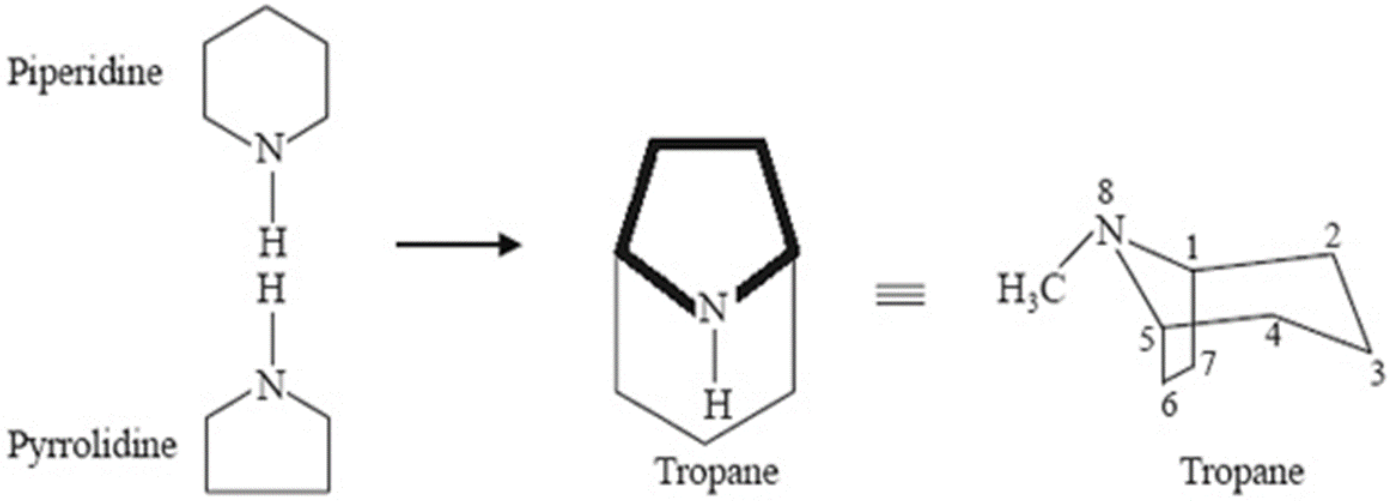
On hydrolysis of piperine we get another alkaloid piperidine which is a liquid alkaloid.



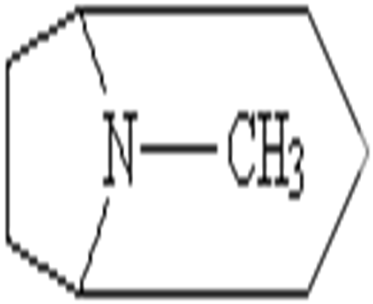
Tropane alkaloids

- The principal alkaloids of medicinal interest in this group are (−)-hyoscyamine; its more stable racemate atropine, and hyoscine (scopolamine). The compounds are esters and are hydrolyzed by heating at 60°C with baryta water; atropine yields tropic acid and tropine; hyoscine gives tropic acid and oscine (scopine is actually formed by enzymatic hydrolysis but the chemical treatment converts it to the more stable geometric isomer, oscine).
- **They are extremely poisonous.**

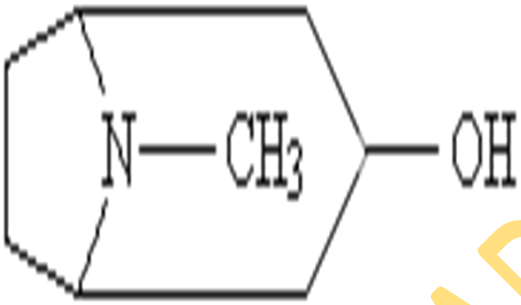
Tropane is a dicyclic compound found by the condensation of a pyrrolidine precursor (ornithine) with three carbon atoms derived from acetate.
Both pyrrolidine & piperidine ring systems can be recognized in the molecule.



The 3-hydroxy derivative of tropane is known as tropine.

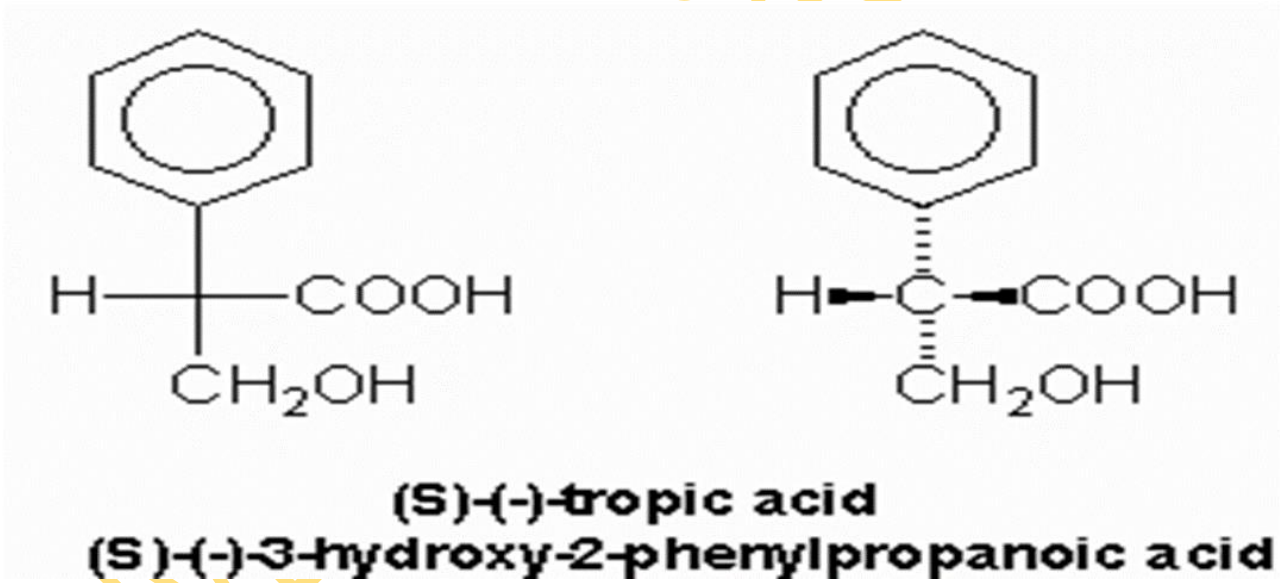


Tropane



Tropine

Its esterification with (-)-tropic acid yields hyoscyamine (tropine-tropate) ester, which may be racemized to form atropine.

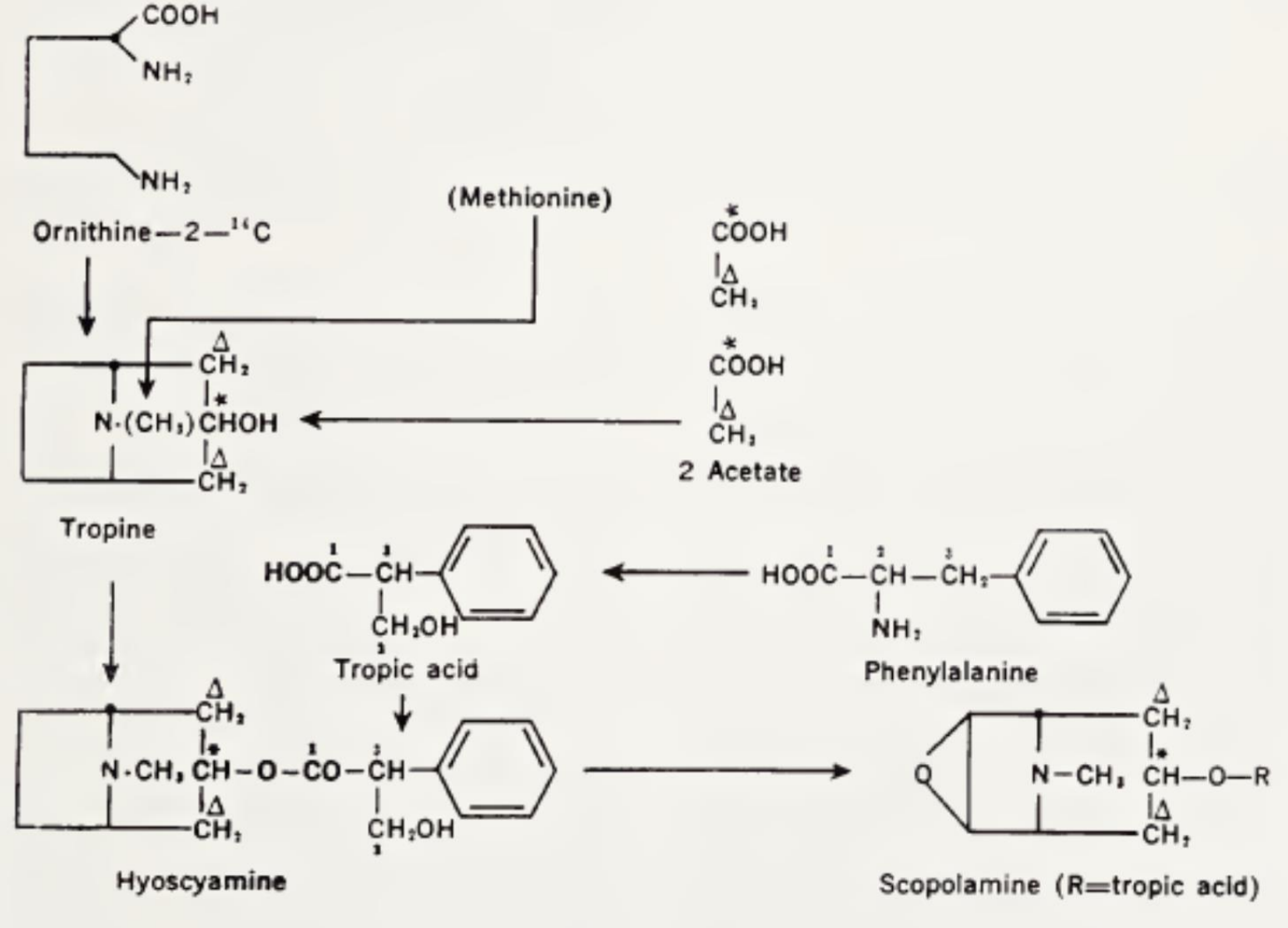


(S)-(-)-tropic acid
(S)-(-)-3-hydroxy-2-phenylpropanoic acid

BIOSYNTHESIS OF TROPANE ALKALOIDS:

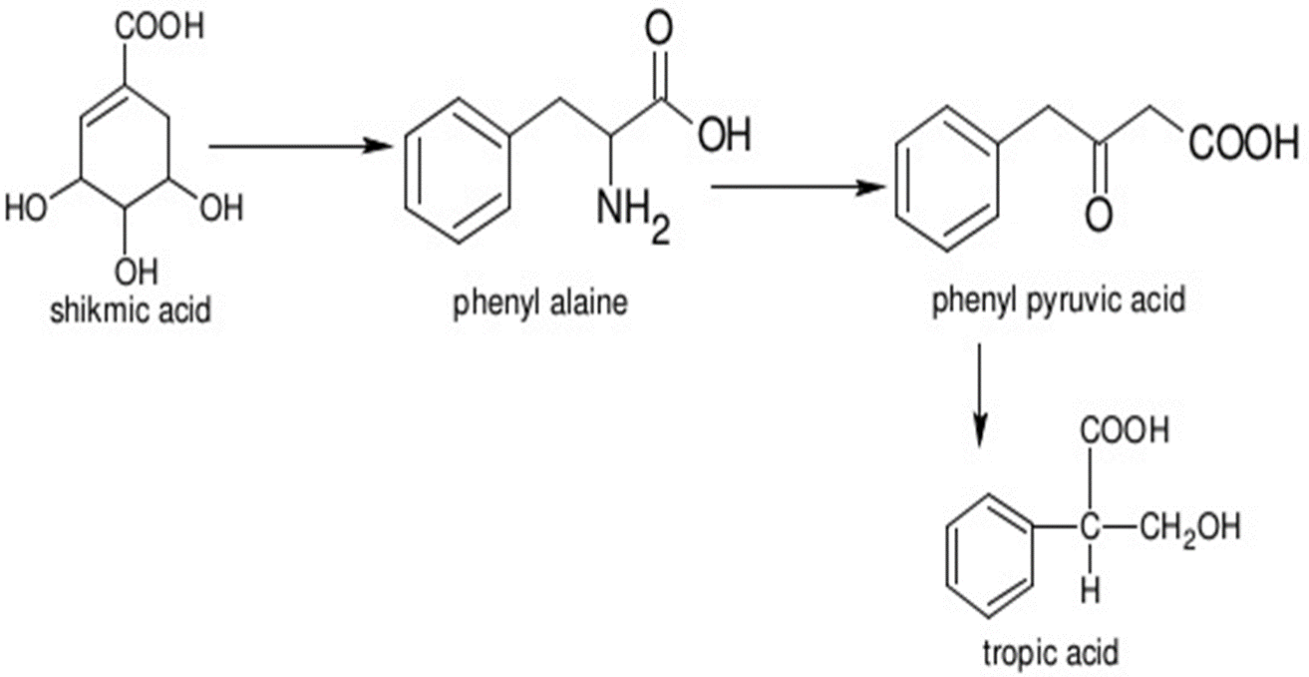
Hyoscyamine and Scopolamine.

Feeding studies with labeled ornithine have revealed that this amino acid is incorporated stereospecifically to form the pyrrolidine ring of tropine. The remaining three carbon atoms derive from acetate, thus completing the piperidine moiety. Methylation results via transmethylation front a suitable donor, e.g., methionine, to complete the tropine nucleus. Esterification of tropic acid with tropine produces hyoscyamine.



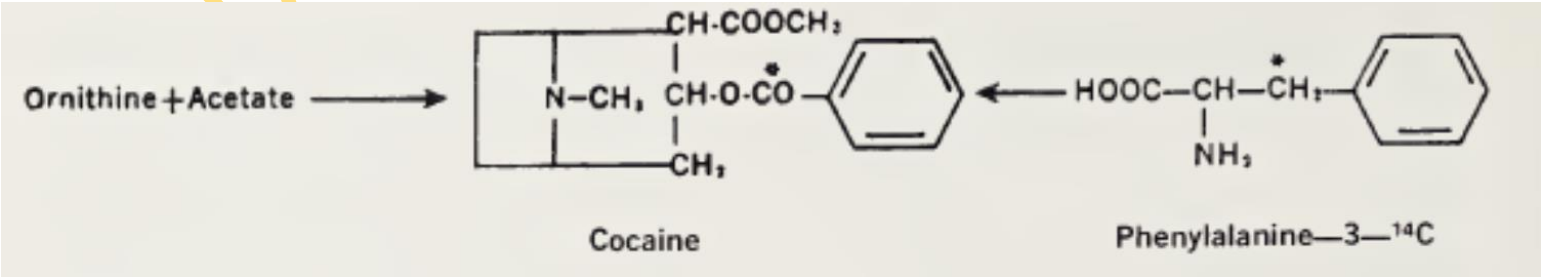
Biosynthesis of hyoscyamine and scopolamine.

Tropic acid is formed by an intramolecular rearrangement of phenyllactate.



- The (-)-isomer is hyoscyamine, the (+)-isomer is not found in the plant, the (±)-isomer is atropine.
- Hyoscyamine is more active than atropine.
- Hyoscine (scopolamine) is an epoxide of atropine & it is the (-)-isomer.
- The (±)-isomer of scopolamine is atrosine.
- All together over 200 tropane alkaloids have now been recorded. Semi synthetic derivatives e.g. N-butyl bromide (buscopan) are of medicinal importance.

