



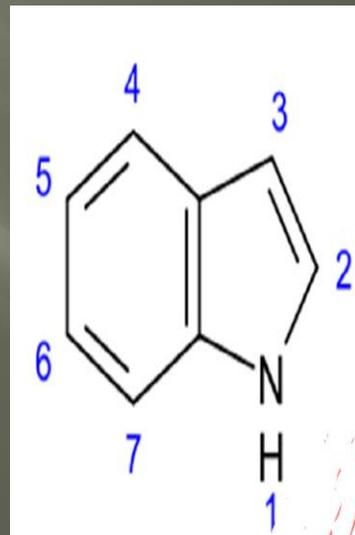
PHARMACOGNESY III

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

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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; non isoprenoids and Iso prenoind derived indole alkaloids

A- Non-isoprenoid:

- Simple derivatives of indole
- Simple derivatives of β -carboline
- Pyrroloindole alkaloids

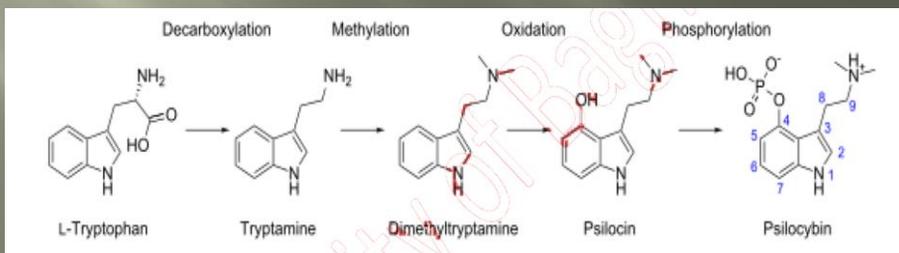
B- Isoprenoid: include terpenoid structural elements, synthesized by living organisms from dimethylallyl pyrophosphate (DMAPP) and/or isopentenyl pyrophosphate (IPP), these include:

- Hemiterpenoids: ergot alkaloids .
- Monoterpenoids.

A- Non-isoprenoid indole

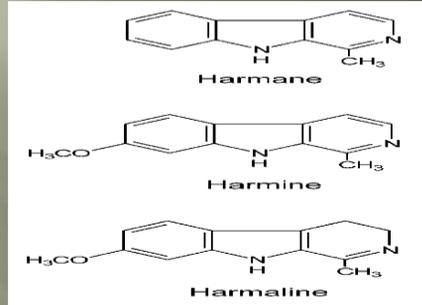
1- Simple indole:

- One of the simplest widespread indole derivatives are the biogenic amines tryptamine and 5-hydroxytryptamine(serotonin).
- The first synthesis step is decarboxylation of tryptophan to form tryptamine.

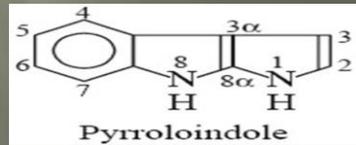


A- Non-isoprenoid indole

- ▣ **2- β -carboline** : This type includes harmine, harmaline.

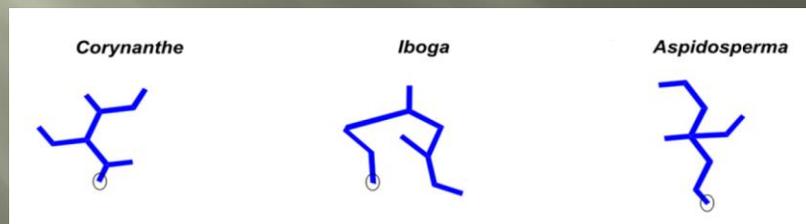


- ▣ **3- Pyrolo-indole alkaloids** : physostigmine



B- Isoprenoid indole alkaloids

- ▣ Composed from 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 serpentina* (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:

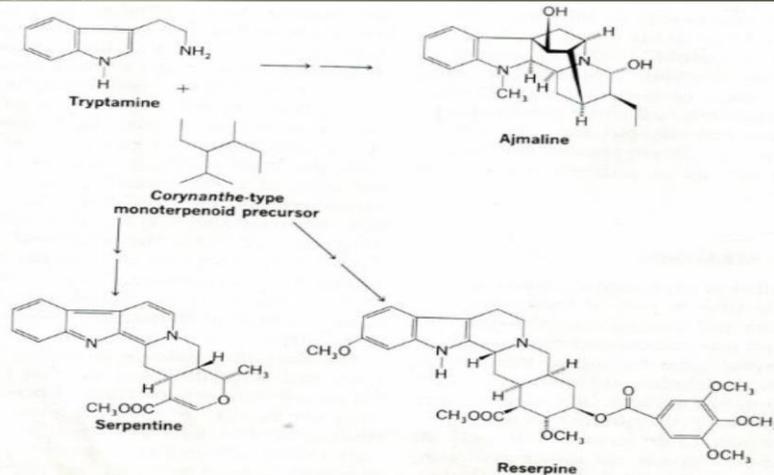
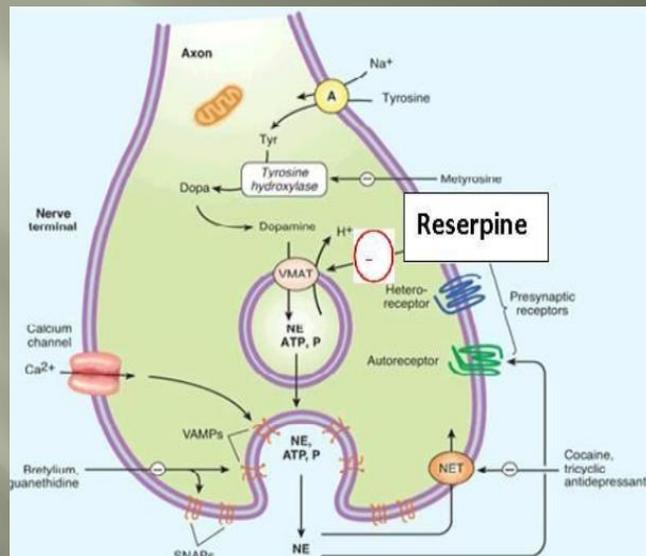


Fig. 8-16. Biosynthesis of Rauwolfia alkaloids.

- ❑ **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.

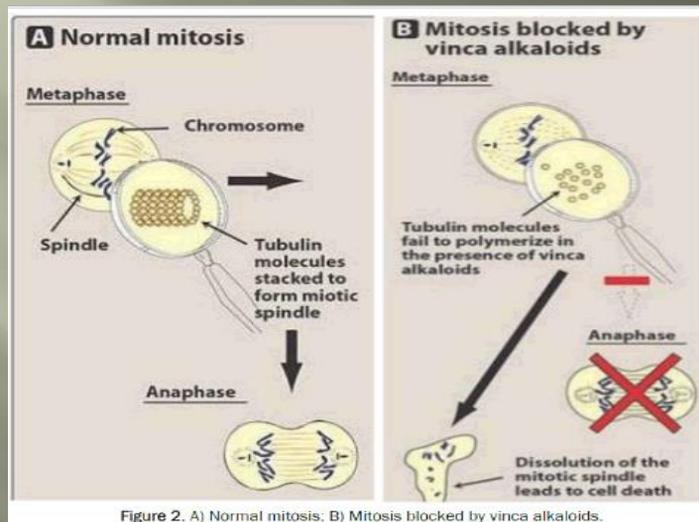


Mechanism of reserpine action

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.

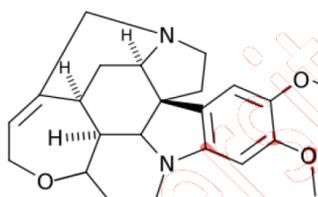


- ▣ **Vinblastine (VBL)**, sold under the brand name Velban , is used to treat a number of types of cancer . These includes Hodgkin's lymphoma, non-small cell lung cancer, bladder cancer, brain cancer, melanoma, and testicular cancer. It is given by injection into a vein.
- ▣ Most people experience some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

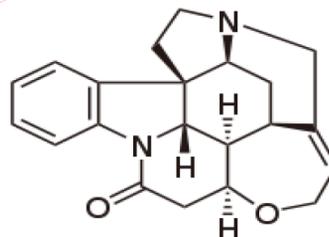
- ▣ **Vincristine**, also marketed under the brand name Oncovin , is a chemotherapy medication used to treat a number of types of cancer.
- ▣ This includes acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin's disease, neuroblastoma, and small cell lung cancer among others. It is given intravenously.
- ▣ Most people experience some side effects from vincristine treatment.
- ▣ Commonly it causes a change in sensation, hair loss, constipation, difficulty walking, and headaches.

