ALKALOIDS

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CINCHONA:

- Cinchona is a dried bark obtained from the cultivated trees of ***Cinchona calisaya, Cinchona ledgeriana, Cinchona officinalis, Cinchona succirubra*** of the family Rubiaceae.
- Cinchona is called as *Jesuit's bark* as this bark was identified and used by the Jesuits for its anti-pyretic property. As it was first discovered in Peru it is also known as *Peruvian bark*.

Cultivation

- Propagation: either seeds or budding or layering, in WB only budding is used and in TN budding or layering methods are applied.
- sub-tropical/tropical climates, height of about 1000-3000 m. If growing below this height, found to have less % of quinine.
- Rainfall: Uniform, 250-380 cm in a year. Atmospheric temp.: 16-24 degree C
- Soil: drained forest soil and rich in organic matter, acidic soil having pH of 4.5. to 6, small amount of N favorable for growth.
- Specification: Needs slopping situation, high humidity and protection from wind.
- Seeds are very small and light in weight, about 1 gm seeds contain 3500 seeds so that seeds are admixed with soil during sowing Seeds immediately used for propagation , on storage they lose their viability Germination take place in 3-6 weeks.

- Seedlings with 2 pairs of leaves are transplanted and space of 6-10 cm is maintained in between 2 seedlings and 2 rows. Young seedlings are protected from direct sunlight. In forest soil, transplanted after 15 months of growth and before heavy rainfall. Distance of 2X2m is maintained between 2 plants.
- Collection: 4-20 yrs of age, plants, selected for harvesting, but the maximum alkaloid content is found in 6-10 yrs old plants. Bark is collected by coppicing method, vertical incisions are made on branches , trunk of tree and incisions are connected by horizontal circles, the bark is then stripped off. Preparation: Dried in sun light and further by artificial heat, drying is done below 80 degree C. During drying loses 70% of its wt. Avoid molding and fermentation during drying.

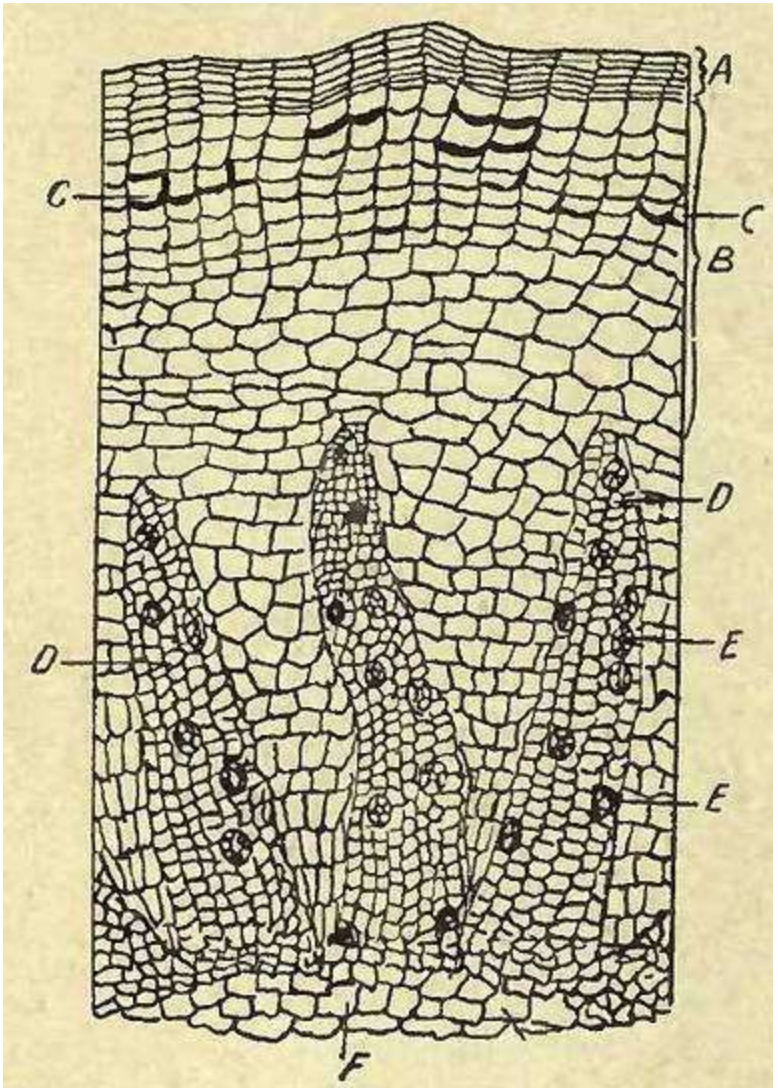


FIG. 232.—*Cinchona rubra*—Cross-section of bark. *A*. Cork cells. *B*. Cortical parenchyma. *C*. Coloring matter, deposits between and within the cells. *D*. Medullary ray. (Black line from *D* should not extend beyond the first two rows of cells of the figure.) *E*. Bast fibers.