Cocaine. Feeding experiments with Erythroxylon coca have shown that phenylalanine-3-14C is incorporated into cocaine, the radioactivity being located in the benzoyl group. Presumably, the ecgonine moiety derives from ornithine and acetate in a manner analogous to tropine biosynthesis.



Drugs containing tropane alkaloids

- **Belladonna (Deadly night shade leaf)**
- Two parts of belladonna are official, the root & the leaf.
- It is the dried leaf or root of *Atropa belladonna* F: Solanaceae.
- The root is richer than the leaf in alkaloids. The root contains 0.6% while the leaves 0.4%.
- Most of the alkaloids found in the leaf are: (-) hyoscymine, and traces of atropine in fresh plant. Atropine is formed by racemization during the extraction process. Small amount of other bases are found in the root but not in the leaf these include the anhydride of atropine (apoatropine) and it's stereoisomer belladonnine and scopolamine(hyoscine).
-  

Uses

- Belladonna acts as a parasympathetic depressant which accounts for its use as a spasmolytic agent. It possesses anticholinergic properties and is used to control excess motor activity of the gastrointestinal tract and spasm of the urinary tract.

Hyoscyamus or Henbane

The dried leaves & flowering tops of Hyoscyamus niger F: Solanaceae.

It contains 0.04% of total alkaloids calculated as hyscyamine, the drug also contains hyoscine & traces of atropine.

Uses: Hyoscyamus is a parasympatholytic, but the crude drug is rarely employed in medicine today.

- **Egyptian Henbane:**
- It is the dried leaves & flowering tops of *Hyoscyamus muticus*, yield about 1.5% of total alkaloids consisting largely of hyoscyamine.
- The plant is indigenous to & cultivated in Egypt.
- The plant is used perhaps entirely for the extraction of its alkaloids.



- **Stramonium:**
- It is the dried leaves & flowering tops of *Datura stramonium*
- F: Solanaceae.
- It contains up to 0.4% of total alkaloids calculated as hyoscyamine.
- Use: Stramonium is an anticholinergic having an action like that of belladonna.
- Powdered Stramonium is an ingredient in preparations which are intended to be burned and the vapor inhaled for the relief of asthma. These so-called asthma

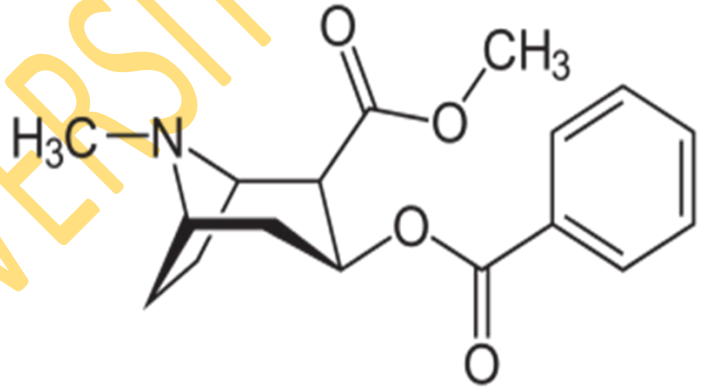
powders. Food and Drug Administration placed Stramonium-containing asthma powders in the category of drugs which could be dispensed only on prescription.

- 

All these drugs are used as mydriatic (dilate the pupils of the eyes) & as antispasmodic, & as parasympatholytic or anticolinergic & to decrease all the secretions (sweat, saliva, milk etc…).

It is used as adjunctive therapy in the treatment of peptic ulcer, functional digestive disorder, and diarrhea.

Cocaine



It is a habit forming drug from the leaves of Erythroxylum coca F: Erythroxylaceae.

The plant is also called coca or coca leaves.

Coca leaves contain 3 basic types of alkaloids:

1. Derivatives of ecgonine (cocaine, cinnamyl cocaine, α & β truxilline).

2. Tropine (tropacocaine, valerine).

3. Hygrine (Hygroline, cuscohygrine).

Only the ecgonine derivatives are commercially important.

The most important of these is cocaine.

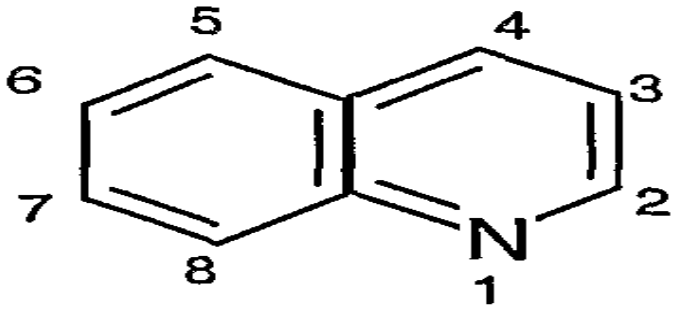
Cocaine is the methyl ester of benzoyl ecgonine.

Cocaine & cocaine hydrochloride, are agents of abuse, are generally inhaled or sniffed & are rapidly absorbed across the pharyngeal mucosa, resulting in cerebral stimulation & euphoria.

Cocaine hydrochloride is a local anesthetic.

It is applied topically to mucous membrane as 2-5% solution.

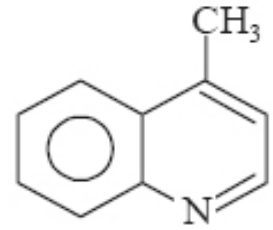
Quinoline Alkaloids



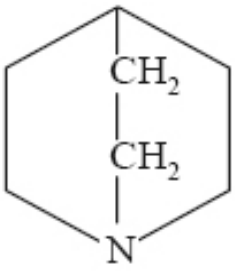
- In general, the alkaloids containing essentially the 'quinoline' nucleus include a series of alkaloids obtained exclusively from cinchona bark, the major members of this particular group are, namely:
- quinine
- quinidine
- cinchonine

  cinchonidine.
- more than twenty five alkaloids have been isolated and characterized either from the *Yellow Cinchona i.e.*
- *Cinchona calisaya* and *Cinchona ledgeriana*,
- OR from the *Red Cinchona i.e.*
- *Cinchona succirubra*
- (Family: *Rubiaceae*).
- **Basic Structures of Cinchona Alkaloids:**
- Cinchona alkaloids usually possess two ring : quinolone (which consist from benzene ring + pyridine) and bicyclic quinuclidine.
- Cinchona possess the basic skeleton of 9'-rubanol that is derived from the parent compound known as ruban.
- Thus, ruban is obtained from the combination of two distinct heterocyclic nuclii, namely:

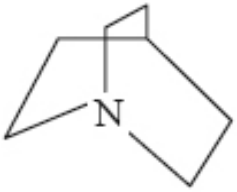
- (a) 4-methyl quinoline nucleus, and
- (b) quinuclidine nucleus.



4-Methyl Quinoline Nucleus

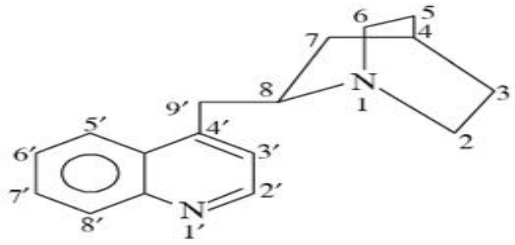


Quinuclidine Nucleus

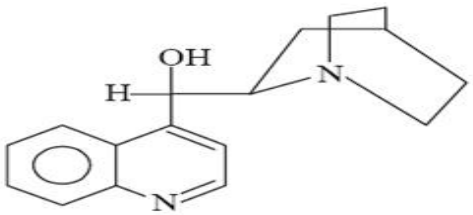


Quinuclidine Nucleus

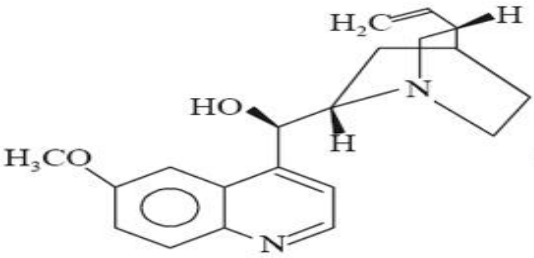
- However, this particular nomenclature was suggested by Rabe so as to simplify the naming of such compounds and also to signify its origin from the natural order *Rubiaceae.*



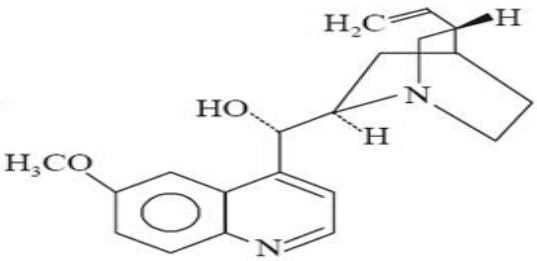
Ruban



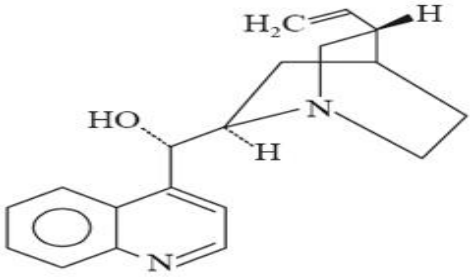
9′-Rubanol



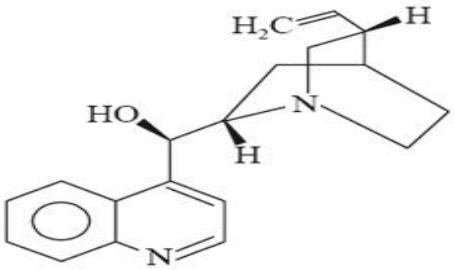
Quinine



Quinidine

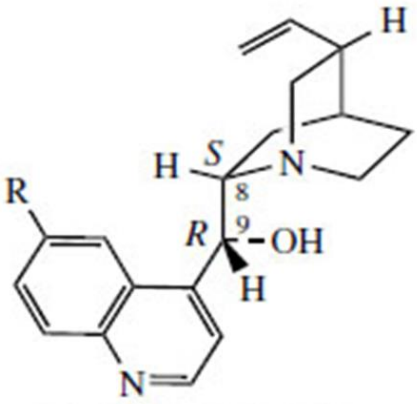


Cinchonine

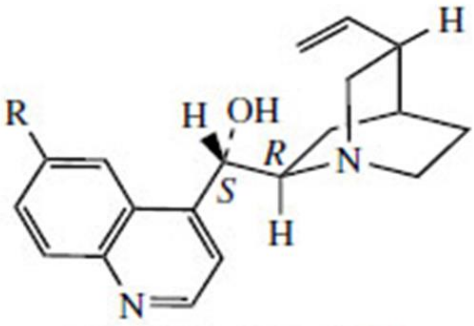


Cinchonidine

- Quinine & quinidine are stereoisomers
- Cinchonine & cinchonidine are stereoisomers
- For cinchonine & quinidine C_8= R , C_9 = S
- For cinchonidine & quinine C_8 = S , C_9 = R
- Stereoisomers are isomeric molecules that have the same molecular formula and sequence of bonded atoms (constitution), but that differ *only* in the three-dimensional orientations of their atoms in space.



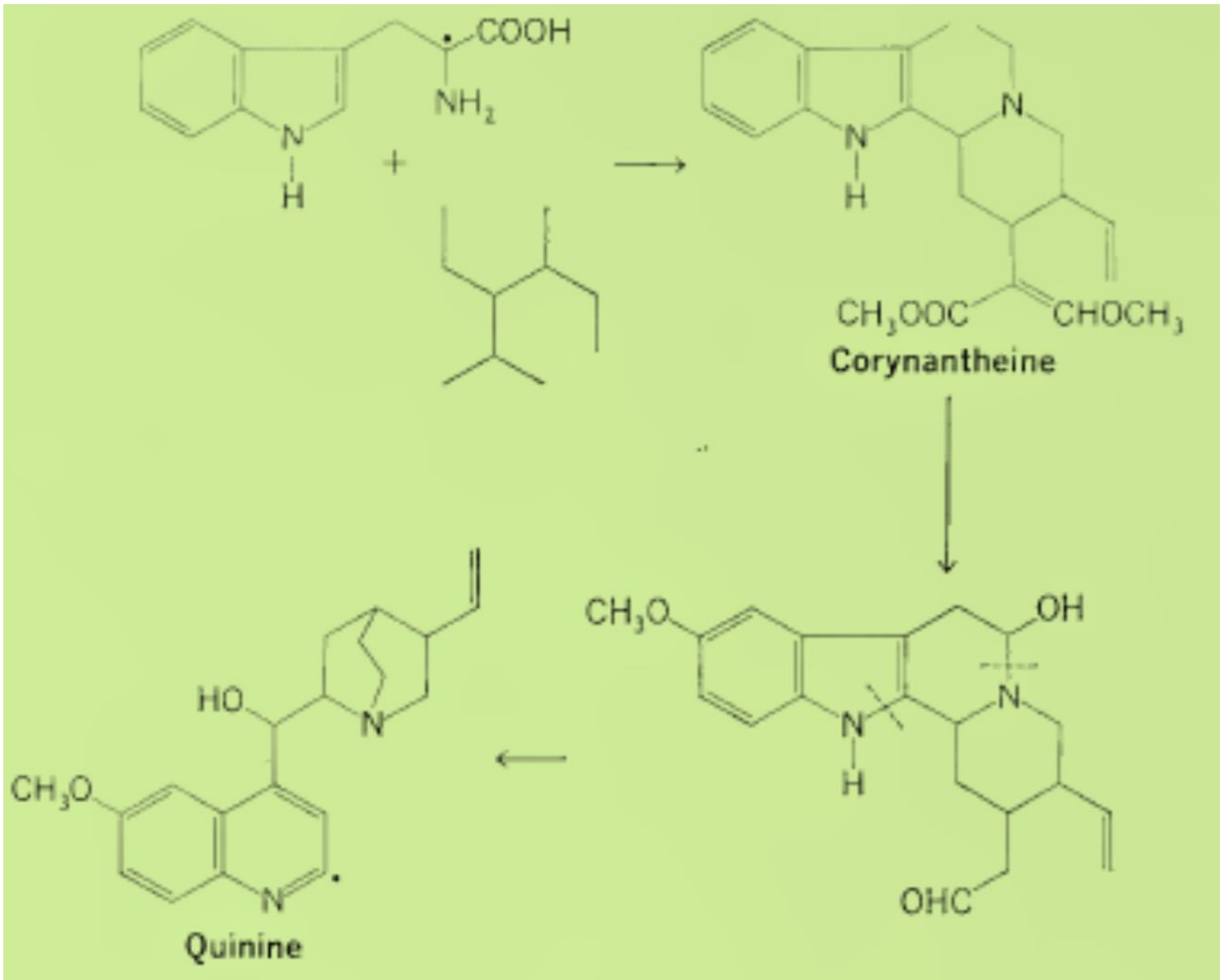
R = OMe, (–)-quinine
R = H, (–)-cinchonidine



R = OMe, (+)-quinidine
R = H, (+)-cinchonine

Biosynthetic pathway:

Studies with labeled geraniol and tryptophan indicate that quinine is metabolically derived from the monoterpenoid-tryptophan pathway.



Identification Tests of Quinine:

- **Fluorescence Test:** Quinine gives a distinct and strong blue fluorescence when treated with an *oxygenated acid*, such as: acetic acid, sulphuric acid.
- This test is very marked and pronounced even to a few mg concentration of quinine.
- Note: The hydrochloride and hydroiodide salts of quinine do not respond to this fluorescence test.
- **Thalleioquin Test:** Add to 2-3 ml of a weakly acidic solution of a quinine salt a few drops of bromine-water followed by 0.5 ml of strong ammonia solution, a distinct and characteristic emerald green color is produced.
- The colored product is termed as thalleioquin, the chemical composition of which is yet to be established.
- This test is so sensitive that quinine may be detected to a concentration as low as 0.005%.
- Notes: Quinidine gives also a positive response to this test; but cinchoninine and cinchonidine give a negative test.

