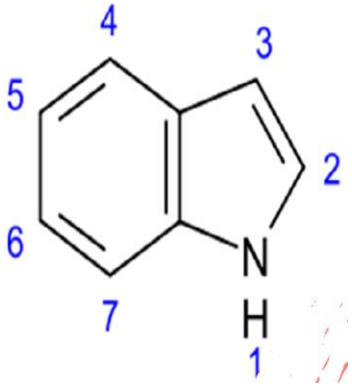
Pharmacognesy III

From textbooks: ***(Pharmacognesy and Pharmacobiotechnology, 9th ed, Robbers JE, Speedie MK, Tyler VE.)***

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.
- Iso prenoid derived indole alkaloids include terpenoid structural elements, synthesized by living organisms from dimethylallyl pyrophosphate (DMAPP) and/or isopentenyl pyrophosphate (IPP):

A- Non-isoprenoid:

1. Simple derivatives of indole
2. Simple derivatives of β-carboline
3. Pyrroloindole alkaloids

B- Isoprenoid:

1. hemiterpenoids: ergot alkaloids
2. monoterpenoids.

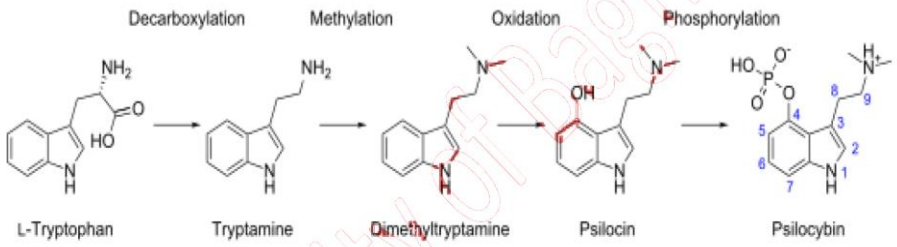
A- Non-isoprenoid indole

1- 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 derivative psilocybin also simplest derivatives of tryptamine.

A- Non-isoprenoid indole

- **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.**



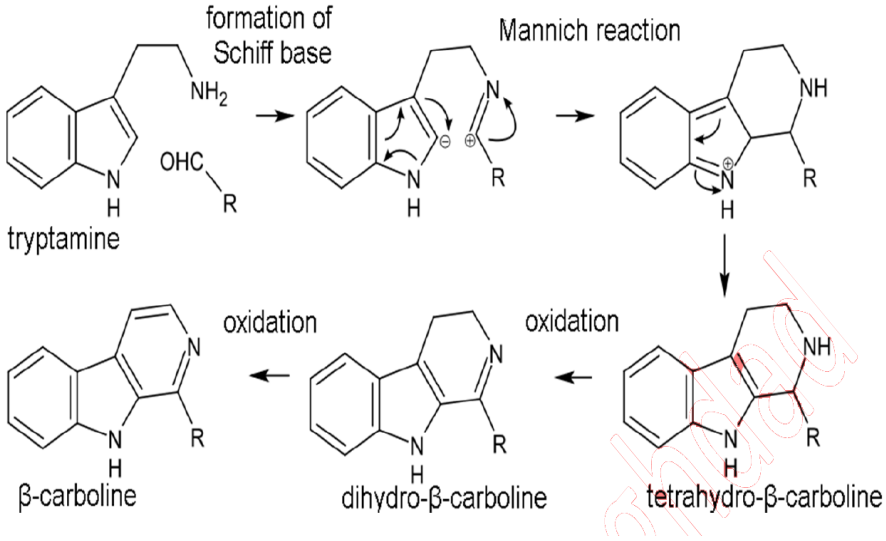
- **Some simple indole alkaloids do not contain tryptamine such as gramine and glycozoline**

A- Non-isoprenoid indole

- **2- 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.

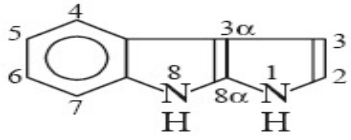
Then, the aromaticity is restored via the loss of a proton at the C(2) atom. This type includes harmine, harmaline.



