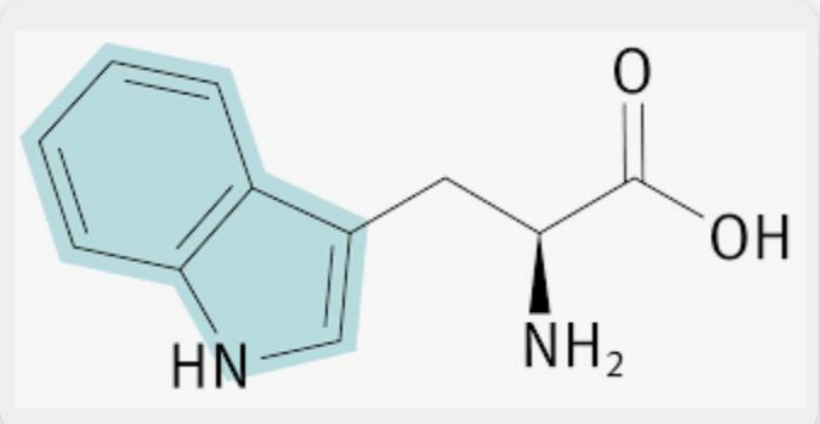
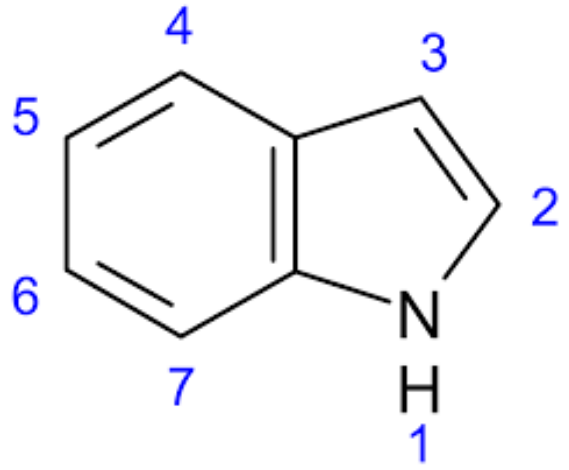
Indole alkaloids

Pharmacognosy Three Stage

By D. Zainab Tuama

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.





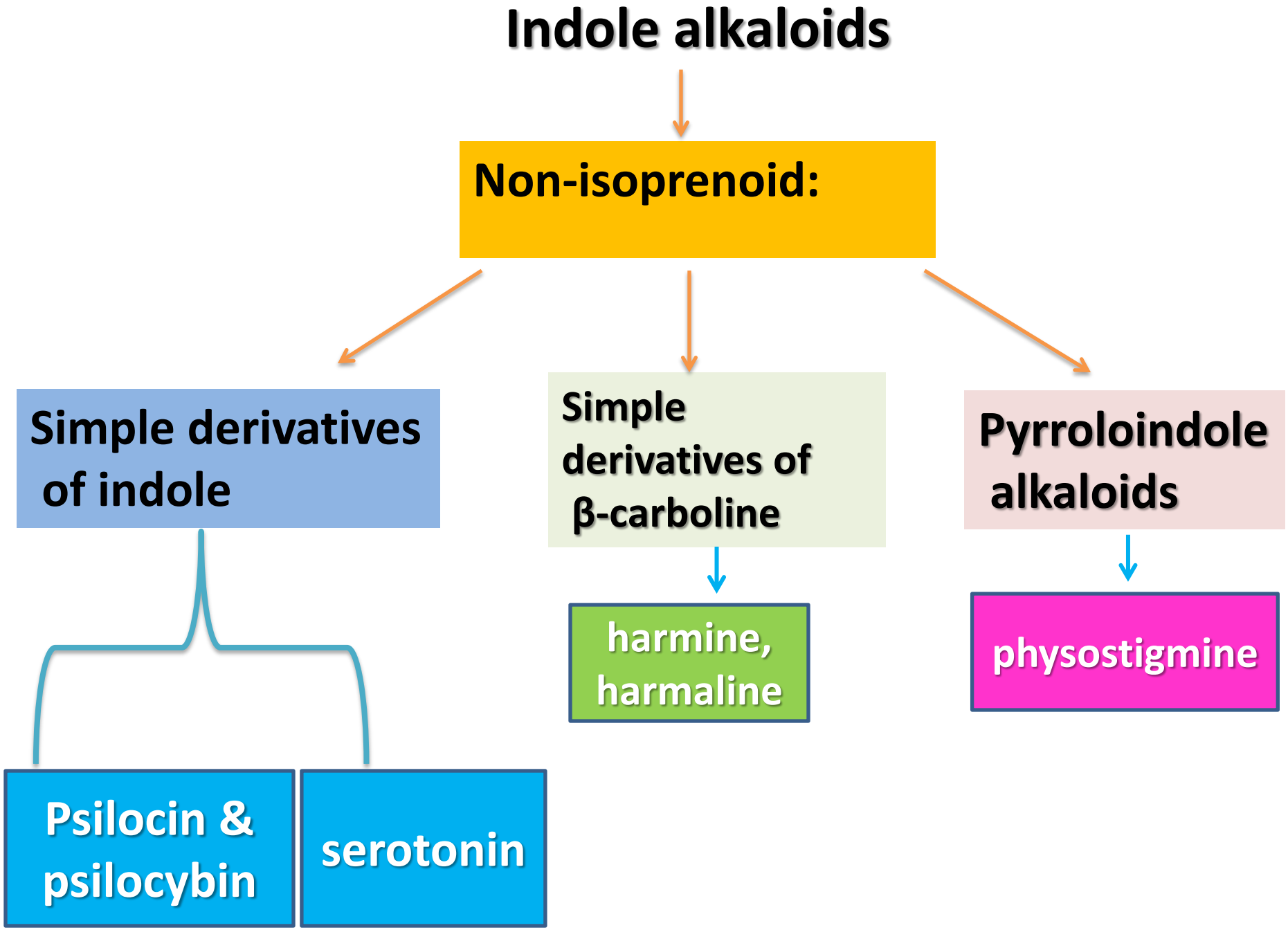
Indole alkaloids:- are distinguished depending on their biosynthesis. The two types of indole alkaloids are isoprenoids and non-isoprenoids. The isoprenoids include terpenoid structural elements, synthesized by living organisms from dimethylallyl pyrophosphate (DMAPP) and/or isopentenyl pyrophosphate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

Non-isoprenoid:

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

Isoprenoid:

- hemiterpenoids: ergot alkaloids
- monoterpenoids.