Uses:

- Cinchona & its alkaloids have been used in the treatment of malaria fever for many years.
- Quinine sulfate continues to be used for malaria in many parts of the world (it poison the protozoa), as tonic, analgesic, in the treatment of cold.

Quinidine is used to treat various cardiac arrhythmias e.g. arterial & ventricular tachycardia, atria fibrillation & ventricular contraction.

Quinidine is found as salts (sulfate & gluconate).

It depresses myocardial excitability, conduction velocity & contractility.

Totaquine

- It is a mixture of total alkaloids, containing not less than 7% & not more than 12% of anhydrous quinine.

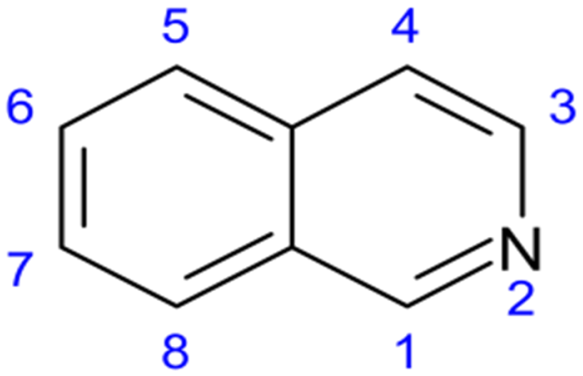
- It should contain 70-80% of total alkaloids.

It is used as anti malarial & for cold but it cannot be used as cardiac depressant. Usual dose 600mg.

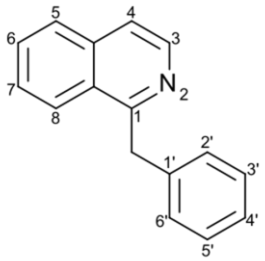
Cinchonism or quinism:

- Treatment with cinchona products result in symptoms of mild cinchonism (which may occur from standard therapeutic doses of quinine).
- These symptoms include flushed and sweaty skin, ringing of the ears (tinnitus), blurred vision, impaired hearing, confusion, reversible high-frequency hearing loss, head ache, abdominal pain, rashes, dysphoria, nausea, vomiting and diarrhea Ringing in the ears is a symptom of toxicity.
- When these symptoms are produced as the result of continuous use of cinchona or of quinine the condition has been called cinchonism.

Isoquinoline alkaloids:

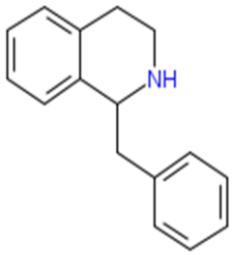


- **Isoquinoline is a heterocyclic aromatic organic compound.**
- **It is a structural isomer of quinoline.**
- **Isoquinoline and quinoline are benzo pyridines derivatives , which are composed of benzene ring fused to a pyridine ring.**
- **Types of isoquinoline alkaloids:**
- **Benzylisoquinoline or BIQ alkaloids**
- About 4000 BIQ alkaloids are known.
- There are many important structural types. Many BIQ alkaloids are important in medicine. Others are highly toxic. Some are used as arrow poisons.

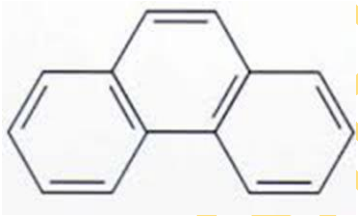


- **Tetrahydrobenzylisoquinoline or THBIQ alkaloids:**
- The simplest alkaloids of this series are those in which the nitrogen-containing ring is completely saturated. These alkaloids are found in almost all families that contain BIQ alkaloids.
- About 100 compounds of this type are known.

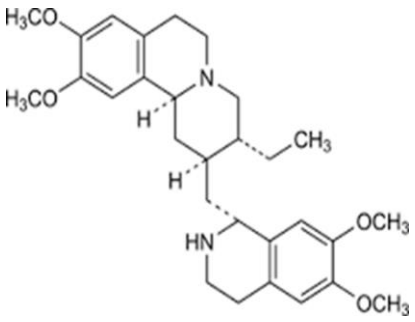
- The most important compound from a biosynthetic point of view is (+)-reticuline.



- **Phenanthrene alkaloids:**
- They are mainly found in papaveraceae family as morphine & related alkaloids.

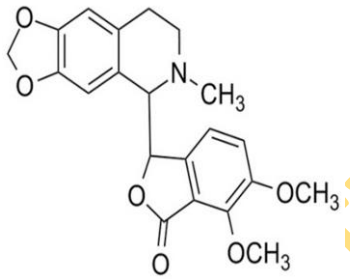


- **The important drugs & their alkaloids in this group are:**
- -Ipecac which contains emetine
- -Hydrastis which contains hydrastine
- -Curare which contains (+)-tubocurarine
- -Berberis which contains berberine
- -Opium which contains morphine & related alkaloids
- -Sanguinaria which contains sanguinarine.
- ***Drugs containing isoquinoline alkaloids:***
- Ipecac:
- It consists of the dried rhizomes & roots of Cephaelis ipecacuanha (Brazilian ipecac) or Cephaelis acuminate (Nicaragua or Panama ipecac) F: Rubiaceae.
- Ipecac yields not less than 2% of ether-soluble alkaloids.
- Ipecac contains five alkaloids, 3 main alkaloids namely: emetine, cephailine, & psychotrine.

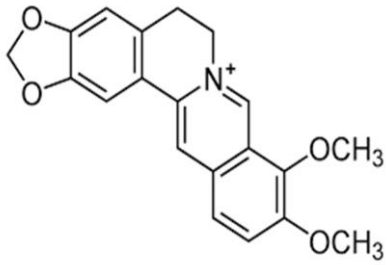


Emetine

- Hydrastis or golden seal:
- It consists of the dried rhizomes & roots of *Hydrastis canadensis* F: Runuculaceae.
- Three alkaloids have been isolated from hydrastis namely: hydrastine, berberine, & canadine.
- Of these, hydrastine (1.5-4%) is the most important.
- Hydrastis yields not less than 2.5% of anhydrous ether-soluble alkaloids.



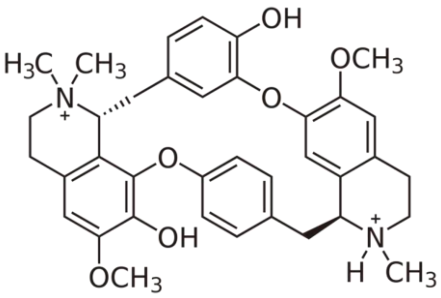
Hydrastine



Berberine

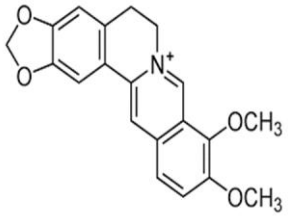
- **Uses:**
- Hydrastine & berberine are used as astringents in inflammation of the mucous membrane.
- Curare:
- Curare or South American arrow poison, is a crude dried extract from the bark & stems of *Strychnos castelnaei* or *S. crevauxii* F: Loganiaceae.

  The drug contains several alkaloids & quaternary compounds, the most important of which is (+)-tubocurarine, which is a quaternary compound that contains a bis-benzyl isoquinoline structure. The crude extract exhibits a paralyzing effect on the voluntary muscles (curariform effect) by blocking nerve impulses to skeletal muscles. It also produces a toxic action on blood vessels.



Tubocurarine

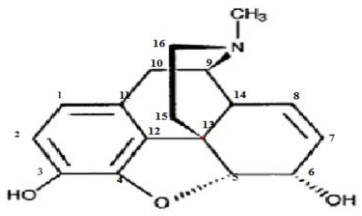
- **Uses:**
- Tubocurarine is used as a skeletal muscle relaxant in surgical procedures without deep anesthesia.
- It is also used to control convulsions of strychnine poisoning & of tetanus.
- It is an adjunct therapy in neuro psychiatry & as a diagnostic aid in myasthenia gravis.
- Currently, tubocurarine is rarely used as an adjunct for clinical anesthesia because several alternatives, such as cisatracurium and rocuronium, are available.
- Berberis (barberry):
- Sixteen isoquinoline alkaloids were isolated from Berberis vulgaris.
- In addition to quaternary proto berberines and bisbenzyl isoquinolines, a new seco-bisbenzyl isoquinoline, (-)-tejedine, is reported.
- Barberry is considered to be antibacterial, anti-inflammatory, hypertensive, haemostatic, diuretic and vasodilator.
- Due to its constituent berberine, Barberry can act as a very efficient remedy against bacterial, viral, fungal and parasitic infections.



Berberine

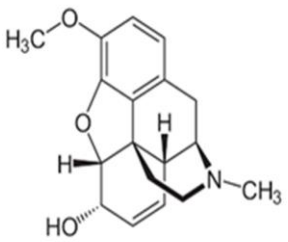
- Opium:
- Opium or gum opium, is the air-dried milky exudates obtained by incising the unripe capsules of *Papaver somniferum* F: Papaveraceae.
- The term opium is from Greek opion meaning poppy juice; papaver is the Latin name for the poppy; somniferum is Latin & means to produce sleep.
- The cultivation of opium poppy is controlled internationally by the International Narcotic Control Board of the United Nations.
- Lately it was decided to be grown in Turkey, India, Russia, Romania, Australia, France, China & Spain.
- **Cultivation:**
- It is cultivated by planting in October.
- In spring, the plant reaches 15cm height, then the fruit appears.
- In June or July when it is fully grown & unripe, each plant contains 5-8 poppy (fruit) & then it is superficially cut & a milky juice is obtained, left for one day & collected in the second day.
- The main constituents are 30 different alkaloids, the most important of which are:
- morphine 4-21%
- codeine 0.8-2.5%
- noscapine (narcotine) 4-8%
- papaverine 0.5-2.5%
- thebaine 0.5-2%.
- Other alkaloids include narceine, protopine, laudanine, codamine, cryptopine…..
- Opium also contains 3-5% of meconic acid which exists free or in combination with morphine, codeine & other alkaloids.
- It gives a red color in solution of ferric chloride.
- The color is not altered when dilute HCl is added.
- Because meconic acid is found only in opium, this test may be used for the detection of opium.
- <u>Classification of opium alkaloids:</u>
- Opium alkaloids can be sub-classified into 3 main groups with different basic nuclei:

- 1.Phenanthrene alkaloids: they act primarily on the CNS to produce depressant effect & they stimulate the contraction of the smooth muscles e.g. morphine, codeine, thebaine
- 2.Benzylisoquinoline alkaloids: these have little action on the CNS but mainly act as antispasmodic (smooth muscles relaxant) e.g. papaverine & noscapine.
- 3.Phenylethylamine alkaloids e.g. narceine
- **Phanathrene derivatives:**

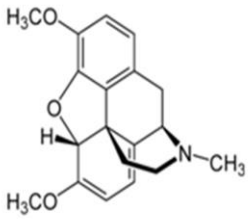


The structure contain:

- benzene ring
- phenolic OH
- N-CH_3 (tertiary amine)
- ether linkage.
- If OH at position-3 is changed to OCH_3we get codeine, & if the other OH is changed to OCH_3 with changing of the double bonds we end up with thebaine.



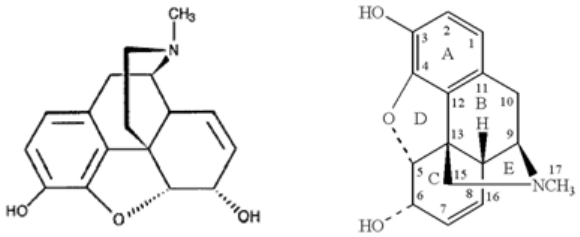
codeine



Thebaine

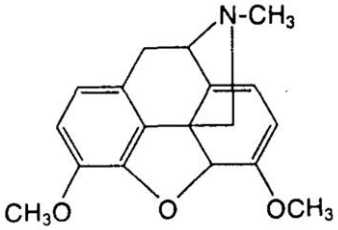
- ***Alkaloids of opium:*** **Morphine**
- It is the most important of the opium alkaloids.
- Morphine & related alkaloids are derivatives of phenanthrene.
- The molecule contains a phenolic & an alcoholic hydroxyl group.

- Morphine & its salts are classified as narcotic analgesics; they are strong hypnotics & narcotics.
- Their use induces nausea, vomiting, constipation, & habit forming.



Morphine

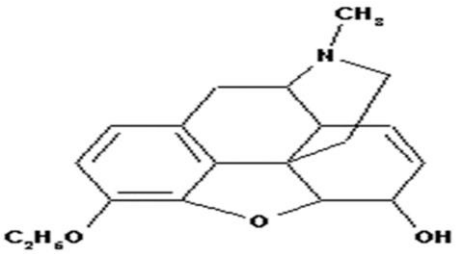
- **Codeine**
- Codeine & its salts are narcotic analgesics & antitussive.
- Although its action is similar to that of morphine but codeine is less toxic & less habit forming.
- **Thebaine**
  It is a phenanthrene derivative used as a CNS stimulant.

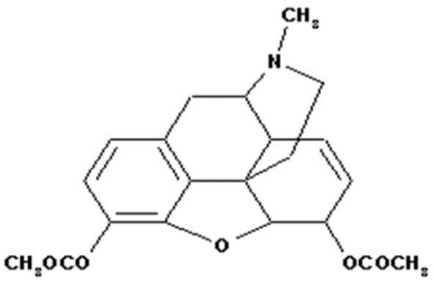


- **Ethyl morphine (dionine):**

  It is used to less extent as codeine.

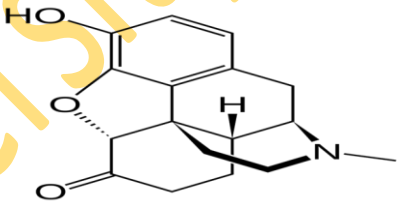
  is formed by the ethylation of phenolic OH of morphine, it is used in ophthalmology as analgesic.



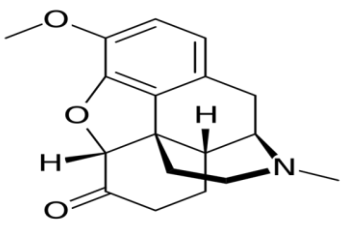
- **Diacetyl morphine (heroine)**
- It is formed by acetylation of morphine.
- It is very toxic & expensive.
- It is 100 times stronger than morphine.
- It is a drug of addiction.
- Heroin is sometimes available in free base form, dulling the sheen and consistency to a matte-white powder.
- Because of its lower boiling point, the freebase form of heroin is also smokable.
- 

heroine

Hydromorphone, also known as dihydromorphinone: prepare by reducing morphine in HCL solution (one of OH group replaced by ketone group and adjacent double bond is removed) , this drug is a powerful narcotic analgesic & tends to strongly depress the respiratory mechanism



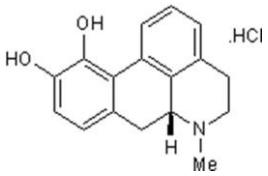
Hydrocodone, also known as dihydrocodeinone, bears the same relation to codeine as hydromorphone dose to morphine, used mainly as a cough suppressant agent.



Apomorphine

Prepared by heating morphine in a sealed tube with HCl.

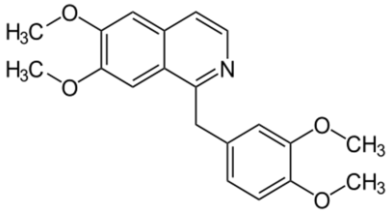
It is used as emetic & particularly valuable in cases of poisoning.



Papaverine

It is a derivative of benzylisoquinoline

It is a smooth muscle relaxant.