A- Non-isoprenoid indole

3- Pyrolo-indole alkaloids :

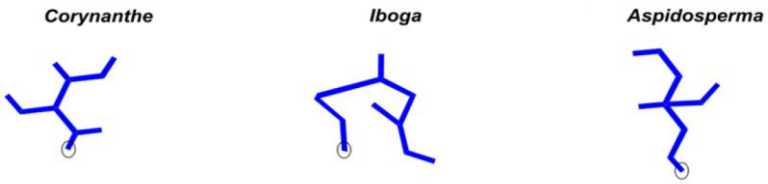
- **Form small group of tryptamine derivatives. They are produced by methylation of indole nucleus at position 3 and subsequent nucleophilic Addition at C2 with the closure of ethylamino group in to a ring example physostigmine**



Pyrroloindole

B- 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 iboga .



- **One of the most important plants containing indole alkaloids:**

1- Rauwolfia:

- Is the dried root of *Rauwolfia serpentin* (F. 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:**

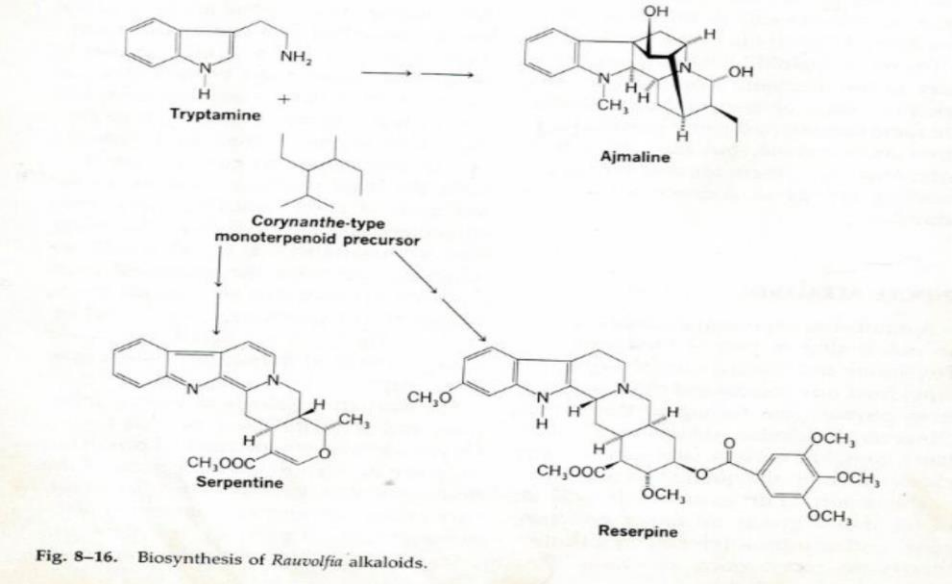
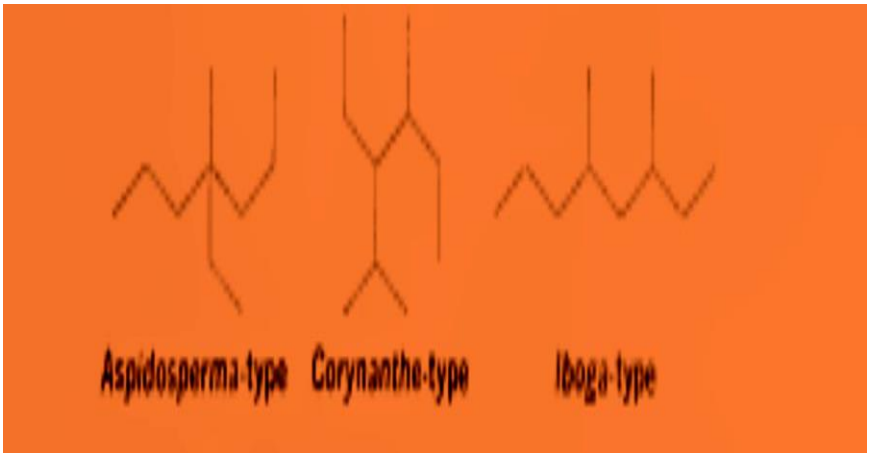
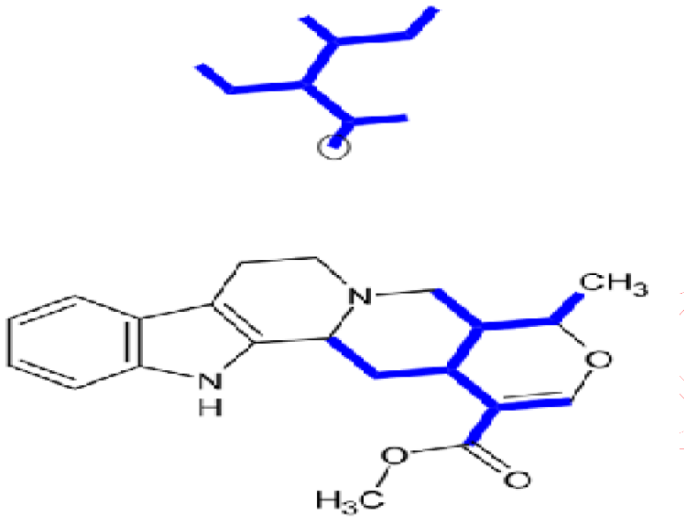