Indole alkaloids
Non-isoprenoid:
Simple derivatives of indole
Simple derivatives of β-carboline
Pyrroloindole alkaloids
harmine, harmaline
physostigmine
Psilocin & psilocybin
serotonin

Non-isoprenoid indole:

1- Simple indole:

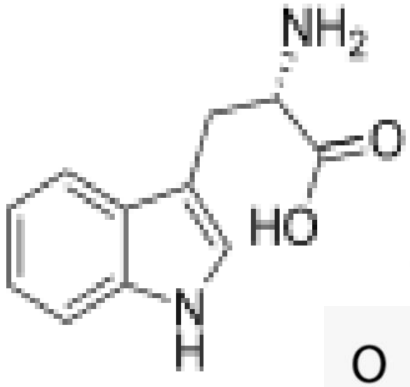
One of the simplest widespread indole derivatives are the

- **biogenic amines tryptamine**
- **5-hydroxytryptamine(serotonin).**

Although their assignment to the alkaloid is not universally accepted, they are both found in plants and animals.

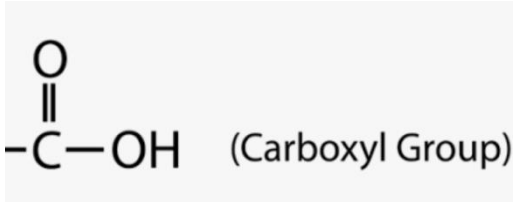
The tryptamine skeleton is part of the majority of indole alkaloids. For example, **dimethyltryptamine** (DMT), **psilocin** and its phosphorylated **psilocybin** are the simplest derivatives of tryptamine.

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

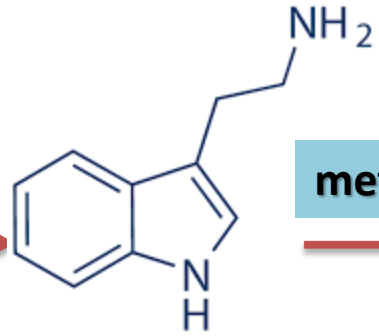


tryptophan

Decarboxylation

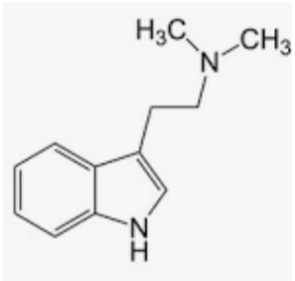


(Carboxyl Group)

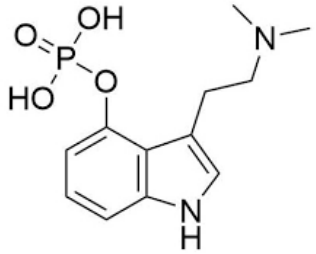


tryptamine

methylation

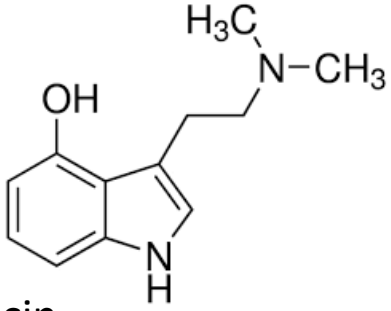


Dimethyltryptamine



psilocybin

phosphorylated



Psilocin

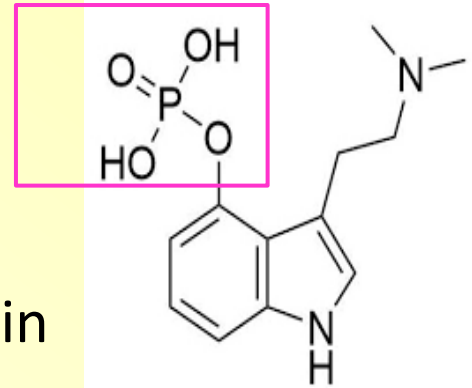
oxidation

Psilocybin alkaloid

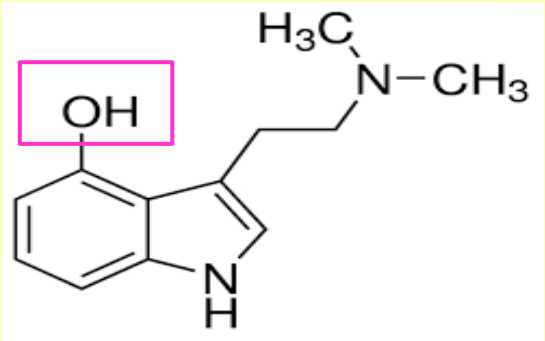
certain Mushrooms of the genera Psilocybe (*Psilocybe mexicana*)

produce substances such as psilocybin, they are not as drug,
but have hallucinogenic effects.