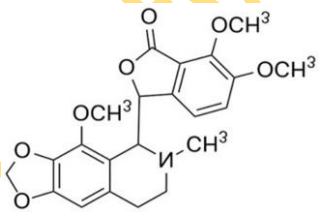
Noscapine

It is commonly called narcotine.

It is also a derivative of benzyl isoquinoline.

It has no narcotic properties & therefore sometimes called anarcotine.

It is used as anti-tussive.

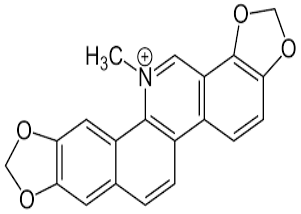


Pantopon:

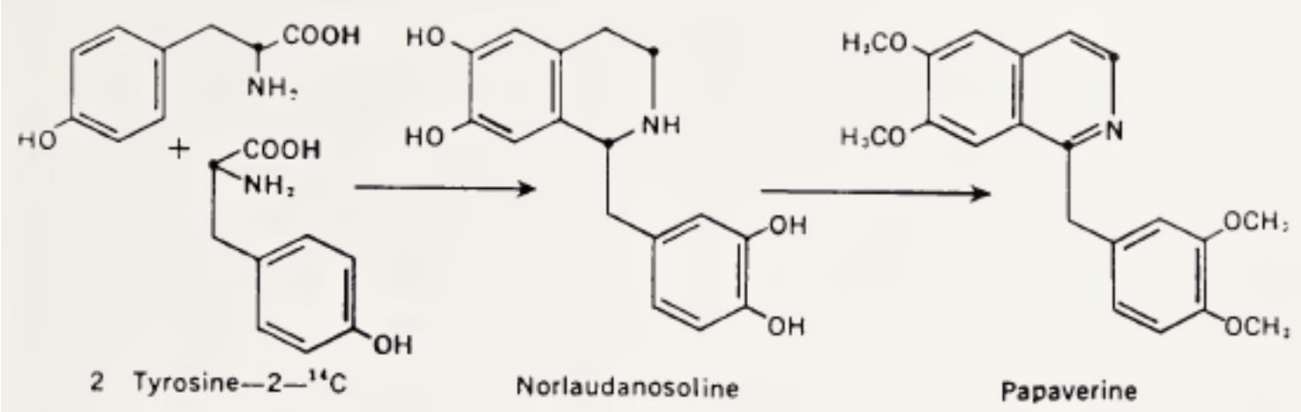
- It refers to a preparation of the total alkaloids of opium deprived or excluded from any other non alkaloidal material.
- The alkaloids are found in the same proportion as it is found inside the opium drug.
- It contains about 50% morphine.
- It is more preferable to be prescribed than morphine alone because if the synergistic effect.
- Opioid is used for compounds which inhibit the pain reaction within the central nervous system, so: opioid is a psychoactive chemical that works by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the

gastrointestinal tract. The receptors in these organ systems mediate both the beneficial effects and the side effects of opioids. The analgesic (painkiller) effects of opioids are due to decreased perception of pain, decreased reaction to pain as well as increased pain tolerance. The side effects of opioids include sedation, respiratory depression, constipation, and a strong sense of euphoria.

- **Opioid :**
- It refers to the synthetic morphine like compounds.
- Many of these substances offer the same narcotic & pain-relieving properties as morphine, but they are not as habit-forming.
- Others possess cough relieving activity of codeine but are not addictive e.g. morphinan opioids, methadone & meperidine.
- Classification of opioids:
- Natural opiates: morphine, codeine, and thebaine.
- Semi-synthetic opioids: created from either the natural opiates or morphine esters, such as hydromorphone.
- Fully synthetic opioids: such as pethidine, tramadol
- Although the term *opiate* is often used as a synonym for *opioid*, the term *opiate* is properly limited to the natural alkaloids found in the resin of the opium poppy *(Papaver somniferum)*, while *opioid* refers to both opiates and synthetic substances, as well as to opioid peptides.
- **Sanguinaria (blood root):**
- It consists of the dried rhizomes & roots of *Sanguinaria canadensis* F: Papaveraceae.
- It contains the benzyl phenanthridine alkaloids sanguinarine, chelerythrine, protopine.
- Sanguinarine & chelerythrine although they are colorless, form red & yellow salts respectively.
- The drug also contains red resin & starch.
- Sanguinaria is mainly used as ingredient of compound white pine syrup.
- Sanguinarine as colchicine, causes doubling of the chromosomes in the cell.



Sanguinarine

- **BIOSYNTHESIS OF ISOQUINOLINE ALKALOIDS**
- Although the isoquinoline alkaloids possess relatively complex structures, the basic biosynthetic reactions which account for their formation in plants are relatively simple. These compounds result from the condensation of a phenylethylamine derivative with a phenylacetaldehyde derivative. Both of these moieties are derived from phenylalanine or tyrosine.
- Administration of tyrosine-2-14C to Papaver somniferum resulted in the formation of papaverine labeled in corresponding positions. Norlaudanosoline is probably an intermediate in this reaction.
- 

Biosynthesis of papaverine.

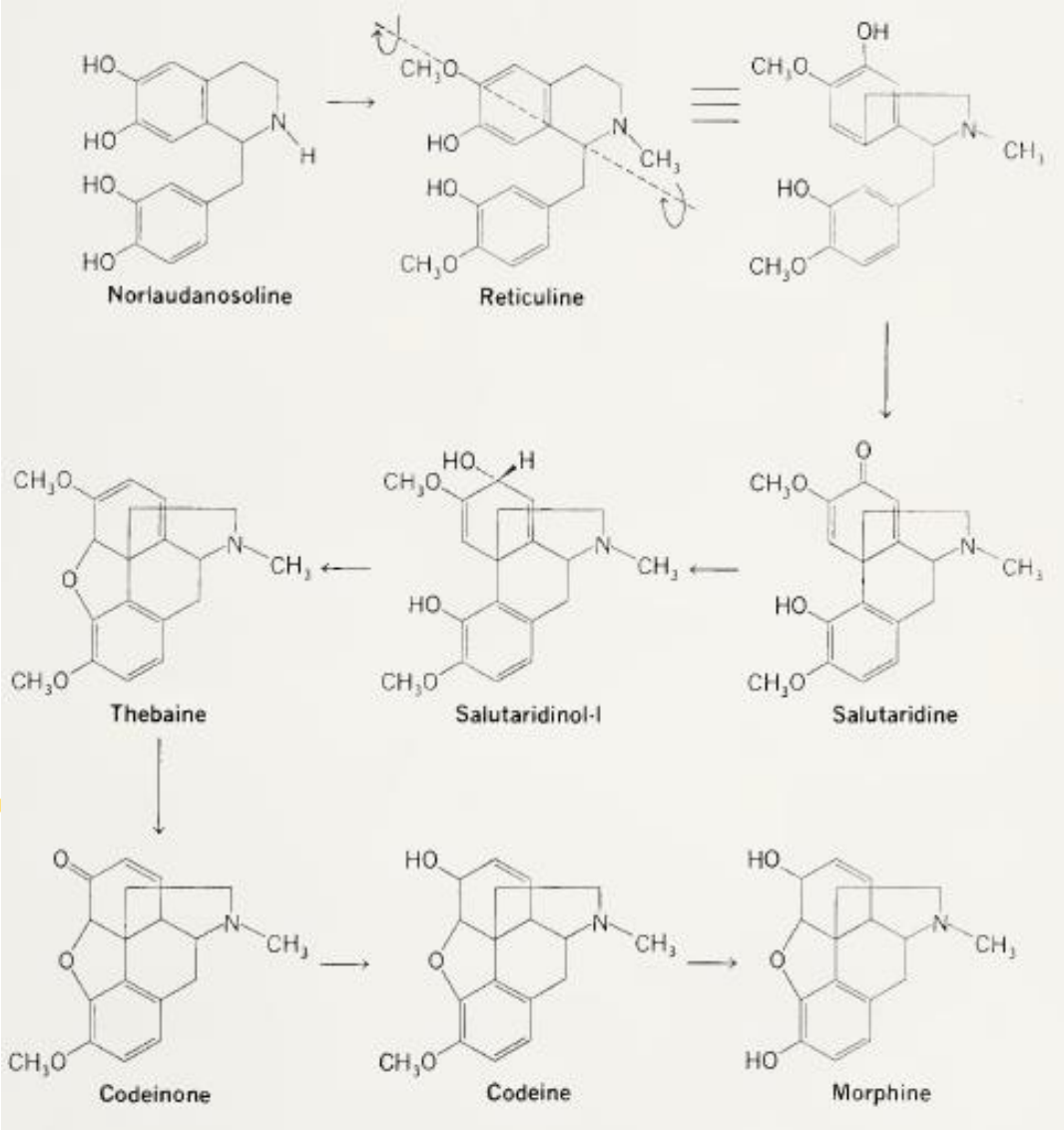
Morphine is also formed from two molecules of tyrosine. This medicinally important alkaloid is derived from a benzyl- isoquinoline metabolite. The biosynthesis of morphine and related alkaloids has been studied extensively, and these experiments provide some of the most complete and detailed observations available for any secondary plant constituent. The biosynthetic pathway starting with nor laudanosoline and leading to morphine.

A key feature of this pathway is the enzymatically controlled methylation pattern which gives rise to reticuline; this facilitates formation of the dienone, salutaridine, which is the first intermediate with a phenanthrene nucleus.

Another interesting aspect of this pathway is the biosynthetic relationship of thebaine, codeine, and morphine; stepwise demethylation of the therapeutically unimportant thebaine leads first to the relatively mild analgesic codeine and then to the potent narcotic morphine.

P. somniferum has a highly evolved and useful secondary metabolism which culminates, at least from the therapeutic viewpoint, in morphine. P. bracteatum, a thebaine-producing poppy, appears to lack any significant demethylation capability; this feature is not only useful for biosynthetic studies, but it has recently become commercially significant.

Since thebaine can be converted to codeine semisynthetically, a source of the latter alkaloid is assured without concomitant production of morphine which is more subject to abuse by drug addicts. These two species emphasize the subtle metabolic difference which so frequently separates useful plants from those of only scientific interest.

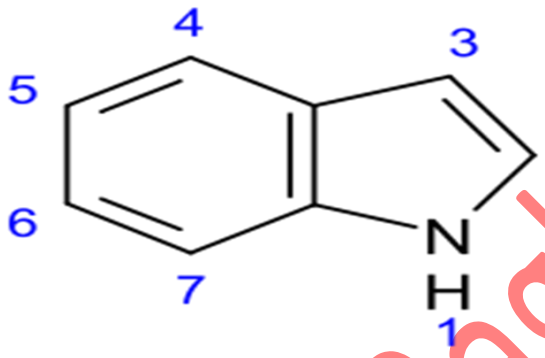


Biosynthesis of morphin

Indole alkaloid:

Indole alkaloids are a class of alkaloids containing a structural moiety of indole.

Many of them possess significant physiological activity and some of them are used in medicine. The amino acid tryptophan is the biochemical precursor of indole alkaloids



Classification

Depending on their biosynthesis, two types of indole alkaloids are distinguished; isoprenoids and non-isoprenoids. The latter include terpenoid structural elements, synthesized by living organisms from dimethylallyl pyrophosphate (DMAPP) and/or isopentenyl pyrophosphate (IPP):

Non-isoprenoid:

-Simple derivatives of indole

-Simple derivatives of β-carboline

-Pyrroloindole alkaloids

Isoprenoid:

-hemiterpenoids: ergot alkaloids

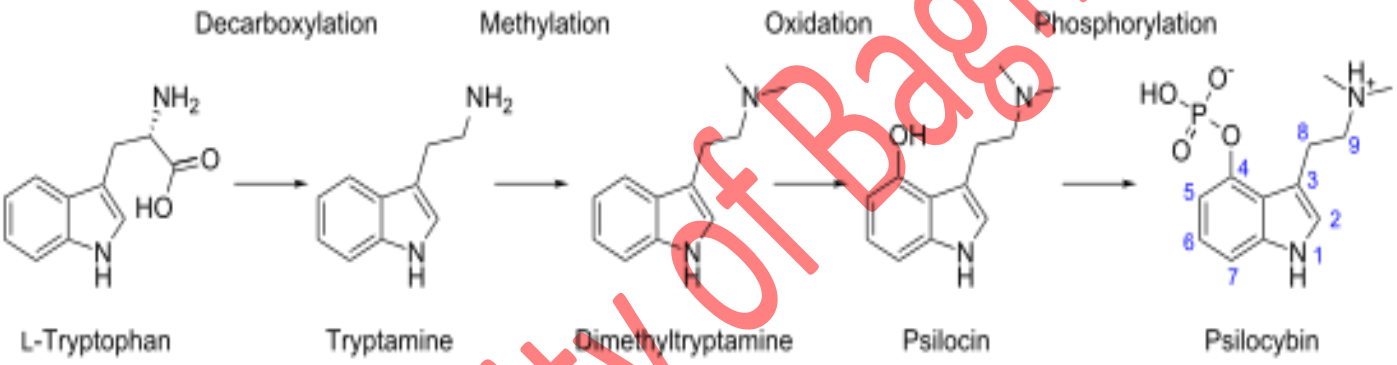
-monoterpenoids.

Non-isoprenoid indole:

Simple indole:

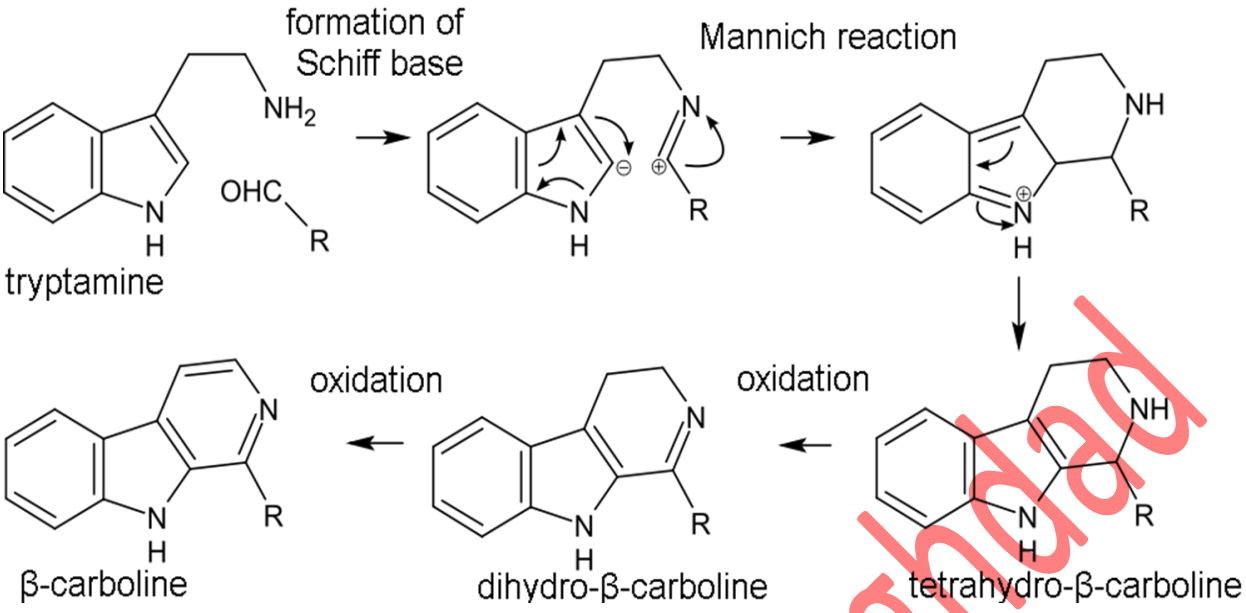
One of the simplest widespread indole derivatives are the biogenic amines tryptamine and 5-hydroxytryptamine(serotonin). Although their assignment to the alkaloid is not universally accepted, they are both found in plants and animals. Tryptamine skeleton is part of the vast majority of indole alkaloids so Dimethyltryptamine (DMT), psilocin and its phosphorylated psilocybin also simplest derivatives of tryptamine.

the first synthesis step is decarboxylation of tryptophan to form tryptamine. Dimethyltryptamine (DMT) is formed from tryptamine by methylation with the participation of coenzyme of S-adenosyl methionine (SAM). Psilocin is produced from dimethyltryptamine by oxidation and is then phosphorylated into psilocybin.



