PharmacognosyIII

Lec. 6 **3rd stage 2nd semester** **Year 23-24**

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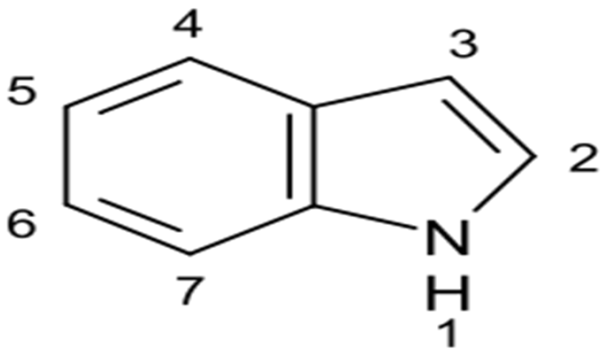
ALKALOIDS

Indole alkaloids



Indole alkaloids

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.

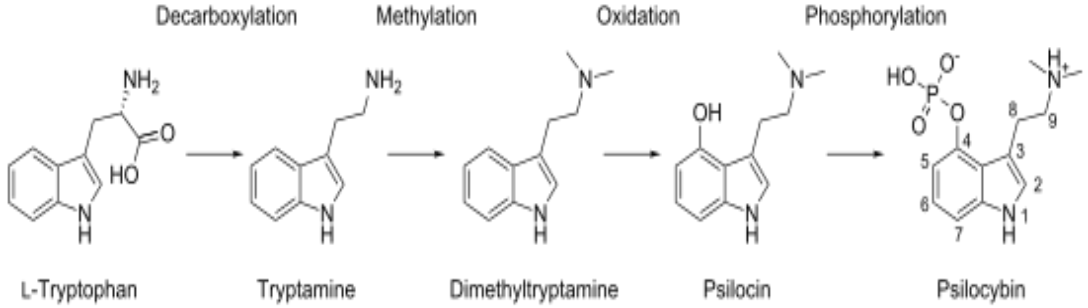
-Hemiterpenoids: ergot alkaloids -monoterpenoids.

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 are also the 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.

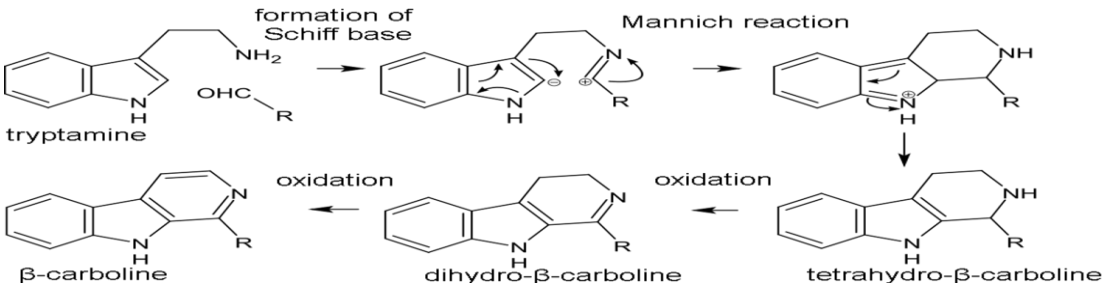


Synthesis psilocybin

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

β-carboline:

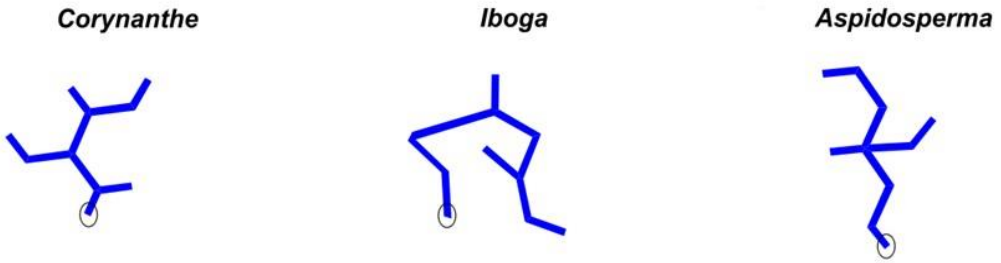
Biosynthesis of β-carboline alkaloids occurs through the formation of Schiff base from tryptamine and aldehyde (or keto acid) and subsequent intramolecular Mannich reaction, where the C(2) carbon atom of indole serves as a nucleophile. Then, the aromaticity is restored via the loss of a proton at the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