Psilocybin alkaloid like LSD (lysergic acid Diethyl amino)



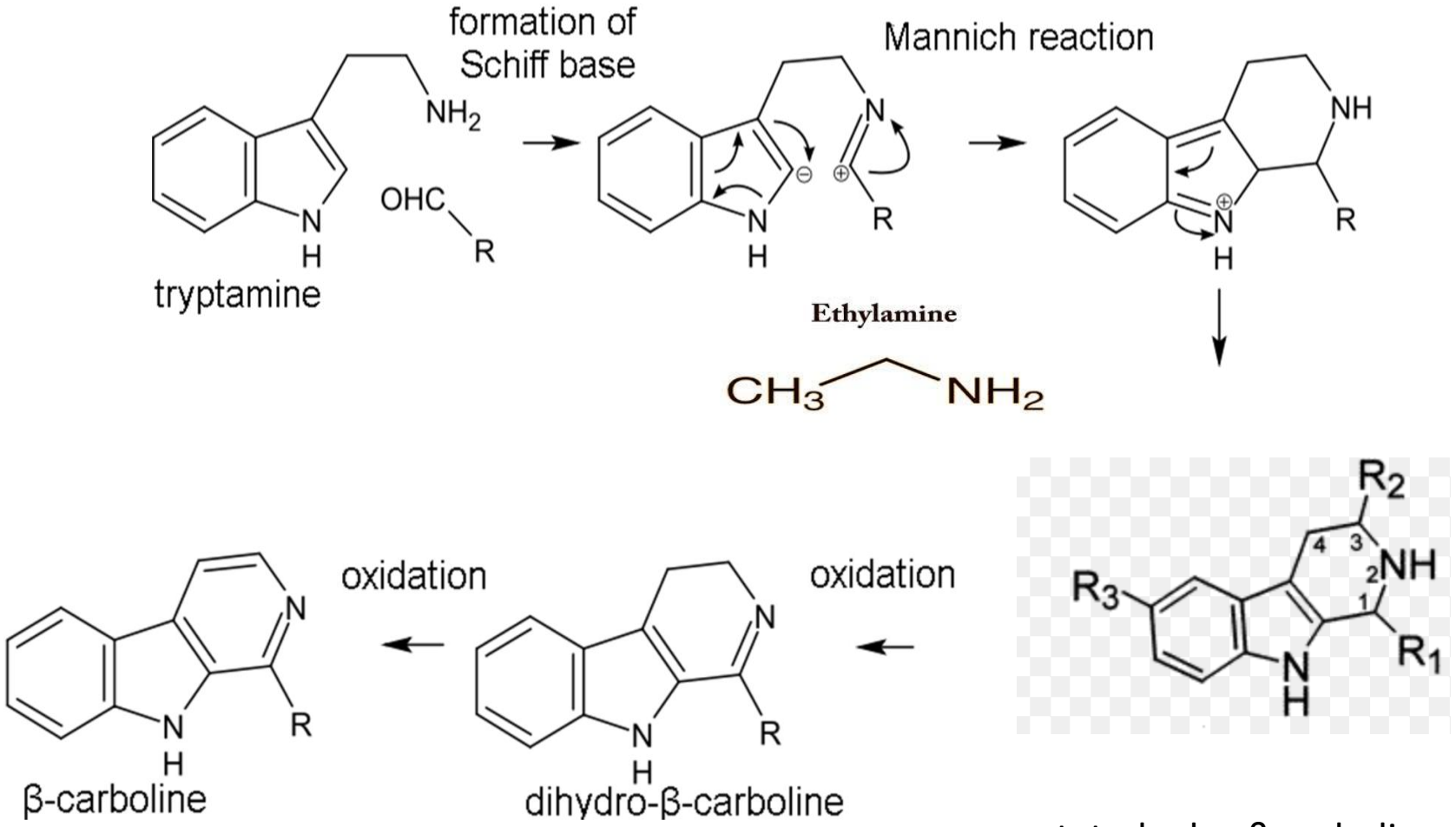
psilocybin



Psilocin

2- Simple derivatives of 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.

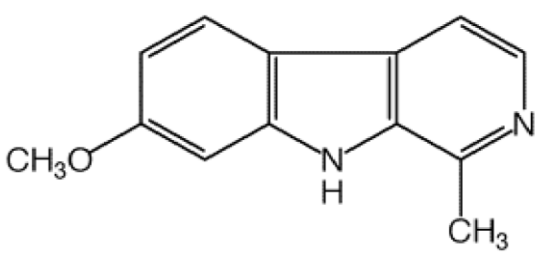


Biosynthesis of β-carboline alkaloids

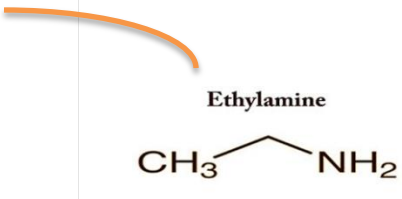
Harmel alkaloids:

The dried seeds of *Peganum harmala*

F: Nitrariaceae, contains several alkaloids as harmine, harmane, harmaline, harmalol, others. Harmine, is a fluorescent harmala alkaloid belonging to the beta-carboline family of compounds.



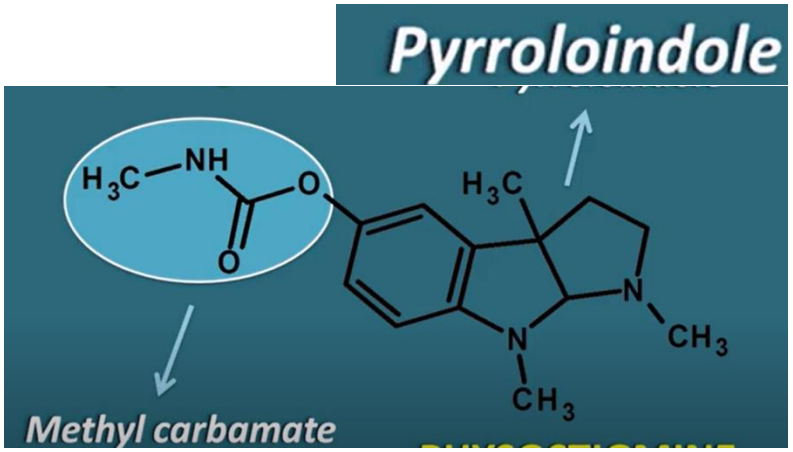
Harmine



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)

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



physostigmine

Physostigma or Calabar bean

Is the dried ripe seed of *Physostigma venenosum*, F. Leguminosae a native of tropical Africa, Calabar bean contains physostigmine (also known as eserine), 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.