Some simple indole alkaloids do not contain tryptamine such as gramine and glycozoline.

β-carboline : Biosynthesis of β-carboline alkaloids occurs through the formation of Schiff base from tryptamine and aldehyde (or keto acid) and subsequent intramolecular Mannich reaction, where the C(2) carbon atom of indole serves as a nucleophile. Then, the aromaticity is restored via the loss of a proton at the C(2) atom. This type includes harmine, harmaline.



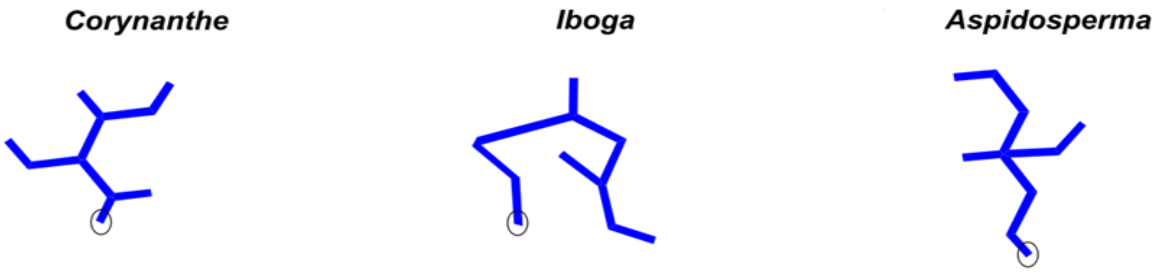
Pyrolo-indole alkaloids

Form small group of tryptamine derivatives. They are produced by methylation of indole nucleus at position 3 and subsequent nucleophilic Addition at C2 with the closure of ethylamino group in to a ring example physostigmine

Isoprenoid indole alkaloids:

Include tryptophane or tryptamine and isoprenoid building blocks derived from IPP and DMAPP e.g. : ergot alkaloids and vinca alkaloids .

three general mono terpenoids skeletons give rise to most of complex indole alkaloids : **aspidosperma, corynanthe and ibogo**



One of the most important plants containing indole alkaloids:

Rauwolfia:

Is the dried root of ***Rauwolfia serpentin*** of the family Apocynaceae. It is native to South and East Asia. It contains 3 type :

1. Weakly basic indole alkaloids e.g. Reserpine Which is used as antihypertensive and tranquilizer other e.g. : Ajmalicine
2. Indoline alkaloids of intermediate basicity e.g.: Ajmaline.
3. Strong anhydronium bases e.g. Serpentine.

Rauwolfia alkaloids, ajmaline, reserpine and serpentine are derived from tryptophan and corynanthe-type monoterpenoid precursor as shown:

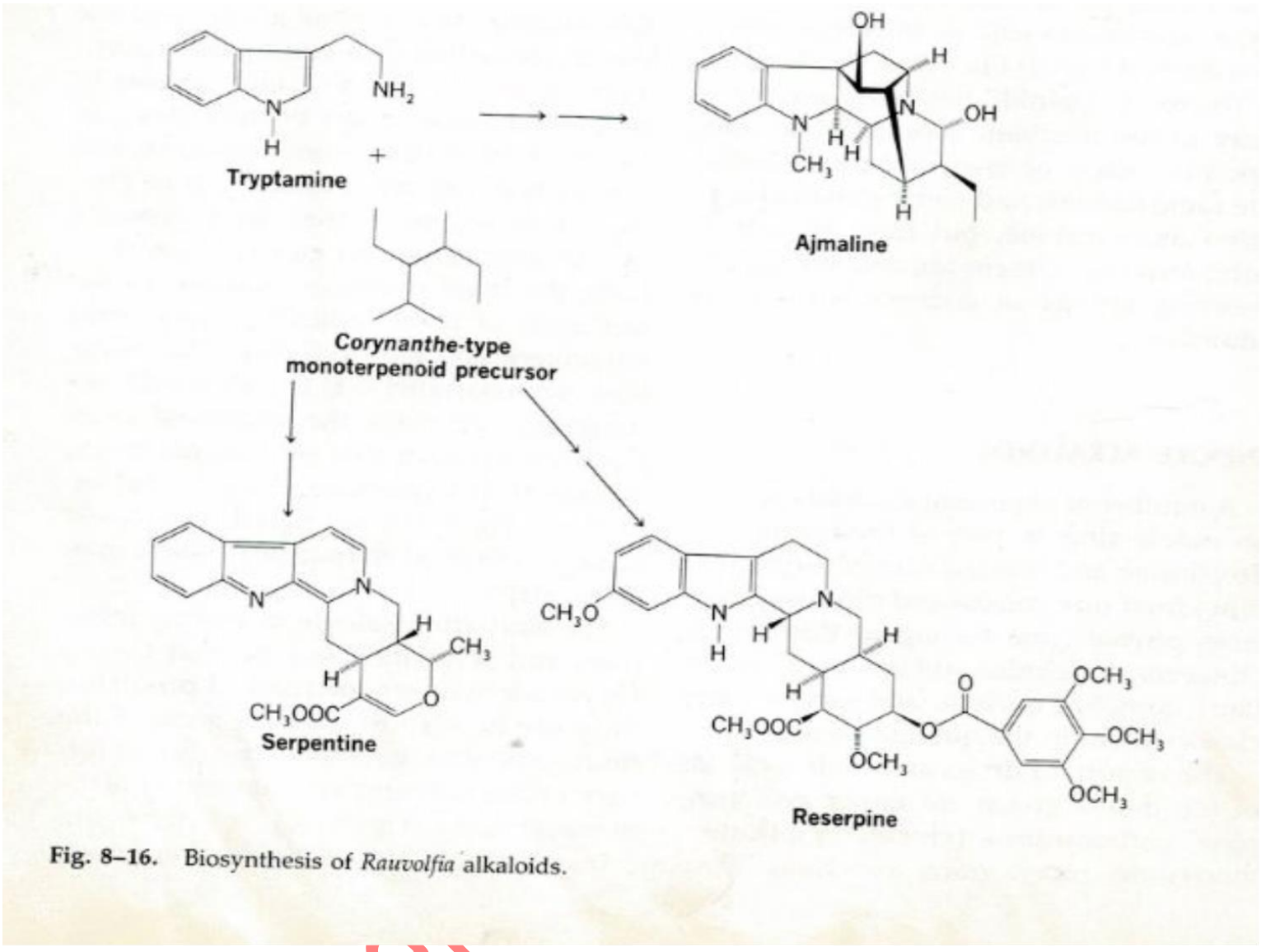
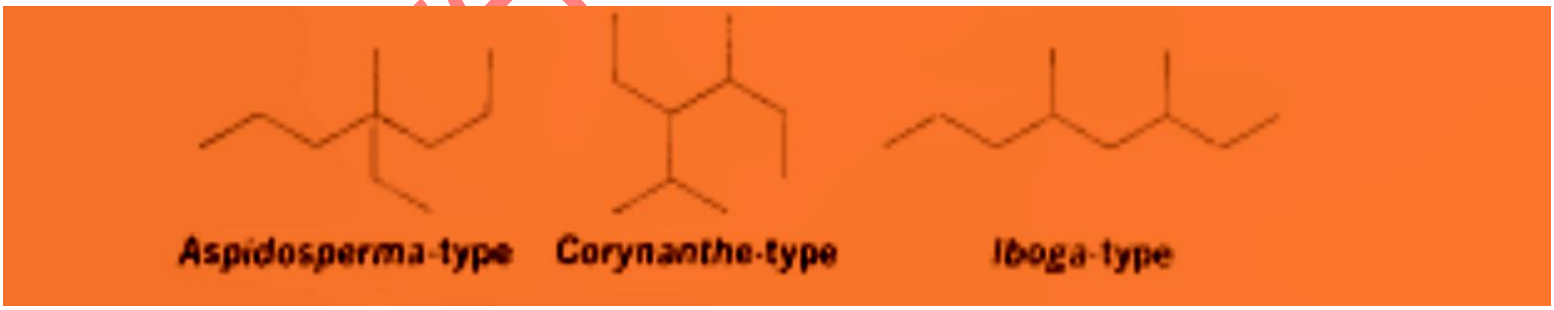
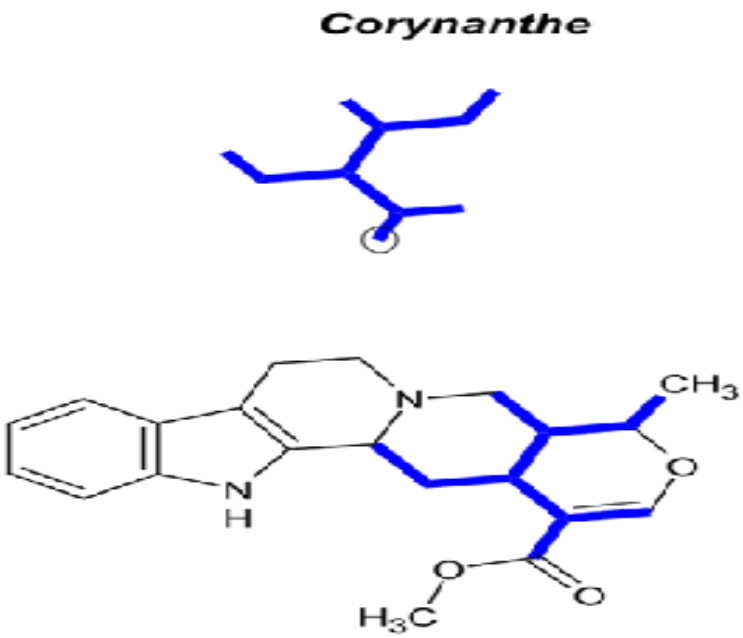


Fig. 8–16. Biosynthesis of *Rauvolfia* alkaloids.



Carbon skeletons of the general types of monoterpenoid precursors of indole alkaloids.



Ajmalicine

Reserpine was widely used as an antihypertensive drug. he antihypertensive actions of reserpine are largely due to its anti-noradrenergic effects, which are a result of its ability to deplete catecholamines from peripheral sympathetic nerve endings. These substances are normally involved in controlling heart rate, force of cardiac contraction and peripheral vascular resistance. Its sedative and tranquilizing properties are thought to be related to depletion of amines in the CNS.

Catharanthus roseus or Vinca F. Apocynaceae:

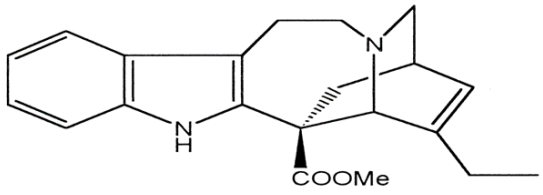
More than 70 different alkaloids have been isolated from Catharanthus roseus they are generally indole and dihydroindole derivatives some of which occur in other members of the apocynaceae these include ajmalicine , serpentine. the alkaloids with anti-neoplastic activity belong to a class of dimeric indole - dihydroindole derivatives . Two of them are available at present as prescription Drugs : Vincristine & Vinblastine.

mechanism of action:

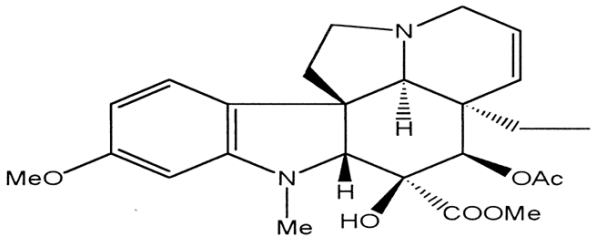
The most characteristic effect of these drugs is the arrest of cell division at metaphase. Tubulin is a structural protein that polymerizes to microtubules. The cell cytoskeleton and mitotic spindle, among other things, are made of microtubules. *Vincristine* & Vinblastine bind to tubulin dimers, inhibiting assembly of microtubule structures. Disruption of the microtubules arrests mitosis in metaphase. Therefore, the

vinca alkaloids affect all rapidly dividing cell types including cancer cells, but also those of intestinal epithelium and bone marrow

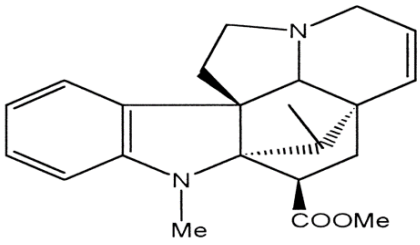
The main side-effects of vincristine are peripheral neuropathy, hyponatremia, constipation, and hair loss.



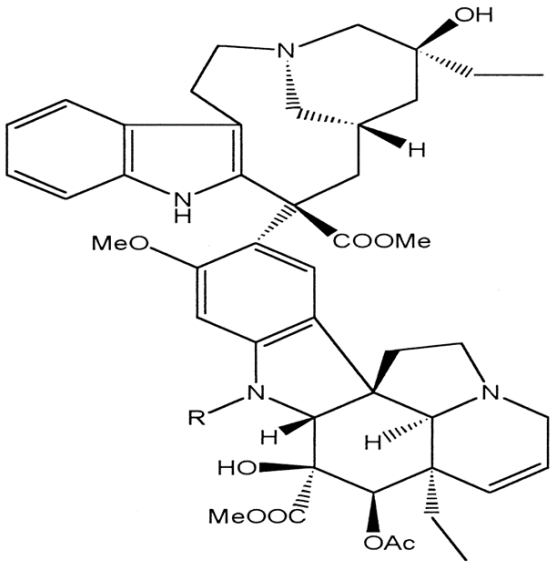
catharanthine



vindoline



vindolinine



R=CHO : vincristine
R=Me : vincaleukoblastine

Vinblastine (**VBL**), sold under the brand name **Velban** , is used to treat a number of types of cancer . This includes Hodgkin's lymphoma, non-small cell lung cancer, bladder cancer, brain cancer, melanoma, and testicular cancer. It is given by injection into a vein.

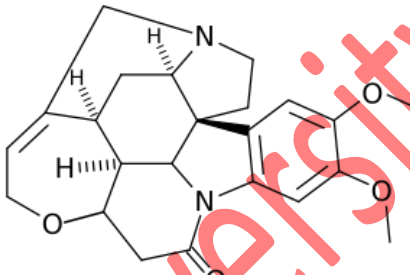
Most people experience some side effects. Commonly it causes a change in sensation, constipation, weakness, loss of appetite, and headaches Severe side effects include low blood cell counts and shortness of breath.

Vincristine, also marketed under the brand name **Oncovin** , is a chemotherapy medication used to treat a number of types of cancer. This includes acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin's disease, neuroblastoma, and small cell lung cancer among others. It is given intravenously.

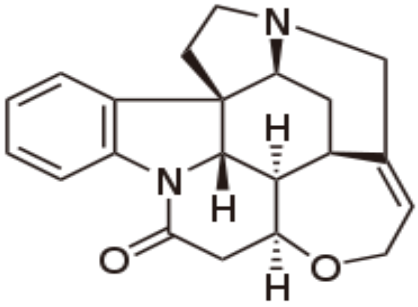
Most people experience some side effects from vincristine treatment. Commonly it causes a change in sensation, hair loss, constipation, difficulty walking, and headaches.

Nux-vomica: It is the dried ripe seeds of *Strychnos nux-vomica* F: Loganiaceae.