Fig. 8–16. Biosynthesis of *Rauvolfia* alkaloids.

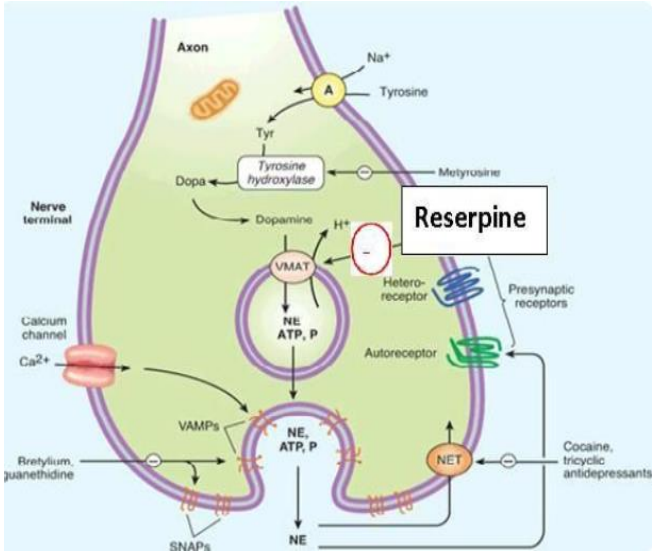


(Carbon skeletons of the general types of monoterpenoid precursors of indole alkaloids)



Ajmalicine

- **Reserpine**
- **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.**



Mechanism of reserpine action

2- 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.**

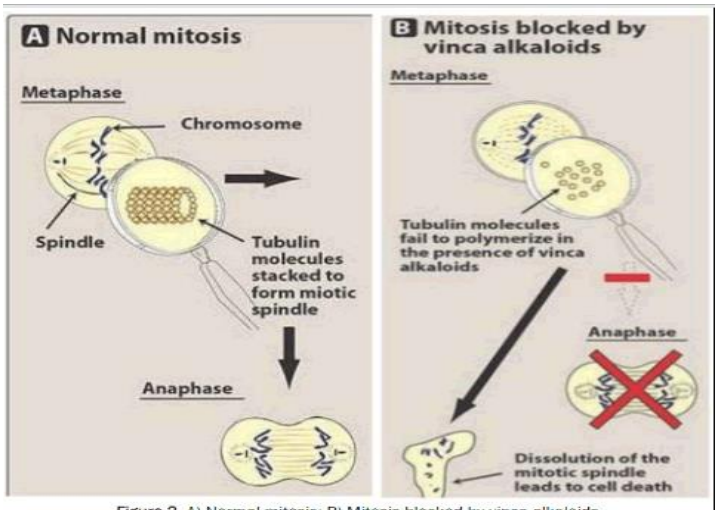
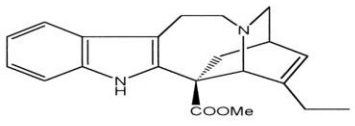
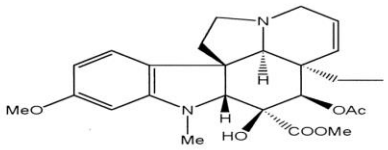