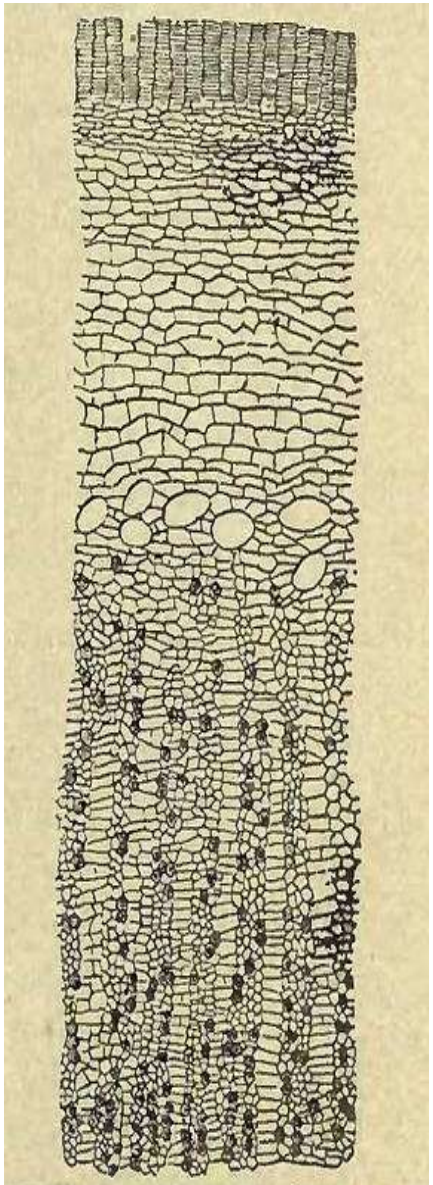


FIG. 230.—Cross-section of *Cinchona calisaya* bark (var. Micrantha).

Morphology

- Odor: slight and characteristic odor
- Taste: astringent and bitter Form : quills and curved pieces. Stem Bark 1. Length about 30 cm
- 2. Thickness about 2-6 cm
- Root bark Length about 2-7 cm
- 3. Outer surface is dull brown grey or Inner and outer surfaces are similar in grey color, color inner surface is pale yellowish-brown to deep reddish in color.
- 4. Presence of mosses and lichens no mosses and lichens Bark is rough and has transverse fissures Bark is scaly and shows depression.
- Microscopy: 1.Cork 2.Phellogen 3.Phelloderm 4.Cortex 5.Starch grains 6.Secretory cels 7.Medullary rays 8.Lignified Phloem fibres 9.Secondary Phloem

- **Extraction of Quinine**
- The bark is powdered and extracted with benzene or toulene in the presence of alkali and are extracted with dilute sulphuric acid. When it is made neutral, quinine sulphate separates as it is sparingly soluble. Cinchona bark has slight, characteristic odour and astringent and intensely bitter taste. It is available in the form of quills and curved pieces.

Chemical constituents of Cinchona:

- Cinchona bark consists of alkaloids which belong to quinoline group.
- quinine, quinidine, cinchonine and cinchonidine, quinicine, cinchonicine hydroquinine, hydrocinchonidine and homocinchonidine.
- Quinidine is also obtained commercially from cuprea bark, Ramijia pendunculata belonging to the family Rubiaceae.
- Quinine and quinidine form many salts, among their salts, sulphates are more significant.
- Quinine and quinidine are stereoisomers of each other.
- Cinchonine and cinchonidine are also isomers of each other.

Chemical Tests:

- 1.Powdered cinchona is slightly moistened with glacial acetic acid & heated in an ignition tube, purple vapours are produced at the upper part of tube.
- 2.Thalleoquin test: Powdered drug gives emrald green color with bromine water and dil. Ammonia solution.
- 3.Quinidine solution gives a white ppt. with silver nitrate solution, which is soluble in nitric acid ,

- Cinchona also contains
  - quinic acid
  - cinchotannic acid
  - a glycoside called quinovin,
  - tannins and
  - bitter essential oil.
- Quinine occurs as white crystals and in dark it shows fluorescent properties.
- It gives blue fluorescence in ultra-violet light.

- **Uses of Cinchona :**

✓ Cinchona bark is ***antimalaria***l in nature

✓ Cinchona preparations like cinchona extract, compound cinchona tincture are used as bitter ***stomachics*** and ***antipyretics***

✓ Quinine and its salts are used in the treatment of ***malaria***.

✓ Quinine is a protoplasmic poison for protozoa like *Plasmodium vivax*, *P.falciparum*, *P.malarie*, *P.fatal*. Hence, used as a powerful antimalarial drug

✓ Quinine is active against *Trypanosoma cruzi* epimastigotes.

✓ It has cardiac ***depressant*** activities.

✓ Used for the prevention of arrhythmias and tachycardia.

✓ Used for preventing atrial fibrillation.

Substituents:

- Cuprea Bark (Remijia pedunculata)
- Cuprea Bark (Remijia purdiena)
- C. Colombia

Isoquinoline alkaloids-Ipecac

- B.S: Dried roots and rhizomes of Cephalis ipecacuanha, family Rubiaceae.