The strychnine tree (Strychnos nux-vomica L.) also known as nux vomica, poison nut, semen strychnos , is adeciduous tree native to India, and southeast Asia. Strychnos is a Greek name for a number of poisonous plants; nux-vomica is from 2 Latin words & means a nut that causes vomiting. It is a major source of the highly poisonous, intensely bitter alkaloids strychnine and brucine, derived from the seeds inside the tree's round, green to orange fruit. The seeds contain approximately 1.5% strychnine, and the dried blossoms contain 1.0%. However, the tree's bark also contains brucine and other poisonous compounds.



Brucine



Strychnine

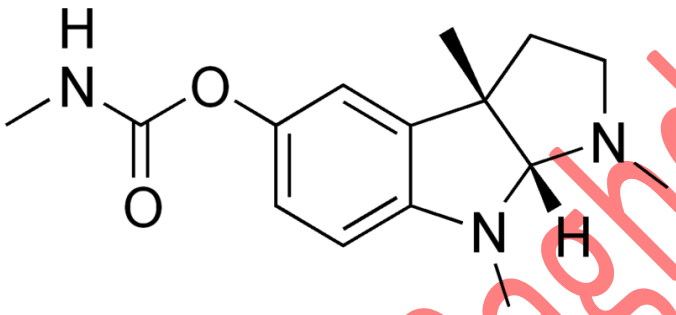
Biosynthetic precursor is tryptophan.

The use of strychnine is highly regulated in many countries, and is mostly used in baits to kill feral mammals, including wild dogs, foxes, and rodents. It is a central stimulant, increases the tone of the skeletal muscles. Most accidental poisoning is by breathing in the powder or by absorption through the skin.

Brucine, which is less toxic than strychnine, is used commercially as an alcohol denaturant. Brucine is dimethoxy strychnine.

Physostigma or Calabar bean

Is the dried ripe seed of *Physostigma venenosum*, F. Leguminosae a native of tropical Africa, Calabar bean contains physostigmine , a reversible cholinesterase inhibitor alkaloid. Physostigmine acts by interfering with the metabolism of acetylcholine. It is a covalent (reversible - bond hydrolyzed and released) inhibitor of acetylcholinesterase, the enzyme responsible for the breakdown of acetylcholine in the synaptic cleft of the neuromuscular junction.



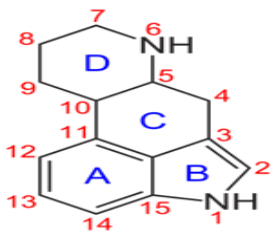
Biosynthesis precursor is from tryptophan.

Physostigmine is used in the eye, increases the cholinergic activity leads to miosis, contraction of the ciliary muscles & a decreases in the intraocular pressure. It is employed in ophthalmology to treat glaucoma.

Ergot

Refers to a group of fungi of the genus Claviceps. *Claviceps purpurea* developed on plants of rye *Secale cereale* F. Gramineae This fungus grows on rye and related plants, and produces alkaloids that can cause ergotism in humans and other mammals who consume grains contaminated with its fruiting structure (called ergot sclerotium).

Main ergot alkaloids: All ergot alkaloids are derivatives of ergoline base (a tetra cyclic structure)

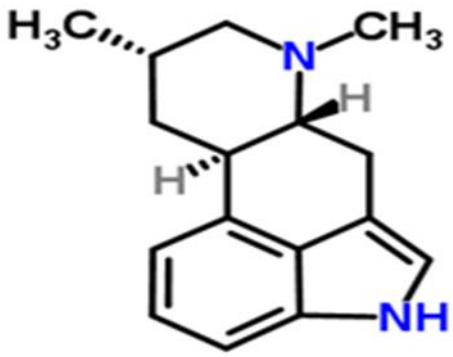


Ergoline base

Ergot alkaloids are classified into:

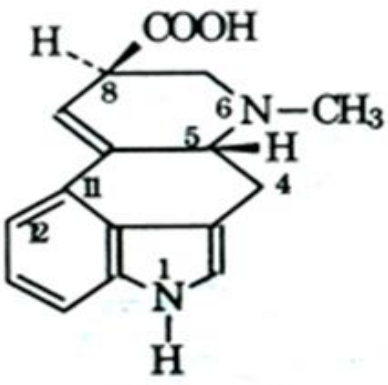
1.Clavine derivatives:

A variety of modifications to the basic ergoline are seen in nature, e.g. agroclavine, elymoclavine, lysergol. Those deriving from dimethyl ergoline are referred to as clavines. Those are alkaloids found in ergot but are pharmacologically inactive.

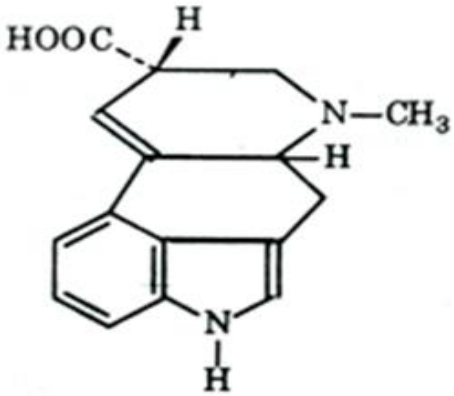


Dimethyl ergoline

2. Lysergic acid-amide derivatives:



Acid lysergic



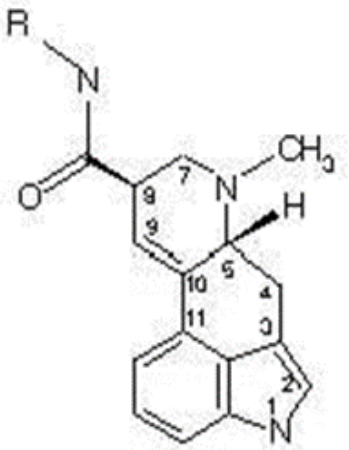
Acid isolysergic

The difference between these two groups is the substituent at position 8. In clavine derivatives C8 contains CH2R (R=H or OH or OCOCH3) while lysergic acid contains COOH.

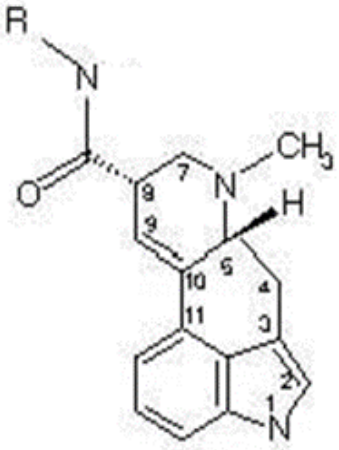
Iso lysergic derivatives are pharmacologically inactive.

Iso lysergic acid is strongly dextrorotatory (+), while lysergic acid is levorotatory (-).

Fresh alkaloids are always levo, upon storage it may isomerizes into iso lysergic acid (dextro).



Lysergic acid amide



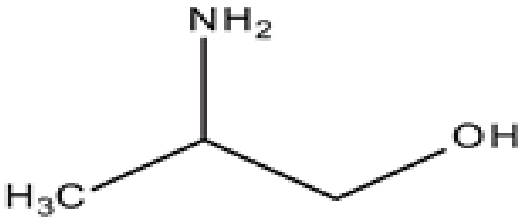
Isolysergic acid amide

Lysergic acid amide derivatives could be further classified into:

1.R= cyclic tri peptide (peptide group) e.g. ergotamine (inine) (inine are derivatives of iso lysergic acid), ergocine (inine). Both are called ergotamine group, they are water soluble.

Ergocristine (inine), ergocryptine (inine), ergonine (inine), these are called ergotoxine group & are also water insoluble.

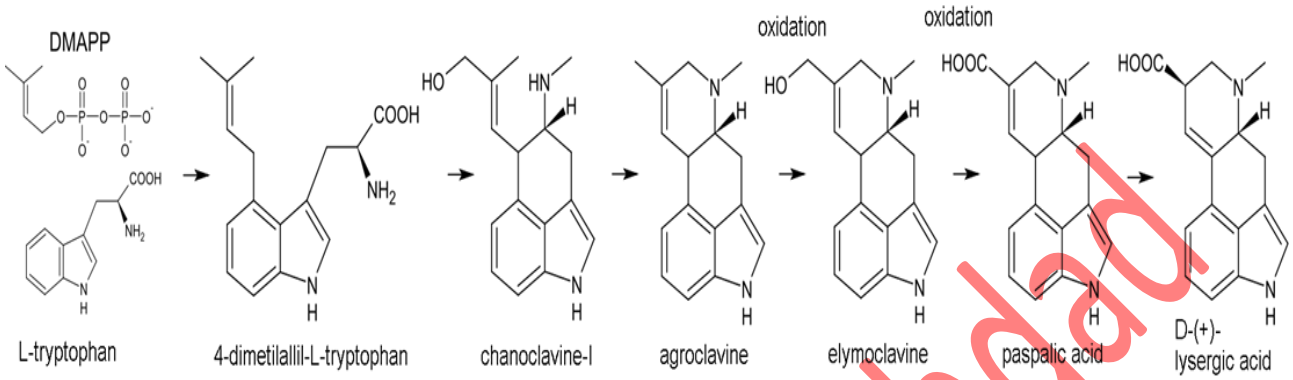
2.R= L-2-amino propanol (alkanol amide), i.e.



E.g. ergometrine (ergonovine) (inine), called ergometric group & are water soluble.

Biosynthesis of lysergic acid:

Lysergic acid is biosynthesized from tryptophan & dimethyl allyl pyro phosphate.



Pharmacological activities of ergot can be classified into:

1.Direct action (direct peripheral action):

a.Uterine contraction

b.Vaso constriction

2.Indirect peripheral action (Humeral i.e. through fluid):

a.Serotonin synergism

b.Adrenergic blocking

3.Central action (central nervous action):

a.Bradycardia , vomiting

b.Syndrome of ergotropic excitation causes mydriasis, hyperglycemia, and hyperthermia.

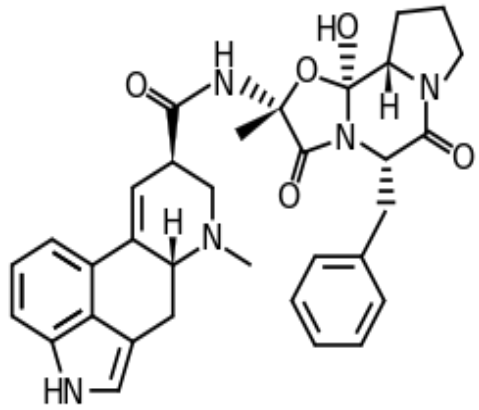
Ergotamine is used in certain headache disorders (migraine).

Ergotoxin group has the same activity like ergotamine but it is more toxic (it is toxic at the therapeutic dose) & so it is not used clinically.

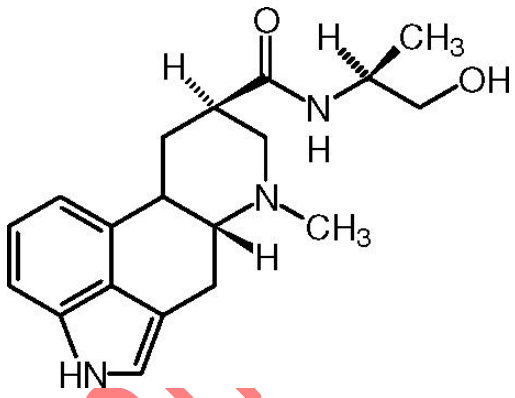
Ergometrine has mainly direct peripheral action & the others are insignificant.

LSD (Diethyl amino lysergic acid):

Preparing lysergic acid with two ethyl groups produce LSD which show increase in the excitation effect of the CNS. It is used for hallucination & for psychoanalysis. LSD is also called lysergic acid diethyl amide.



Ergotamine



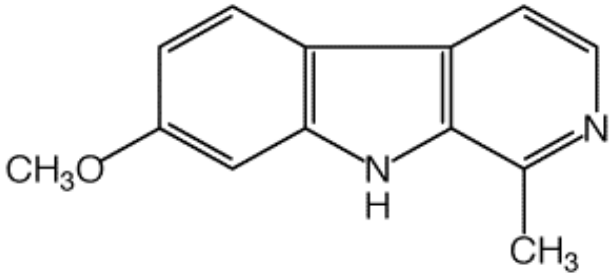
Ergonovine

Harmel:

It is the dried seeds of *Peganum harmala* F: Nitrariaceae.

It contains several alkaloids as harmine, harmane, harmaline, harmalol, others.

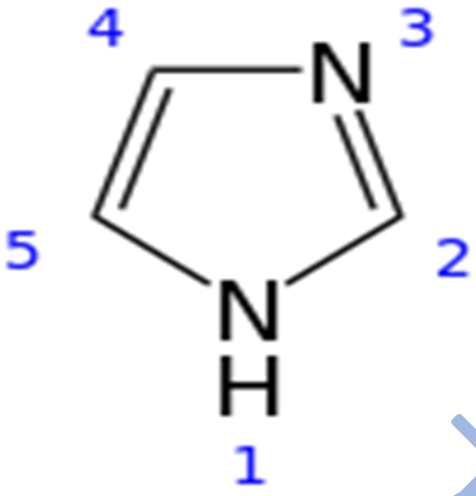
Harmine, is a fluorescent harmala alkaloid belonging to the beta-carboline family of compounds.



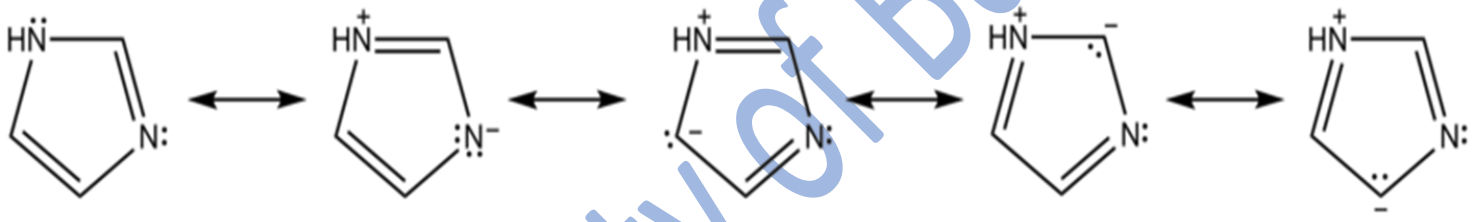
Harmine

Peganum harmala has been used to treat pain and to treat skin inflammations, including skin cancers & as an emmenagogue and abortifacient agent. It is also used as an anthelmintic (to expel parasitic worms). Reportedly, the ancient Greeks used the powdered seeds to get rid of tape worms and to treat recurring fevers (possibly malaria).

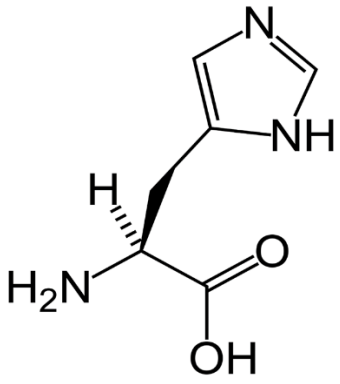
Imidazole alkaloids:



Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms, because the proton can be located on either of the two nitrogen atoms.



The amino acid L-histidine contains an imidazole ring, and is thus the likely precursor of alkaloids containing this ring system.

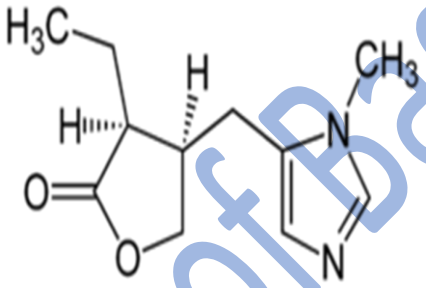


Pilocarpus

Pilocarpus or jaborandi consists of the dried leaflets of *Pilocarpus jaborandi* (Rutaceae) The alkaloid content (0.5–1.0%) consists principally of the imidazole alkaloid pilocarpine . Isomers such as isopilocarpine are readily formed if base or heat is applied during

extraction of the alkaloids. This is a result of enolization in the lactone ring, followed by adoption of the more favorable trans configuration rather than the natural cis. However, the iso alkaloids lack biological activity.