1. Weakly basic indole alkaloids e.g. Reserpine which is used as an antihypertensive and tranquilizer 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:

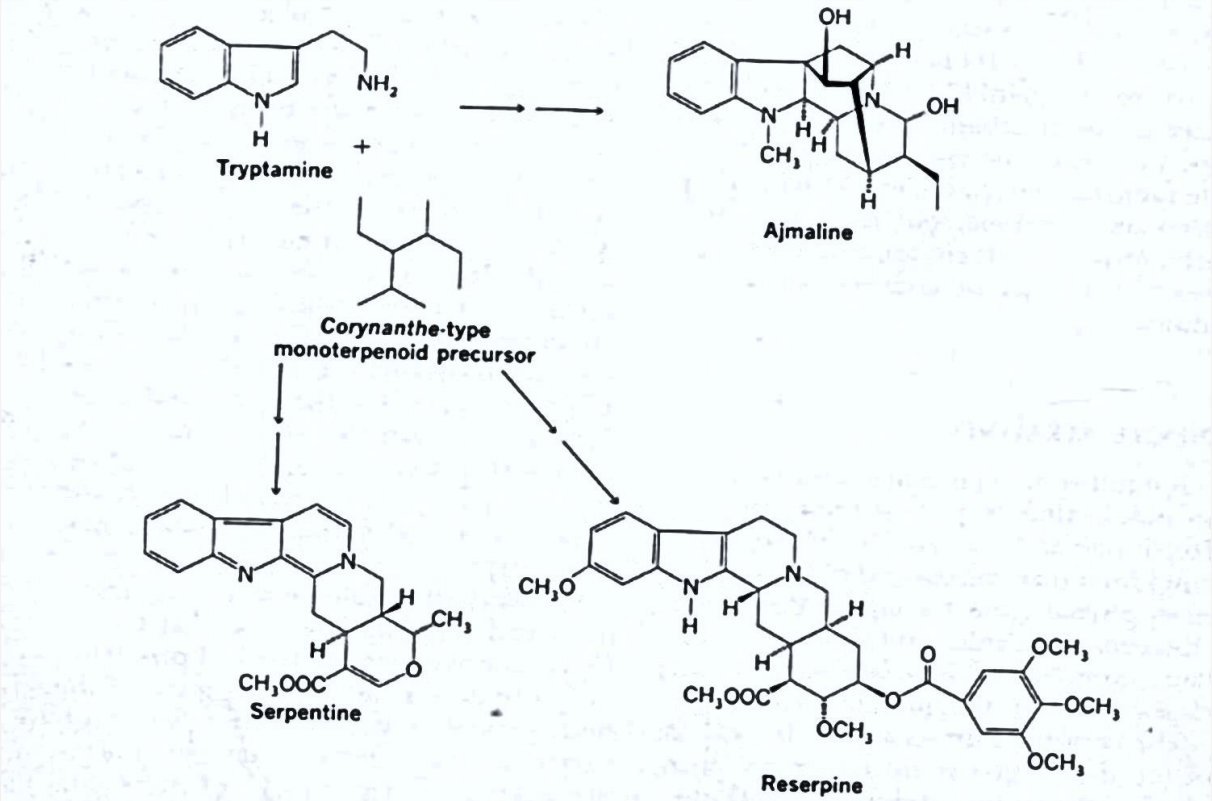
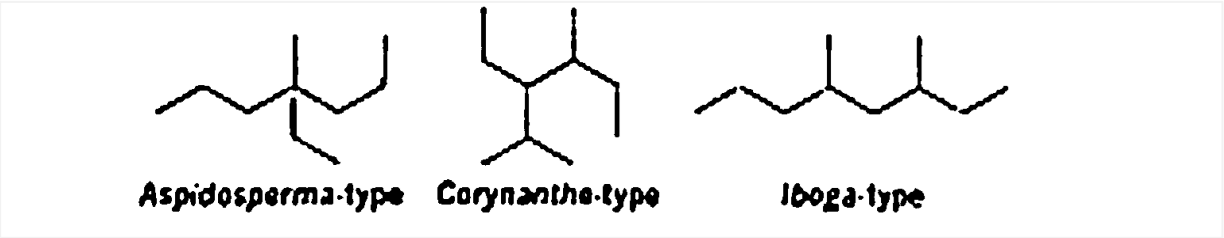
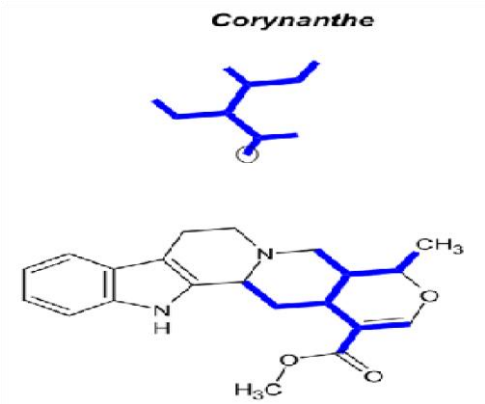