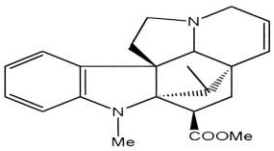
Figure 2. A) Normal mitosis; B) Mitosis blocked by vinca alkaloids.



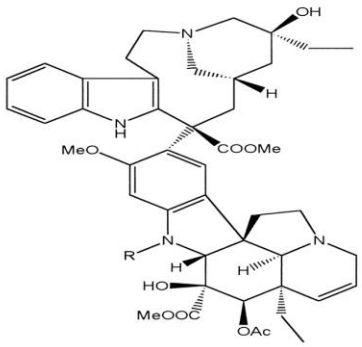
catharanthine



vindoline



vindolinine



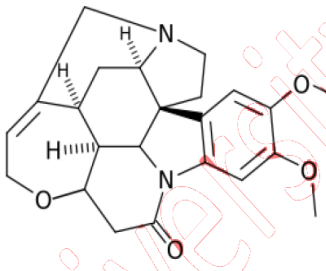
R=CHO : vincristine
R=Me : vincaleukoblastine

- **Vinblastine (VBL), sold under the brand name Velban , is used to treat a number of types of cancer .**
- **These 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.**

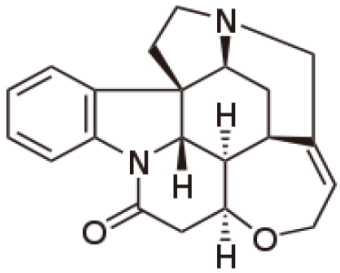
- **Vincristine, also marketed under the brand name Oncovin , is a chemotherapy medication used to treat a number of types of cancer.**
- **This includes acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin's disease, neuroblastoma, and small cell lung cancer among others. It is given intravenously.**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

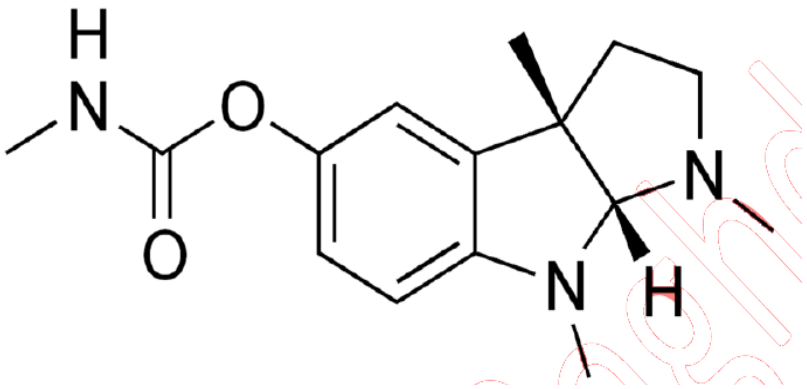


Strychnine

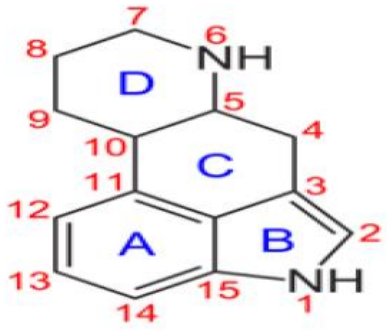
- **Biosynthetic precursor is tryptophan.**
- **The use of strychnine is highly regulated in many countries, and is mostly used in baits to kill feral mammals, including wild dogs, foxes, and rodents.**
- **It is a central stimulant, increases the tone of the skeletal muscles. Most accidental poisoning 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 reversible inhibitor of acetylcholinesterase (covalent- bond hydrolyzed and released).**
- **Acetylcholinesterase is 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.**