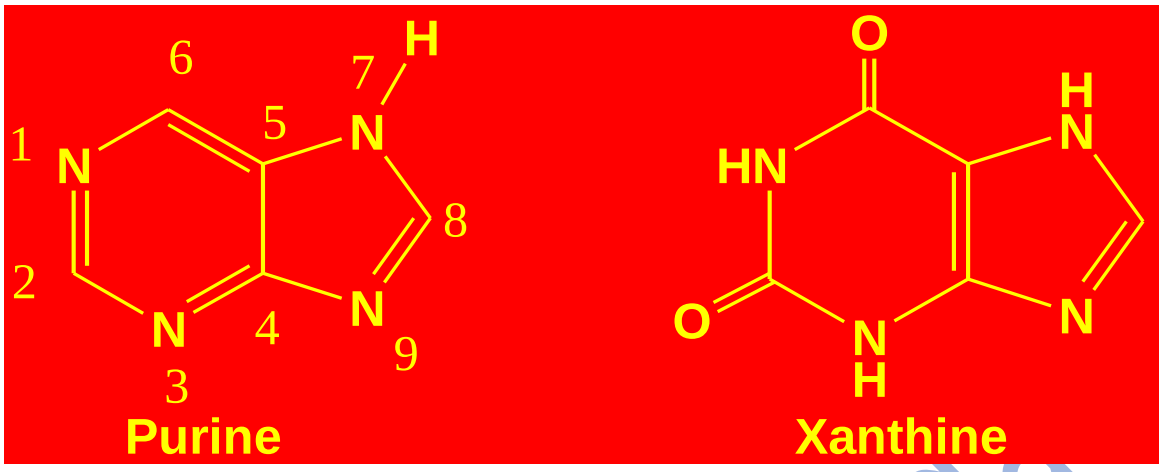
Pilocarpine salts are valuable in ophthalmic practice and are used in eyedrops as miotics and for the treatment of glaucoma. Pilocarpine is a cholinergic agent and stimulates the muscarinic receptors in the eye, causing constriction of the pupil and enhancement of outflow of aqueous humour. Pilocarpine gives relief for both narrow angle and wide angle glaucoma. Pilocarpine is antagonistic to atropine. It has been found that pilocarpine gives relief for dryness of the mouth that results in patients undergoing radiotherapy for mouth and throat cancers. As muscarinic agonists, pilocarpine and analogues are also being investigated for potential treatment of Alzheimer's disease.



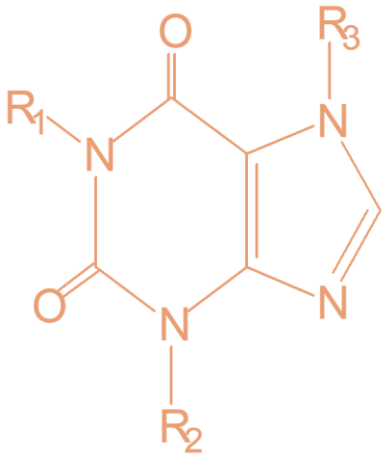
Use of pilocarpine may result in a range of adverse effects, most of them related to its non-selective action as a muscarinic receptor agonist. Pilocarpine has been known to cause excessive sweating, excessive salivation, bronchospasm, increased bronchial mucus secretion, bradycardia, vasodilation, and diarrhea.

Purine (Xanthine) Alkaloids:

- The purines are consisting of **a six-membered pyrimidine** ring fused to **a five-membered imidazole ring**.
- The pharmaceutically important bases of this group are all methylated derivatives of **2,6 dioxy-purine (Xanthine)**. This group includes mainly **Caffeine, theobromine** and **theophylline** alkaloids.
- These alkaloids are weak bases, they give no precipitate with Mayer's reagent.



Caffeine, Theobromine and **Theophylline:**



$R_1=R_2=R_3=CH_3$ Caffeine
$R_1=H, R_2=R_3=CH_3$ Theobromine
$R_1=R_2=CH_3, R_3=H$ Theophylline

- Occurrence:

Tea leaves (2- 5%), Coffee seeds (1-2 %), Cola leaves (2- 3%), Gurana seeds (2.5- 5 %) and Cacao seeds, (0.2- 0.5 %).

- Properties:

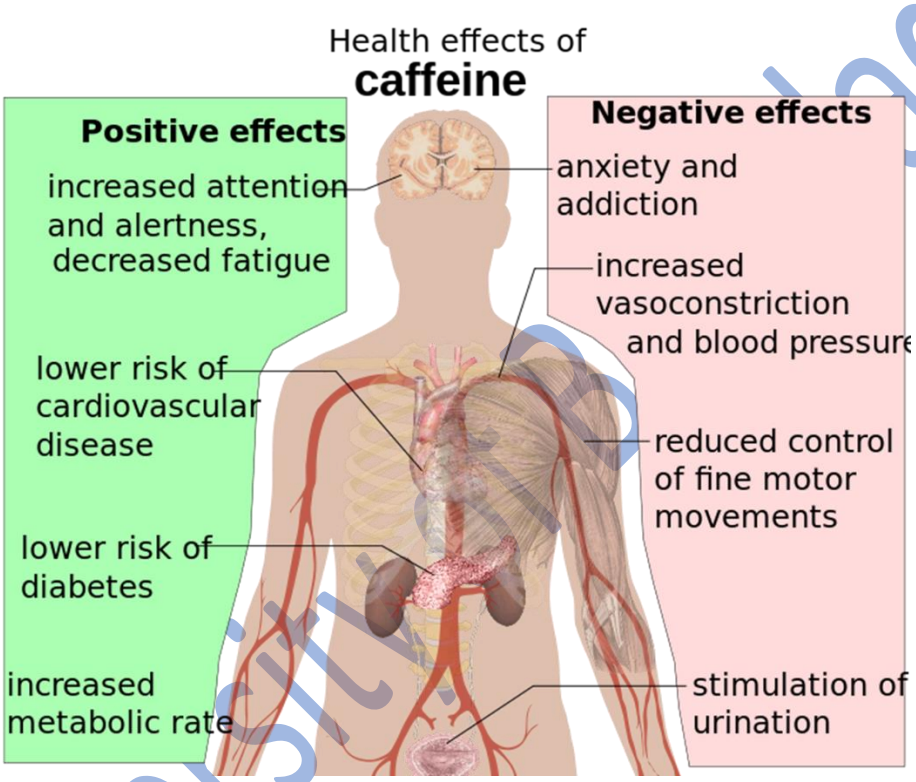
1- Water soluble. 2- Sublimable.

- Uses:

Caffeine has a CNS stimulant effect, it is used mainly to relieve headache.

Inside the body caffeine acts through several mechanisms, but its most important effect is to counteract a substance called adenosine that naturally circulates at high levels throughout the body, and especially in the nervous system. In the brain, adenosine plays a generally protective role, part of which is to reduce neural activity levels. Adenosine acts

as an inhibitor neurotransmitter that suppresses activity in the central nervous system. Consumption of caffeine antagonizes adenosine and increases activity in neurotransmission including acetylcholine, epinephrine, dopamine, serotonin, glutamate, norepinephrine, cortisol, and in higher doses, endorphins which explains the analgesic effect to some users. At very high doses (exceeding 500 milligrams) caffeine inhibits GABA neurotransmission. This evidence explains why caffeine causes anxiety, insomnia, rapid heart and respiration rate.



Theobromine:

Occurrence: Cacao seeds.

- Properties:

1- Sparingly soluble in water. 2- Sublimable. 3- Amphoteric.

.In modern medicine, theobromine is used as a vasodilator (a blood vessel widener), a diuretic (urination aid), and heart stimulant.

- Theobromine increases urine production. Because of this diuretic effect, and its ability to dilate blood vessels, theobromine has been used to treat high blood

pressure and other circulatory problems including arteriosclerosis, certain vascular diseases, angina pectoris, and hypertension.

- Theophylline
- Occurrence: Traces in Tea leaves, mostly synthetic.
- Properties: Sparingly soluble in water.
- Uses: Theophylline and derivatives are smooth muscle relaxant especially in the upper respiratory tract. They used as bronchodilator. Theophylline also act as diuretic.

Color tests:

- Murexide test: (caffeine, theobromine and theophylline).

  Crystals of caffeine + drops of concentrated HCl and traces of $KClO_3$ →evaporated on water bath → red color is produced which turns to violet on exposure to ammonia vapor.

- Tannic acid test: (caffeine and theophylline):

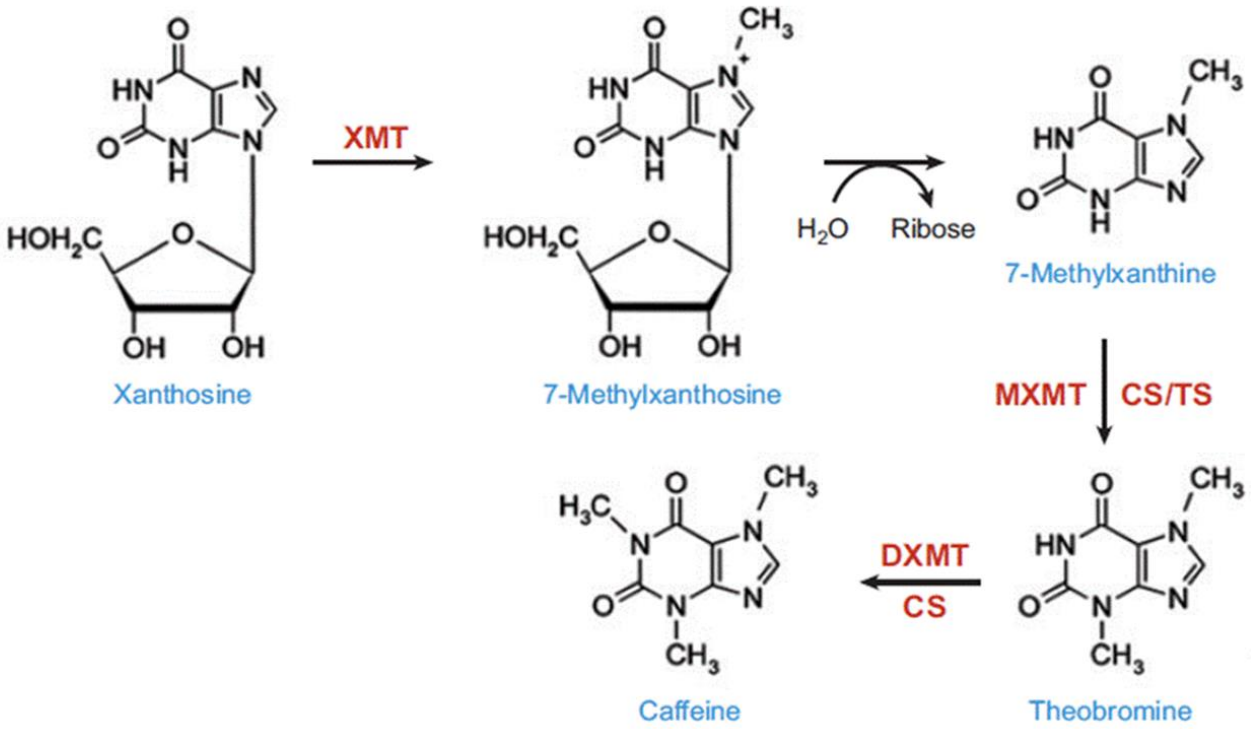
  A concentrated solution of the alkaloid + tannic acid → white precipitate is obtained that dissolves in excess of the reagent.

- Ferrous sulfate test: (theobromine):

  To a solution of the alkaloid + drops of concentrated HCl + few drops of Br_2 water + a drop of $FeSO_4$ + few drops of ammonia → Blue color.

Alkaloid biosynthesis in plant

- purine alkaloids



Amino alkaloids or alkaloidal amines:

General characteristic features:

Proto-alkaloids

Have no nitrogen as the part of the heterocyclic ring (nitrogen atom found in side chain), so it is called atypical alkaloids

Derived from amino acid like phenyl alanine or tyrosine

Physiologically active compounds:

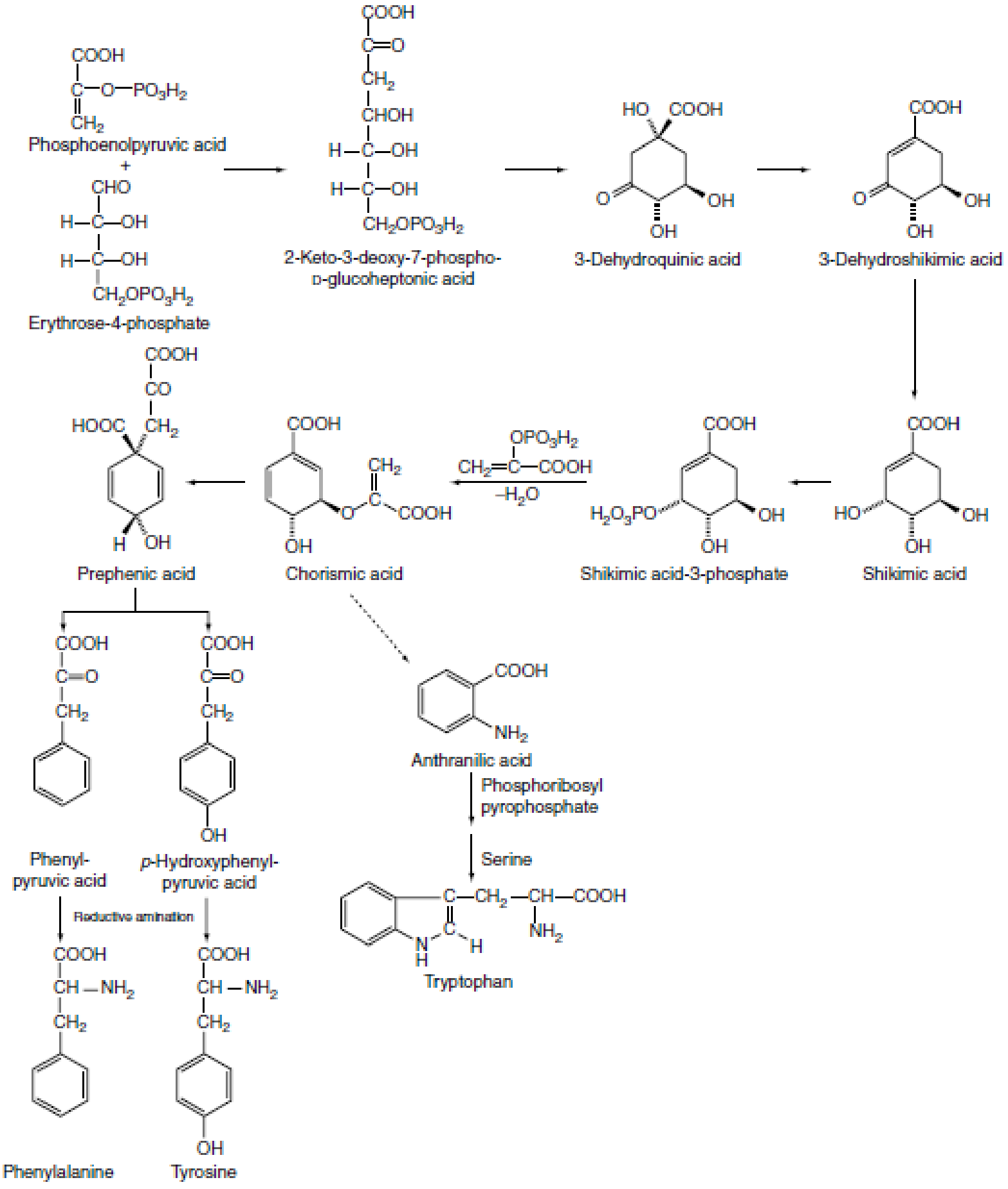
- ❖ Ephedrine (*Ephedra* species)
- ❖ Colchicine (*Colchicum autmnale*)
- ❖ Cathinone (*Catha edulis*).
- ❖ Mescaline (*Lophophora williamsii*).