Fig. 8–16. Biosynthesis of *Rauvolfia* alkaloids.



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



Ajmalicine

Reserpine was widely used as an antihypertensive drug. The 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.

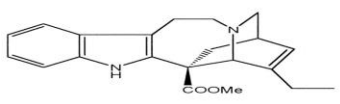
Catharanthus roseus or Vinca F. Apocynaceae:

More than 70 different alkaloids have been isolated from *Catharanthus roseus*. They are generally indole and dihydroindole derivatives. Some of these occur in other members of the Apocynaceae, these include ajmalicine and 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 and Vinblastine.

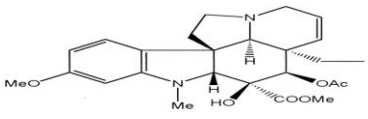
Mechanism of action:

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 and 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.

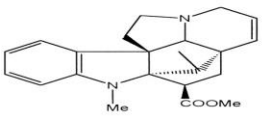
The main side-effects of vincristine are peripheral neuropathy, hyponatremia, constipation, and hair loss.



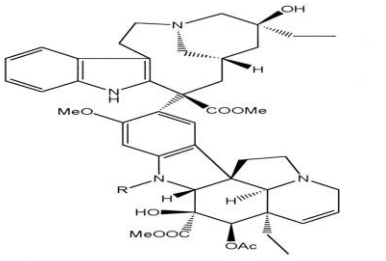
catharanthine



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.

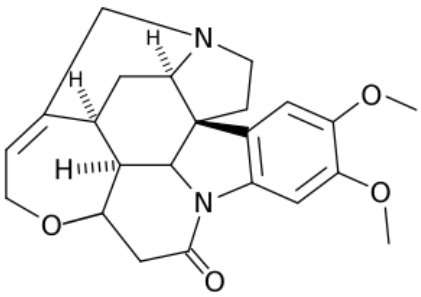
Most people experience some side effects. Commonly it causes a change in sensation, constipation, weakness, loss of appetite, and headaches severe side effects include low blood cell counts and shortness of breath.

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.

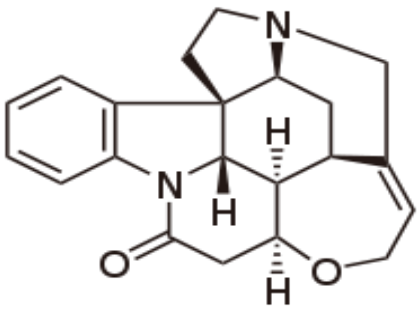
Most people experience some side effects from vincristine treatment. Commonly it causes a change in sensation, hair loss, constipation, difficulty walking, and headaches.