- ❑ Colorless and heat ,light or air sensitive give pink or red color
- ❑ It is not stable, so must be kept in air tight Containers with the exclusion of light.

Physostigmine

1-Treated Alzehemier

2- physostigmine is acholinergic alkaloid, it is inhibtitor of the enzym eacetylcholinesterase . It is used treatment of glaucoma used after atropine to stop mydriasis

3- antidote for anticholinergic drugs as atropin and tricyclic antidepressant

4- stimulate intestinal peristalsis after operations

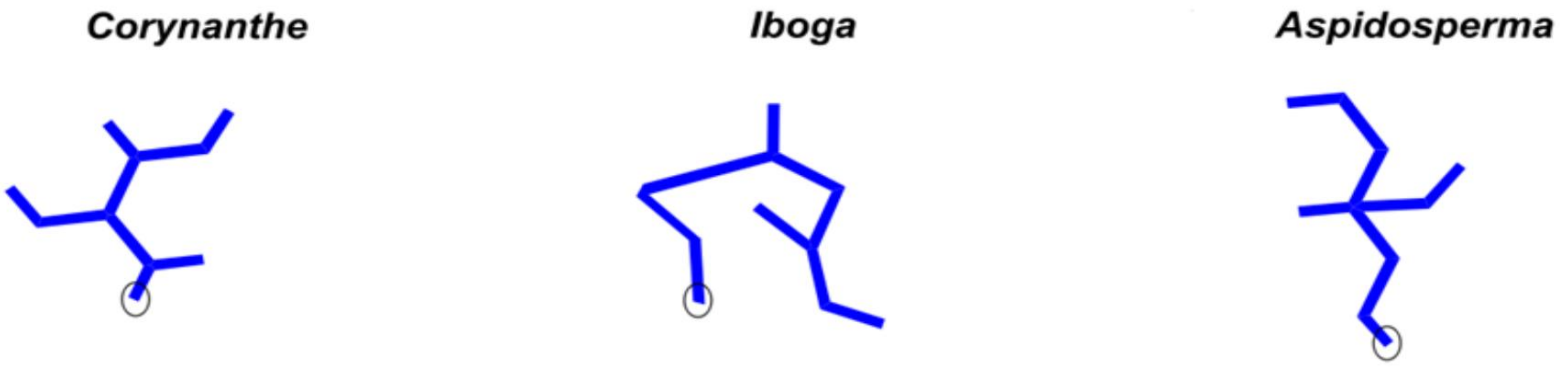
5- analogus are more stable and equally potent (Synthetic compounds based on physostigmine include:

- **Neostigmine**
- **pyridostigmine**

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. (Snake root) 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:

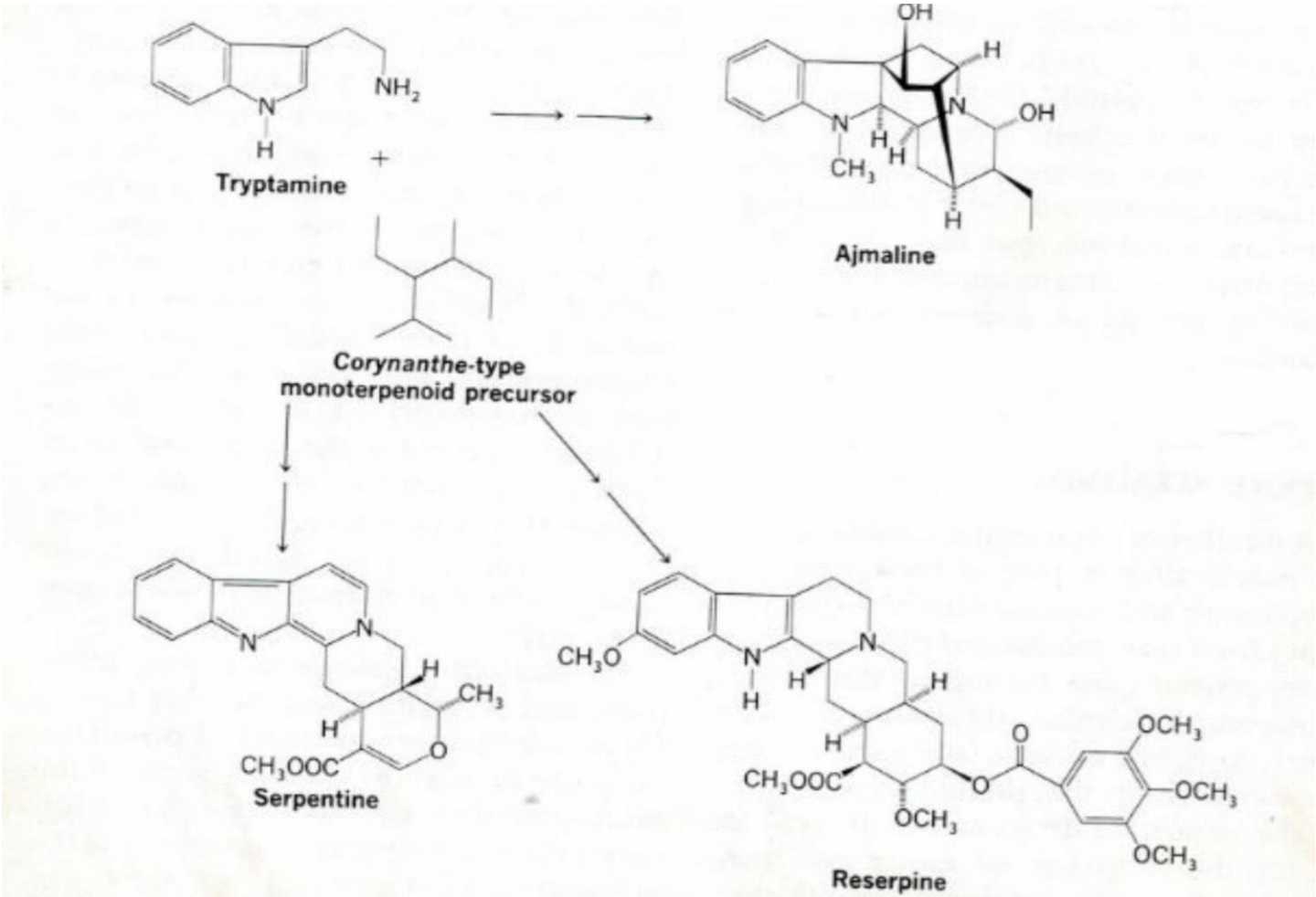
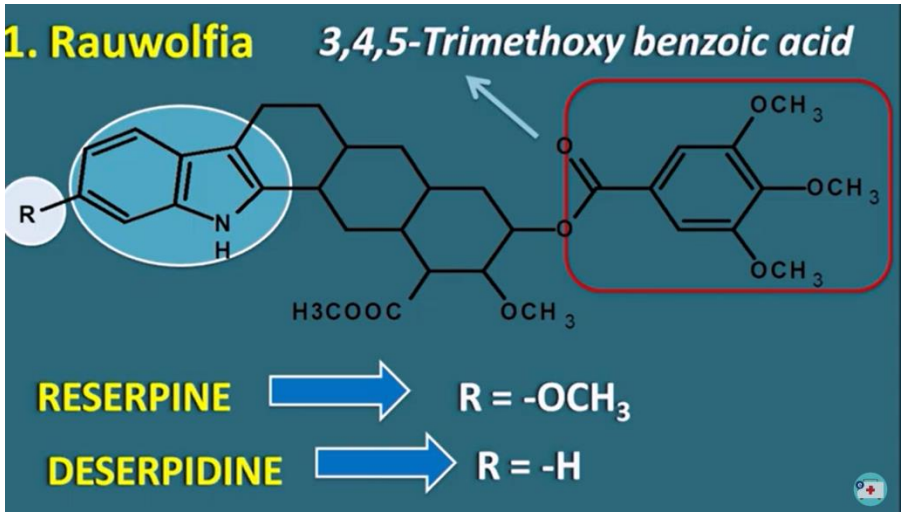
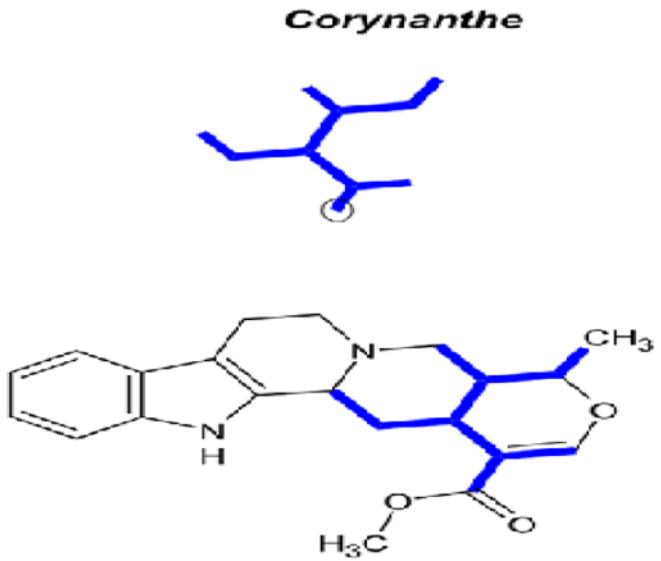


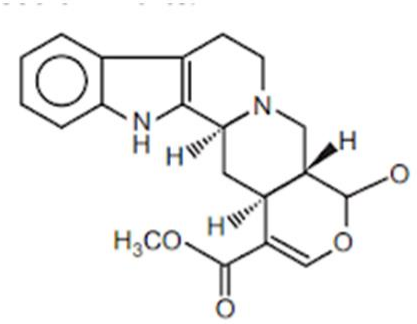
Fig. 8–16. Biosynthesis of *Rauvolfia* alkaloids.


1. Rauwolfia
3,4,5-Trimethoxy benzoic acid
R
N
H
O
O
OCH 3
OCH 3
OCH 3
H3COOC
OCH 3
RESERPINE
R = -OCH3
DESERPIDINE
R = -H

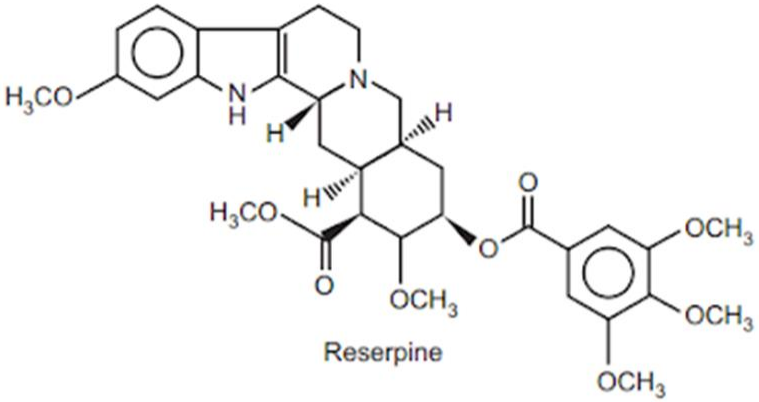

Corynanthe
N
H
CH3
O
O
O
H3C

Ajmalicine

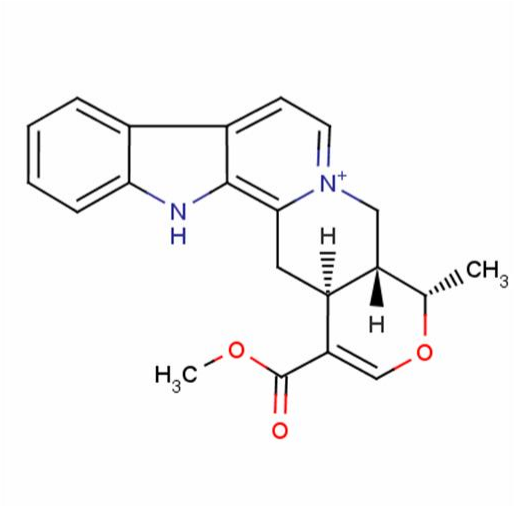
Reserpine is the major component of Snake root was widely used as an antihypertensive drug. The antihypertensive actions of reserpine are largely due to its anti-noradrenergic effects, which are a result of its ability to deplete catecholamines from peripheral sympathetic nerve endings. These substances 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. Due to side effects (neurotoxicity, cytotoxicity and depression) it is now not in use