- ▣ **3- 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 is dimethoxy strychnine.



Brucine



Strychnine

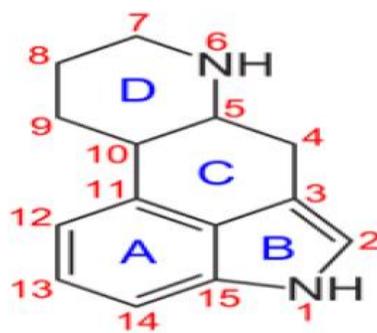
- ▣ **Biosynthetic precursor is tryptophan.**
- ▣ The use of strychnine is highly regulated in many countries, and is mostly used in baits to kill feral mammals, including wild dogs, foxes, and rodents.
- ▣ It is a central stimulant, increases the tone of the skeletal muscles. Most accidental poisoning 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.

- ▣ **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 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 tetra cyclic structure)



Ergoline base

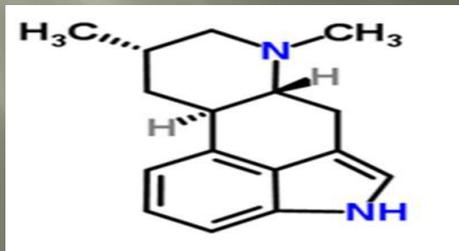
- Ergot alkaloids are classified into 2 classes that differs in the substituent at position 8.

1- In clavine derivatives C8 contains CH₂R (R=H or OH or OCOCH₃).

2- In while lysergic acid C8 contains COOH.

- **1. Clavine derivatives:**

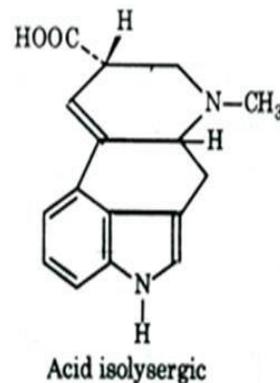
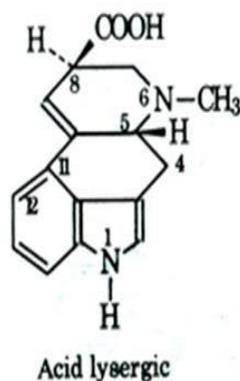
Those deriving from dimethyl ergoline are referred to as clavines, e.g. agroclavine, elymoclavine, lysergol. Those are alkaloids found in ergot but are pharmacologically inactive.



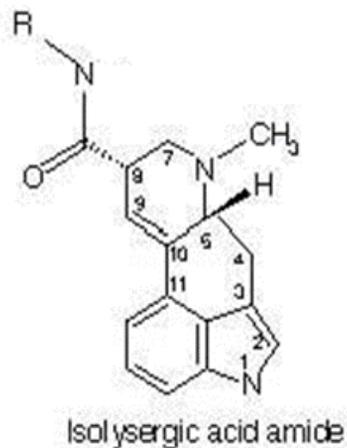
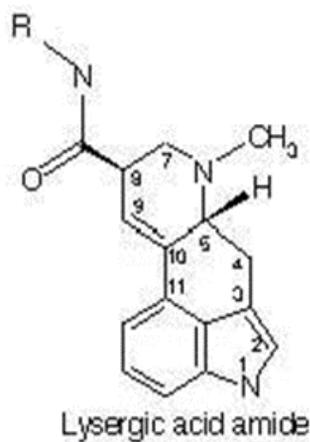
Dimethyl ergoline

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

- Where C8 of the ergoline nucleus contains COOH.



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



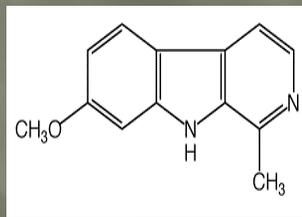
▣ **Lysergic acid amide derivatives could be further classified into:**

- ▣ 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 insoluble.
- ▣ Ergocristine (inine), ergocryptine (inine), ergonine (inine), these are called ergotoxine group & are water insoluble.
- ▣ 2.R= L-2-amino propanol (alkanol amide), i.e. E.g. ergometrine (ergonovine) (inine), called ergometric group & are water soluble.