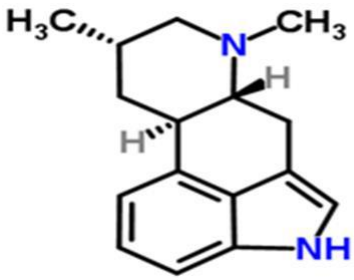


- **Ergot**
- **Refers to a group of fungi of the genus Claviceps. *Claviceps purpurea* developed on plants of rye *Secale cereale (*F. Gramineae).**
- **This fungus grows on rye and related plants, and produces alkaloids that can cause ergotism in humans and other mammals who consume grains contaminated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



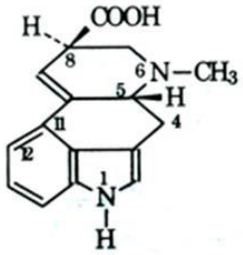
Ergoline base

- **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.**

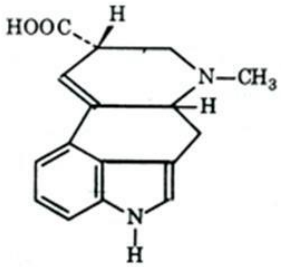


Dimethyl ergoline

- **2. Lysergic acid-amide derivatives:**
- **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.**

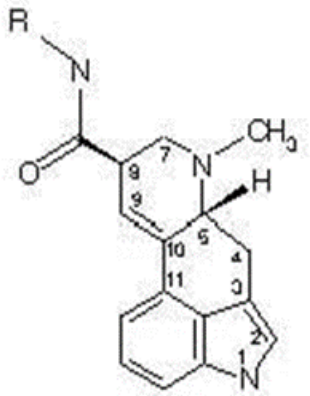


Acid lysergic

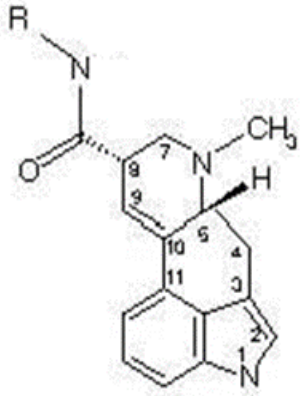


Acid isolysergic

- **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).**

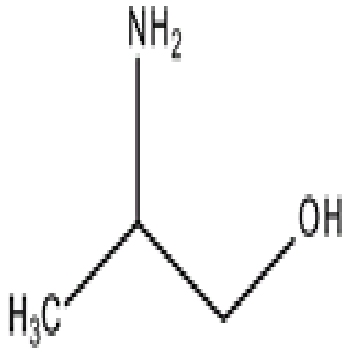


Lysergic acid amide



Isolysergic acid amide

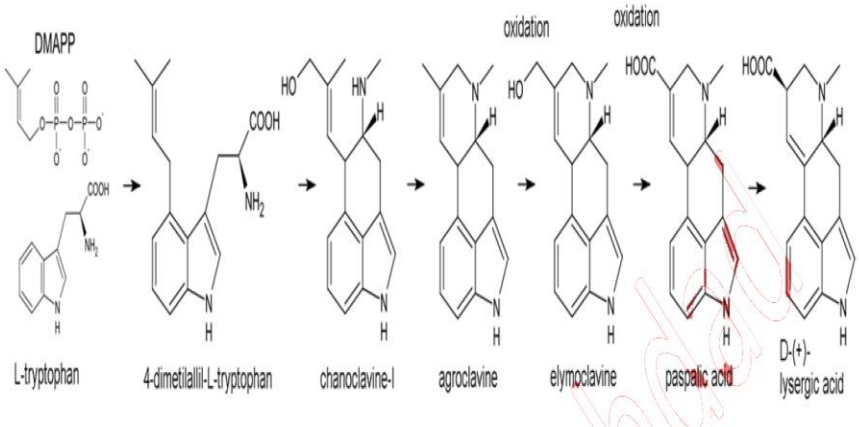
- **Lysergic acid amide derivatives could be further classified into:**
- **1.R= cyclic tri peptide (peptide group) e.g. ergotamine (inine) (inine are derivatives of iso lysergic acid), ergocine (inine). Both are called ergotamine group, they are water soluble.**
- **Ergocristine (inine), ergocryptine (inine), ergonine (inine), these are called <u>ergotoxine group & are water insoluble.</u>**
- **2.R= L-2-amino propanol (alkanol amide), i.e. E.g. ergometrine (ergonovine) (inine), called ergometric group & are water soluble.**