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 and 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

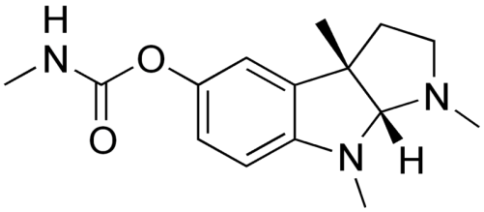
Biosynthetic precursor is from tryptophan.

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 that 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.

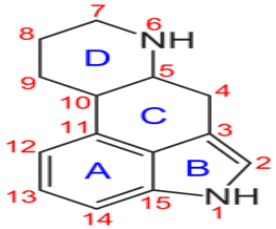
Physostigmine is used in the eye and increases the cholinergic activity and leads to miosis, contraction of the ciliary muscles and a decrease in the intraocular pressure. It is employed in ophthalmology to treat glaucoma.

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 tetracyclic structure).

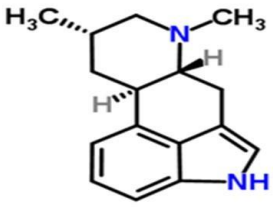
Ergoline base



Ergot alkaloids are classified into:

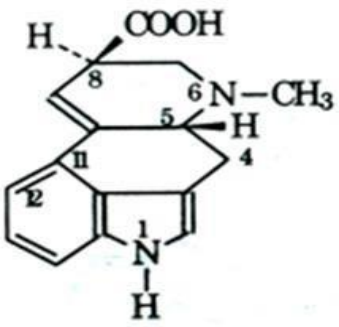
1. Clavine derivatives:

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

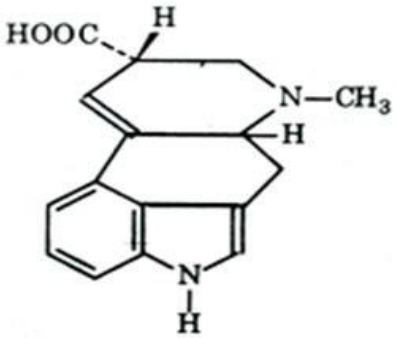


Dimethyl ergoline

2. Lysergic acid-amide derivatives:



Acid lysergic



Acid isolysergic

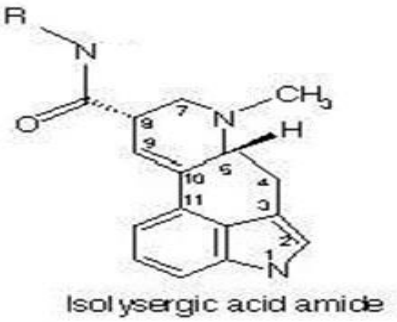
The difference between these two groups is the substituent at position 8. In clavine derivatives C8 contains CH2R (R=H or OH or OCOCH3), while lysergic acid contains COOH.

Isolysergic derivatives are pharmacologically inactive.

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

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

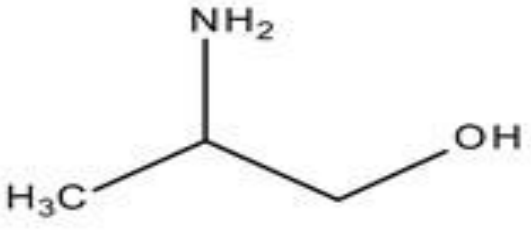
Lysergic acid amide



Isolysergic acid amide

Lysergic acid amide derivatives could be further classified into:

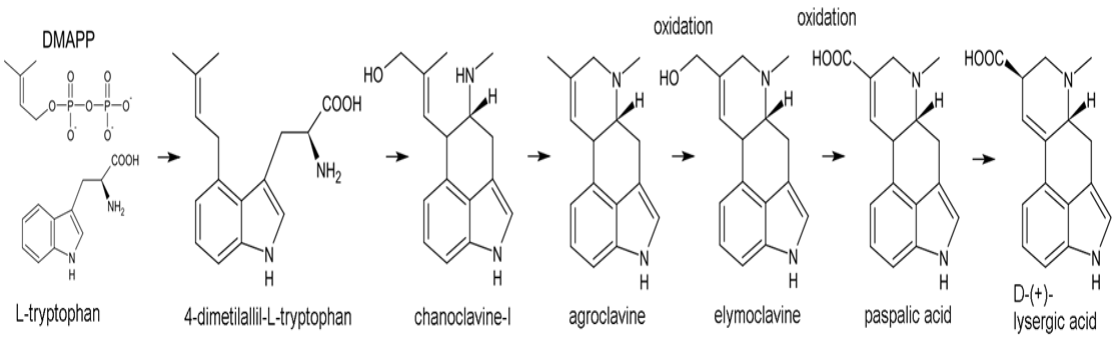
1. R= cyclic tri peptide (peptide group) e.g. ergotamine (inine) (inine are derivatives of iso lysergic acid), ergocine (inine). Both are called ergotamine group, they are water-soluble.
   Ergocristine (inine), ergocryptine (inine), ergonine (inine), these are called ergotoxine group and are also water-insoluble.
2. R= L-2-amino propanol (alkanol amide), i.e



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

Biosynthesis of lysergic acid:

Lysergic acid is biosynthesized from tryptophan and dimethyl allyl pyrophosphate.



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.

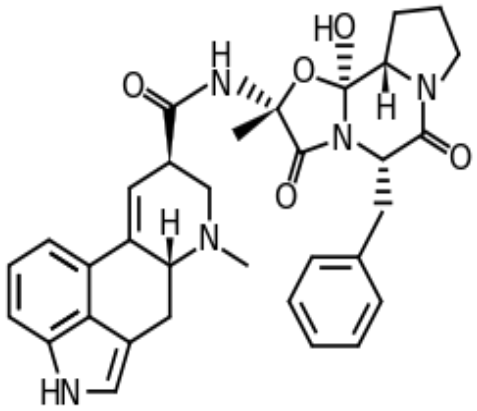
Ergotamine is used in certain headache disorders (migraine).

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

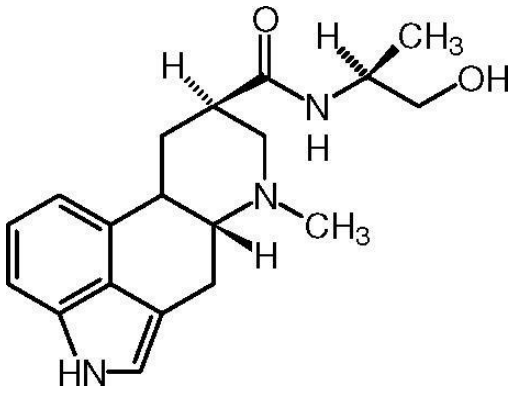
Ergometrine has mainly direct peripheral action and the others are insignificant.

LSD (Diethyl amino lysergic acid):

Preparing lysergic acid with two ethyl groups produces LSD which shows an increase in the excitation effect of the CNS. It is used for hallucination and for psychoanalysis. LSD is also called lysergic acid diethyl amide.



Ergotamine



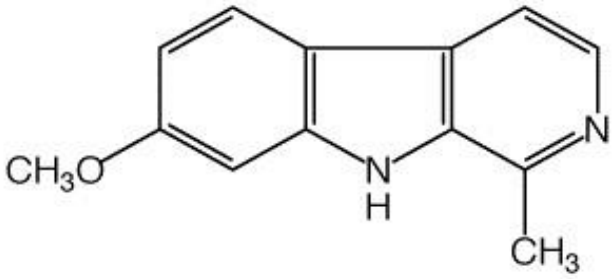
Ergonovine

Harmel:

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

It contains several alkaloids such as harmine, harmane, harmaline, harmalol, and 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 and 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 tapeworms and to treat recurring fevers (possibly malaria).