Ajmalicine



Reserpine



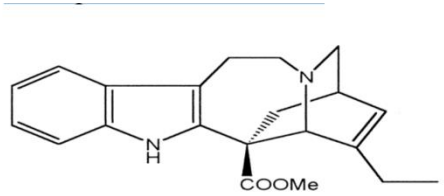
Serpentine

Catharanthus roseus or Vinca
F. Apocynaceae

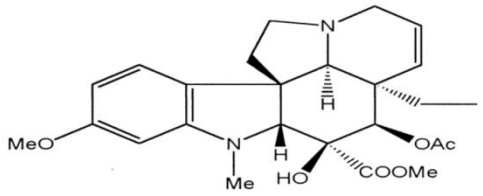
More than 70 different alkaloids have been isolated from Catharanthus roseus they are generally indole and dihydroindole derivatives some of which occur in other members of the apocynaceae these include ajmalicine , serpentine. the alkaloids with anti-neoplastic activity belong to a class of dimeric 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.

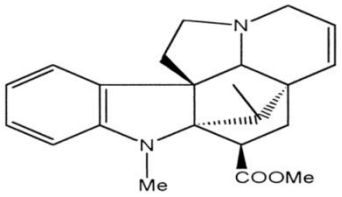
Therefore, the 7 vinca alkaloids affect all rapidly dividing cell types including cancer cells, but also those of intestinal epithelium and bone marrow The main side-effects of vincristine are peripheral neuropathy, hyponatremia, constipation, and hair loss.



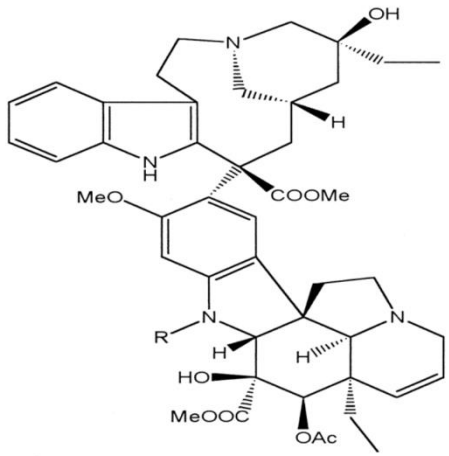
catharanthine



vindoline



vindolinine



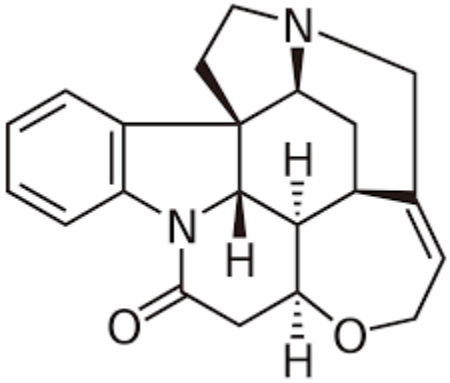
R=CHO : vincristine
R=Me : vincaleukoblastine

Vinblastine (VBL)

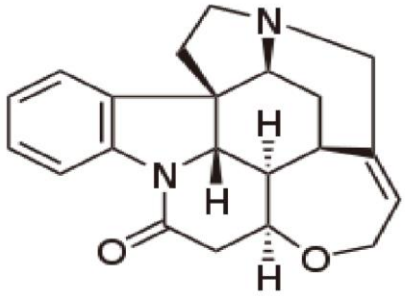
Sold under the brand name **Velban** , is used to treat a number of types of cancer . This includes Hodgkin's lymphoma, non-small cell lung cancer, bladder cancer, brain cancer, melanoma, and testicular cancer. It is given by injection into a vein. Most people experience some side effects. Commonly it 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.

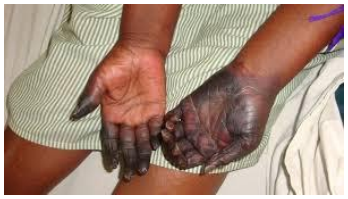
Ergot

Refers to a group of fungi of the genus Claviceps.

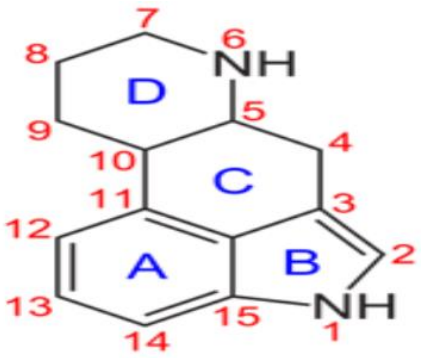
Claviceps purpurea developed on plants of rye *Secale cereale*

F. Gramineae

This fungus grows on rye and relatec , 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:

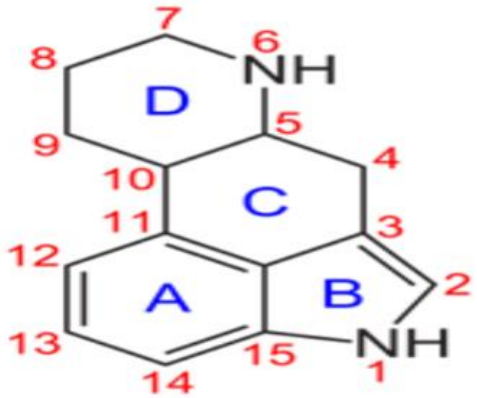
2. Lysergic acid-amide derivatives:

1.Clavine derivatives:

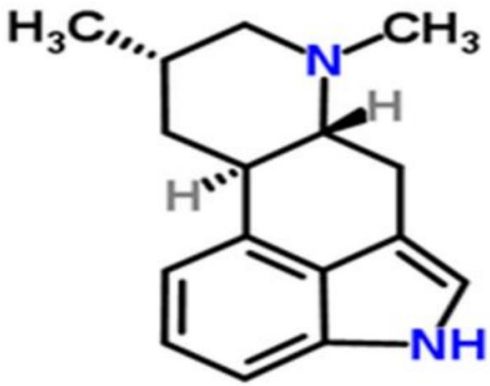
A variety of modifications to the basic ergoline are seen in nature, e.g.

agroclavine, **elymoclavine**, **lysergol**.