(L-2-amino propanol)

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):

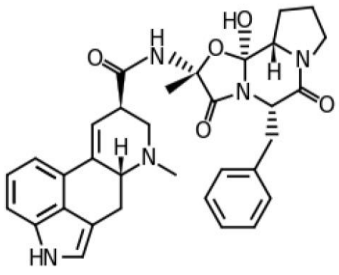
a. Bradycardia , vomiting

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

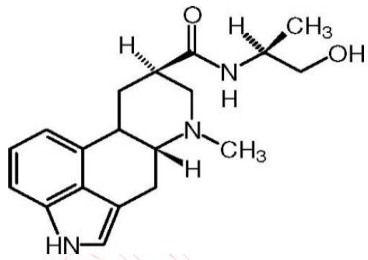
- **Ergotamine is used in certain headache disorders (migraine).**
- **Ergotoxin group has the same activity like ergotamine but it is more toxic (it is toxic at the therapeutic dose) & so it is not used clinically. Ergometrine has mainly direct peripheral action & the others are insignificant.**

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.**

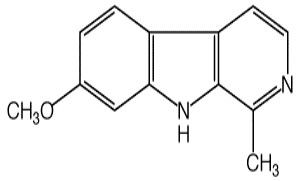


Ergotamine



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.**

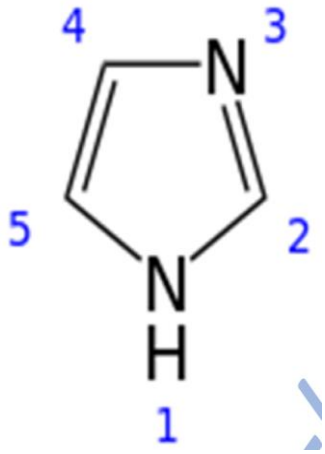


(Harmine)

- ***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

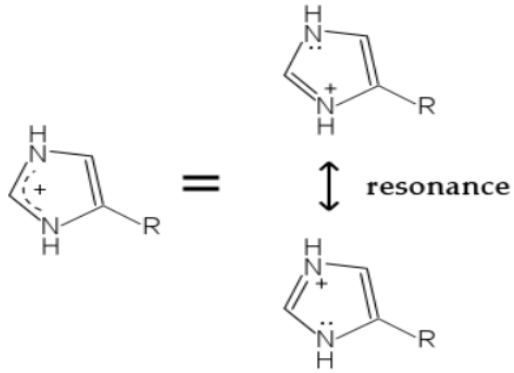
- **Imidazole is a planar 5-membered ring.**
- **It exists in two equivalent tautomeric forms, because the proton can be located on either of the two nitrogen atoms.**