BIOSYNTHESIS OF AMINO ALKALOIDS:

Amino alkaloids are derived from amino acid through shikimic acid pathway. The pathway finds its route from carbohydrates for the biosynthesis of C6-C3 units (i.e., phenylpropane derivatives) like phenyl alanine and tyrosine.

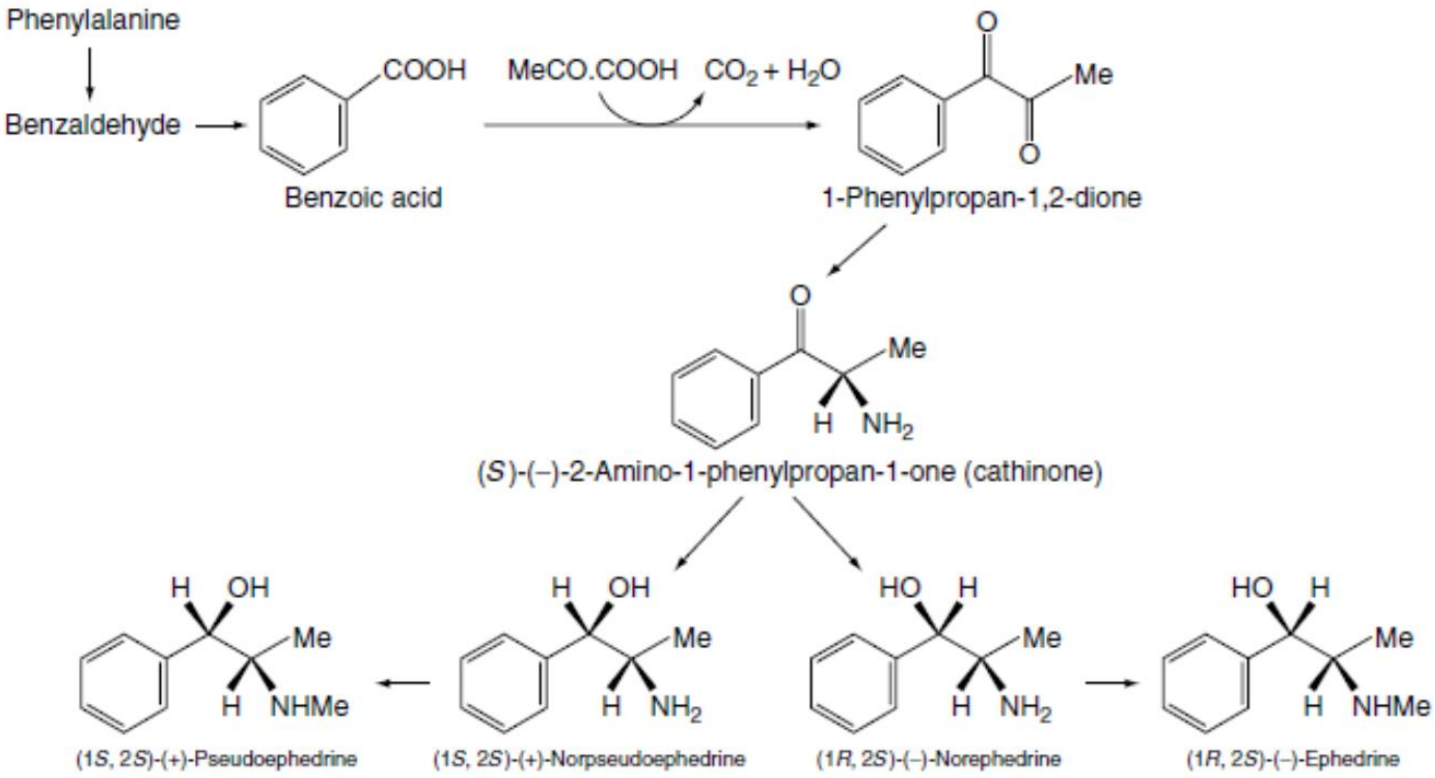
Shikimic acid through a series of phosphorylated intermediates yield chorismic acid which is an important branch-point intermediate. One branch leads to anthranilic acid then to tryptophan. The other leads to prephenic acid which is the last non aromatic compound in the sequence.

Prephenic acid can be aromtized in 2 ways. The first proceeds by dehydration and simultaneous decarboxylation to yield phenyl pyruvic acid, the direct precursor of phenylalanine. The second occurs by dehydrogenation & decarboxylation to give p-hydroxy phenyl pyruvic acid, the precursor of tyrosine.


Phosphoenolpyruvic acid
+
Erythrose-4-phosphate
2-Keto-3-deoxy-7-phospho-D-glucoheptonic acid
3-Dehydroquinic acid
3-Dehydroshikimic acid
Shikimic acid
Shikimic acid-3-phosphate
–H2O
Chorismic acid
Prephenic acid
Anthranilic acid
Phosphoribosyl pyrophosphate
Serine
Tryptophan
Phenyl-pyruvic acid
p-Hydroxyphenyl-pyruvic acid
Reductive amination
Phenylalanine
Tyrosine

Ephedra:

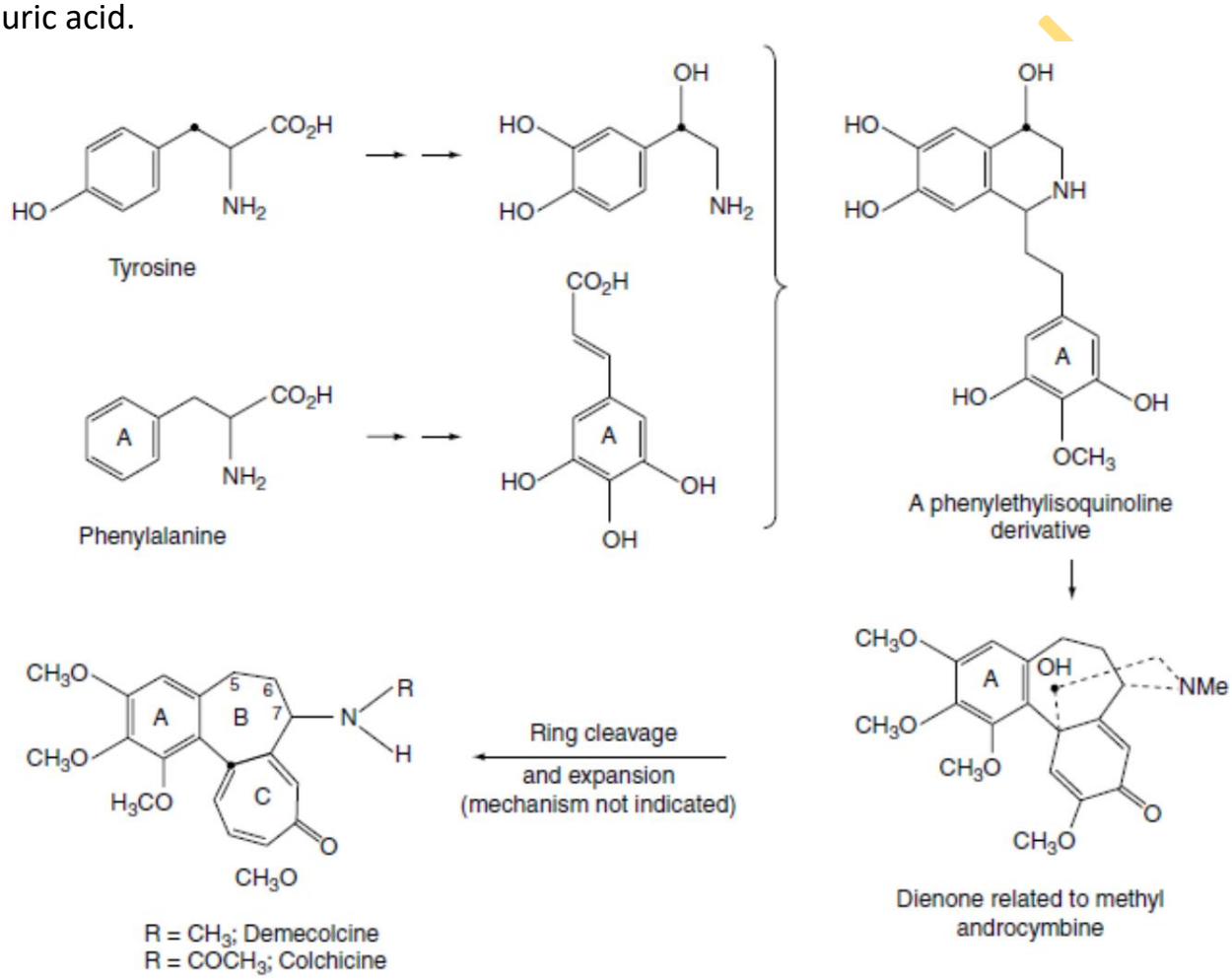
It consists of dried young stems of *Ephedra gerardiana* F. (Ephedraceae). Ephedrine is produced either by extraction of plant material or by chemical procedure or could be produced by fermentation of sugar in the presence of benzaldehyde & methyl amine. By using 13C- and 2H-labelled precursors in feeding experiments have shown that benzoic acid combines with the intact CH_3CO group of pyruvic acid to form ephedrine and related alkaloids with 1-phenylpropan-1,2-dione and (S)-(−)-2-amino-1-phenylpropan-1-one (cathinone) serving as intermediates.



Ephedrine is an adrenergic compound used as Bronchodilator in asthma, it is a potent Sympathomimetic. It excites the sympathetic nervous system cause vasoconstriction, cardiac stimulation & rise in blood pressure. It works mainly by increasing the activity of nor epinephrine (nor adrenaline) on adrenergic receptors. It is used as a stimulant, concentration aid, decongestant, appetite suppressant & to treat hypotension associated with anesthesia also in the treatment of allergic conditions like hay fever.

Colchicum:

It consists of dried ripe seeds and fresh or dried corms of *Colchicum autumnale* Family: Liliaceae. The main alkaloids found in this plant Colchicine which is used in the treatment of gout. Colchicine lacks basicity & does not form a well-defined series of salts as do other alkaloids, it is used in gout to increase the secretion of uric acid.



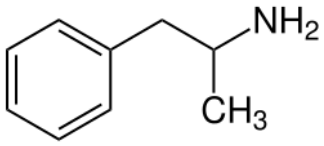
Ring A and carbons 5, 6 and 7 are derived from phenylalanine; the tropolone moiety arises from tyrosine by ring cleavage followed by closure to give a seven-membered ring. In contrast to mold metabolism, acetate does not contribute directly to the tropolone ring but is merely effective in supplying the N-acetyl group. An intermediate formed early in the pathway as the result of union of the two amino acids is a 1-phenylethylisoquinoline derivative.

Khat or Abyssinian tea:

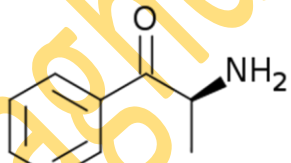
This consists of the fresh leaves of Catha edulis. (Celastraceae).

Khat contains a potent phenylalkylamine alkaloid called (Cathinone). It has pharmacologic properties analogous to those of amphetamine and is of similar potency with a similar mechanism of action. the alkaloid cathinone, a stimulant, cause excitement, loss of appetite, and euphoria.

The World Health Organization (WHO) classified it in 1980 as a drug of abuse that can produce psychological dependence, although the WHO does not consider khat addiction to be a serious problem.

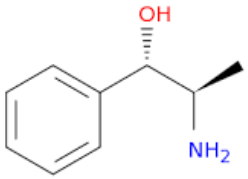


Amphetamine

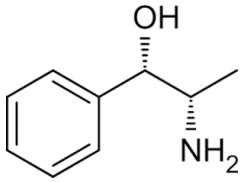


Cathinone

Cathinone is not very stable and breaks down to produce cathine and nor ephedrine. These chemicals belong to the PPA (phenylpropanolamine) family, a subset of the phenethylamines related to amphetamines and the catecholamines epinephrine and norepinephrine.



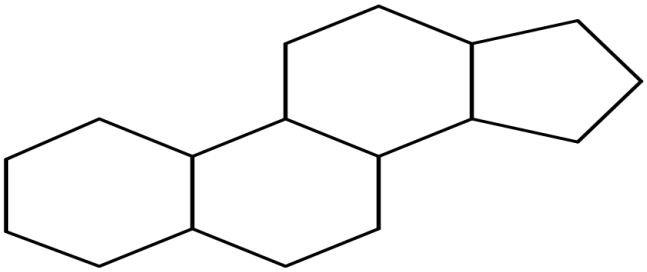
norephedrine



Cathine

Steroidal Alkaloids:

- These contain the **perhydrocyclopentano-phenanthrene skeleton** characteristic of sterols.
- They usually occur in **glycosidal combination** with sugars and thus called **glucoalkaloids** e.g. *Solanum* and *Veratrum* alkaloids.

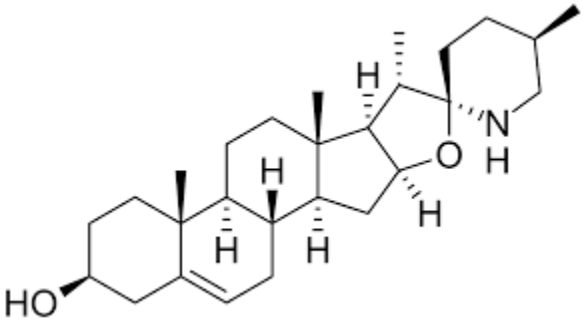


Cyclopentaphenanthrene

1- *Solanum* alkaloids

many plants belonging to *Solanaceae contains several steroidal alkaloids based on C27 cholestane skeleton such as solasodine* , tomatidine, solanidine. These alkaloids usually occur in genus *Solanum (exp. S. nigrum, S. oviculare*)

Solasodine is a poisonous alkaloid chemical compound that found in plants of Solanaceae family . Solasonine and solamargine are glyco alkaloid derivatives of solasodine. Solasodine is teratogenic used as precursor for the production of steroidal compounds like contraceptive pills.



Solasodine

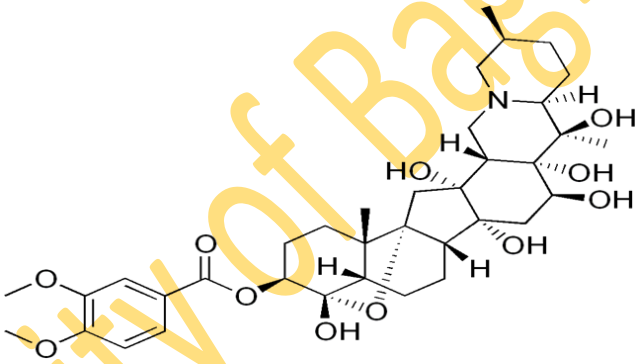
2- *Veratrum* alkaloids (Hellebore)

contain highly toxic steroidal alkaloids that activate sodium ions channels and cause rapid cardiac failure and death if ingested, all parts of plant are poisonous specially root & rhizomes.

They are of 3 types:

1. Group 1 consists of esters of steroidal bases (alkamines) with organic acids like cevadine, germidine, veratridine
2. Group 2 consists of glucosides of the alkamine like pseudo jervin & veratrosine
3. Group 3 consists of the alkamines themselves like germine, jervine, veratramine

The 1st group only is pharmacologically active & used as hypotensive and cardiac depressant and sedative.



veratridine