Those deriving from dimethyl ergoline are referred to as clavines. Those are alkaloids found in ergot but are pharmacologically inactive.



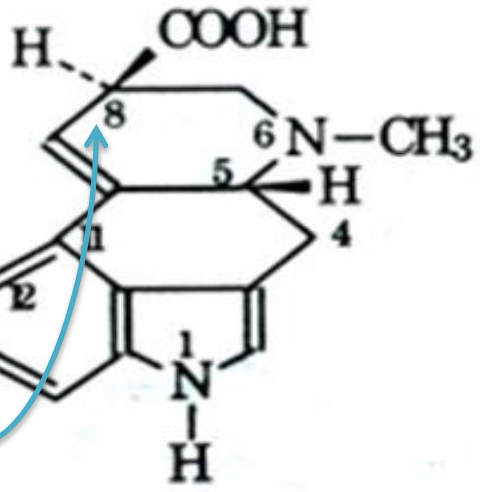
Ergoline base



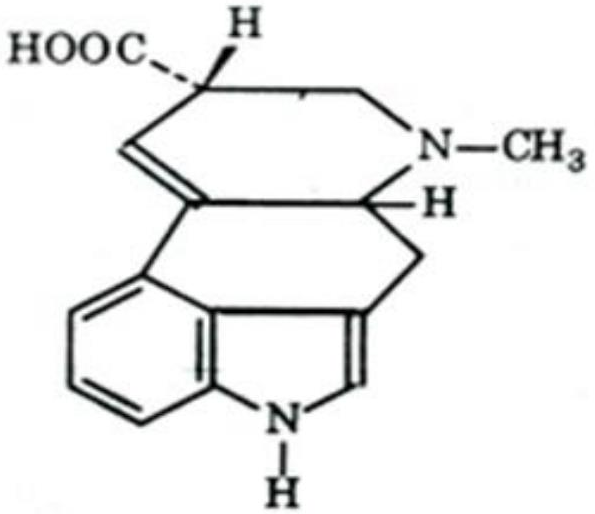
dimethyl ergoline

2. Lysergic acid-amide derivatives:

- lysergic acid
- Iso lysergic



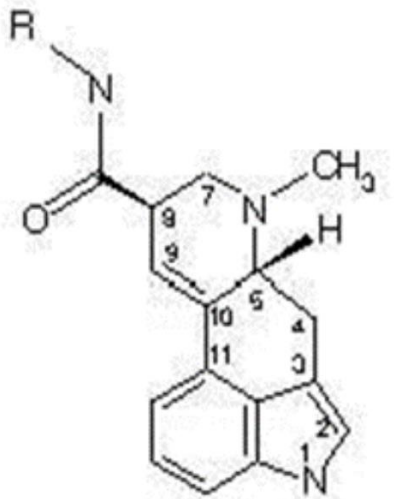
Acid lysergic



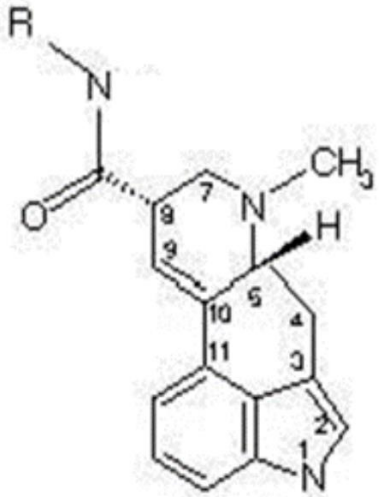
Acid isolysergic

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

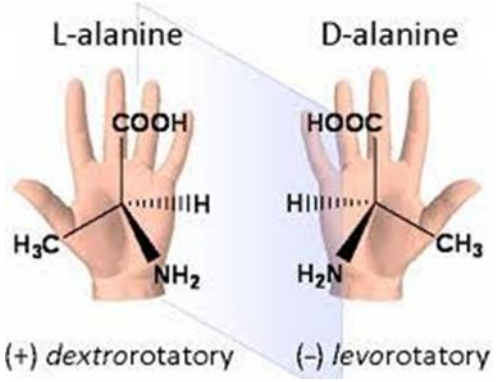
Iso lysergic derivatives are pharmacologically inactive. Iso lysergic acid is strongly dextrorotatory (+), while lysergic acid is levorotatory (-). Fresh alkaloids are always levo, upon storage it may isomerizes into iso lysergic acid (dextro).



Lysergic acid amide

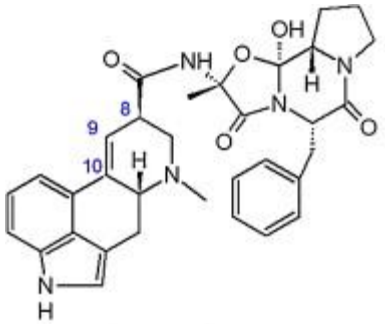


Isolysergic acid amide

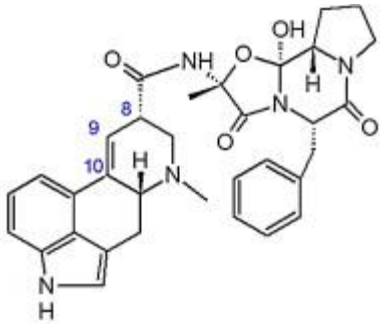


Lysergic acid amide derivatives could be further classified into:

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 insoluble.