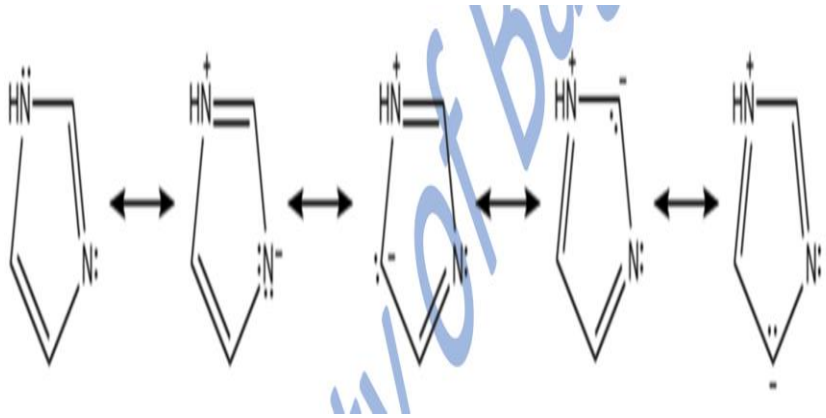


- **In the neutral form of the imidazole ring:**

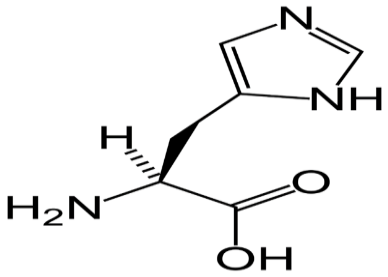
The nitrogen without a hydrogen is nucleophilic and can act as a hydrogen bond acceptor, while the nitrogen with the hydrogen bond is electrophilic and can act as a H-bond donor.

- **The protonated form of the imidazole ring loose its ability to act as a nucleophile, so it is stabilized by resonance, by which the positive charge is shared by both nitrogen atoms of the ring.**



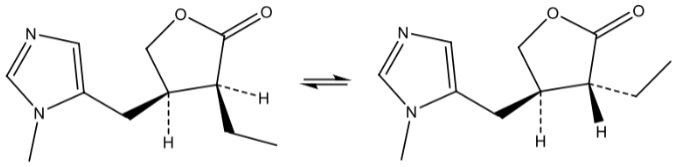


- The amino acid L-histidine contains an imidazole ring, and is thus the likely precursor of alkaloids containing this ring system.



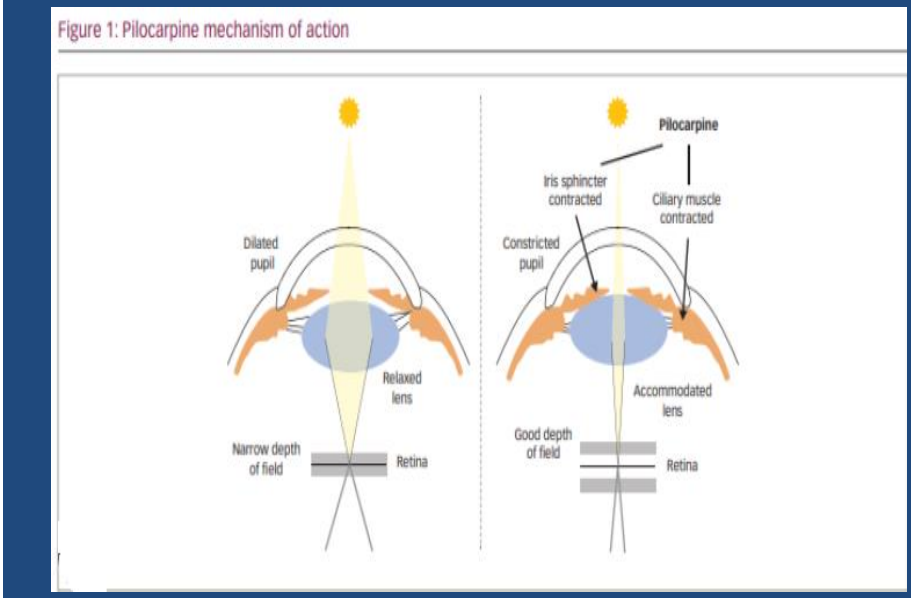
Plants containing imidazole alkaloids

- 1- **Pilocarpus :**
- Pilocarpus or jaborandi consists of the dried leaflets of *Pilocarpus jaborandi* (F. 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 Isopilocarpine

- **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. It 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.**

THANK YOU