▣ **Pharmacological activities of ergot can be classified into:**

- a. Uterine contraction (ergometrine and methyl ergometrine to induce labor).
- b. Vaso constriction (ergotamine in certain headache disorders (migraine).
- c. Syndrome of ergotropic excitation causes mydriasis, hyperglycemia, and hyperthermia.
- d. 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.

- ▣ **Harmel:**
- ▣ It is the dried seeds of *Peganum harmala* (F: Nitrariaceae).
- ▣ It contains several alkaloids as harmine, harmane, harmaline, harmalol, others.
- ▣ belonging to the beta-carboline family of compounds.

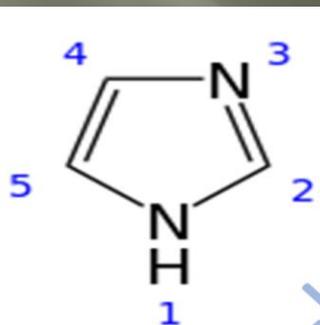


(Harmine)

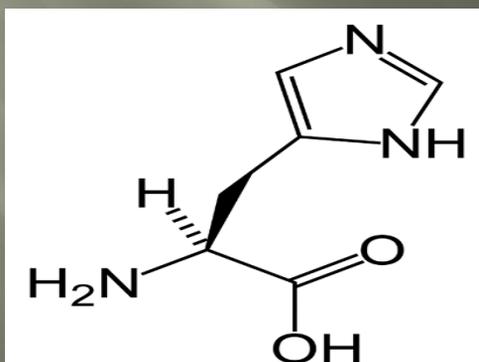
- ▣ *Peganum harmala* has been used to treat pain and to treat skin inflammations, including skin cancers & as an emmenagogue and abortifacient agent.
- ▣ It is also used as an anthelmintic (to expel parasitic worms). Reportedly, the ancient Greeks used the powdered seeds to get rid of tape worms and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

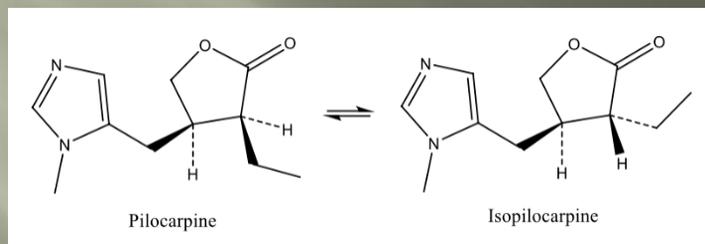


- The amino acid L-histidine contains an imidazole ring, and is thus the likely precursor of alkaloids containing this ring system.



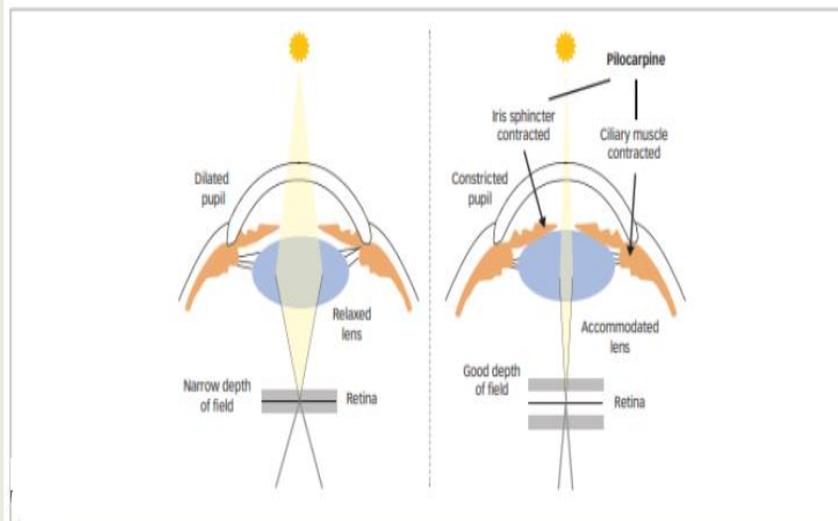
Plants containing imidazole alkaloids

- ▣ **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 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.

Figure 1: Pilocarpine mechanism of action



- ▣ 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.
- ▣ Pilocarpine has been known to cause excessive sweating, excessive salivation, bronchospasm, increased bronchial mucus secretion, bradycardia, vasodilation, and diarrhea.

THANK YOU