Ergotamine

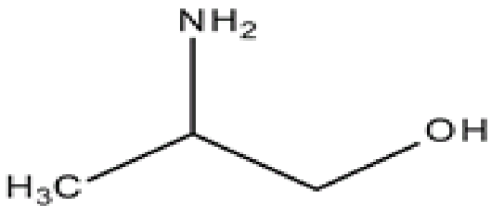


Ergotaminine

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

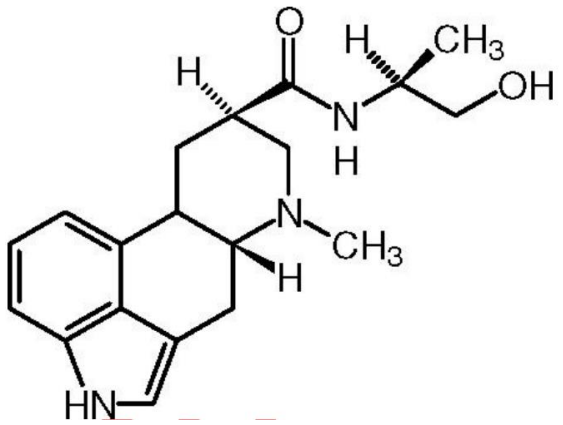
ergotoxine

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



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

Ergonovine

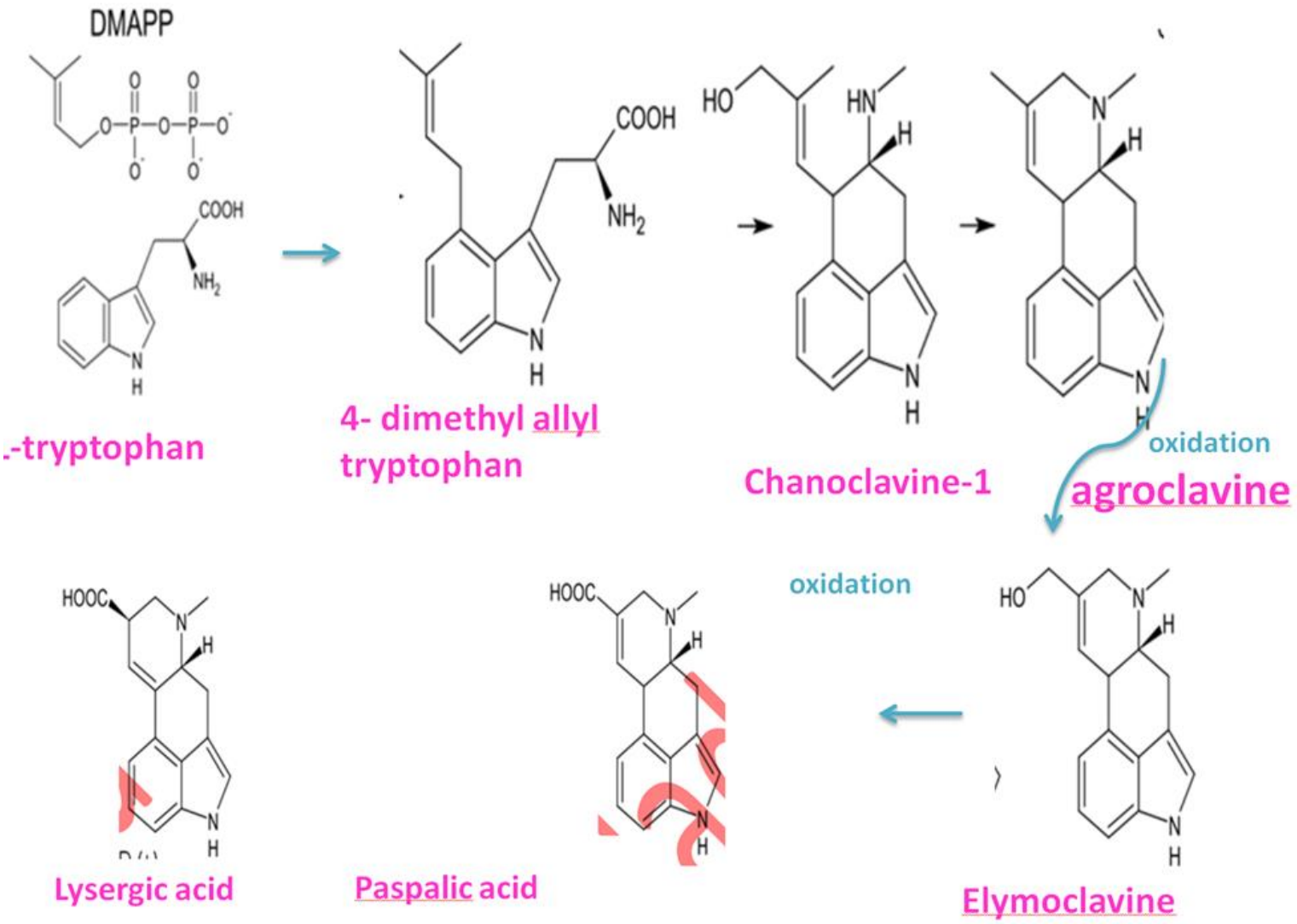


Lysergic acid amide derivatives classified into:

peptide group (water insoluble)		Alkanol amide (Water soluble)
A) Ergotamine Group	B) Ergtoxine Group	Ergometric Group
Which is formed 2 pairs 1. **Ergotamine& Ergotaminine** 2. **Ergosine &Ergosinine**	Which is formed 3 pairs 1. **Ergocristine &Ergocristinine** 2. **Ergocryptine& Ergocryptinine** 3. **Ergocornine& Ergocorninine**	Which is formed **one pairs Ergometrine (Ergonovine) & Ergometrinine**

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.