- G.S: C.ipecacuanha is called Rio or Brazil ipecac, obtained from Brazil, Myanmar, Malaysia. C.acuminata called Panama ipecac, obtained from Columbia, Panama, India.

HISTORY

- 1817- Pelletier and Magnedi first isolated emetine in crude form.
- 1894- Paul and Cownley separated emetine in pure form.
- 1917- Pyman isolated emetamine, o-methyl psychotrine.

CULTIVATION & COLLECTION

- Propagation done by sowing seeds in mid January to February.
- Germination improved by treatment of seeds with lime water.
- 2months old seedlings are transplanted at spacing of 10x10cm.
- Temperature is 23-38C.
- Rainfall 300cm needed.
- Harvesting of roots done after three years.

DESCRIPTION

- **Brazilian characters:**
- **(a) Root:**
- Colour - Dark brick red to dark brown
- Odour - Faint
- Taste - Bitter
- Size - Up to 150 mm in length and 6 mm in thickness
- Shape - Roots are found in tortuous pieces.

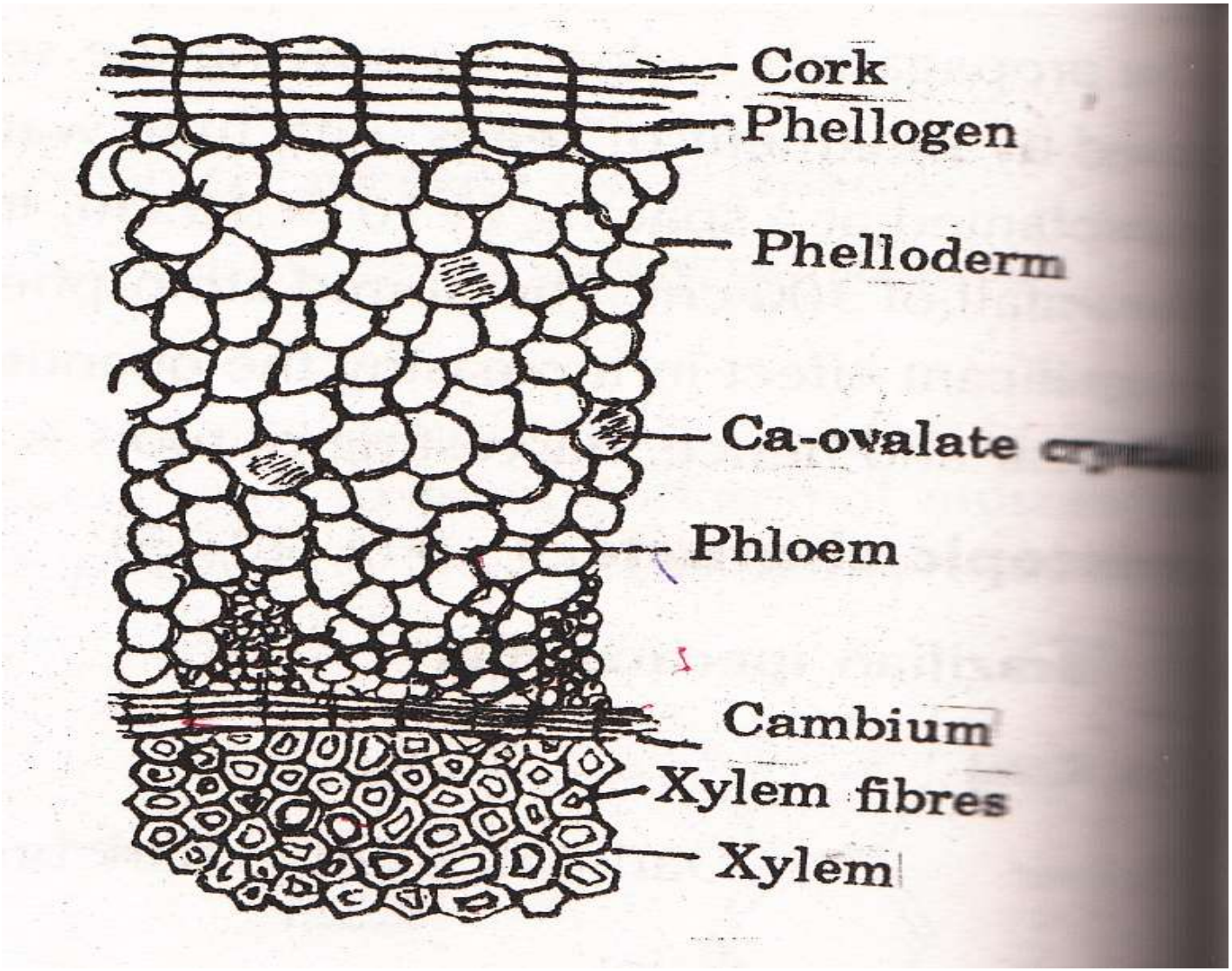
- **Rhizomes:**
- Color - Brick red to dark brown.
- Size - About 2 mm in diameter and short, attached to the roots
- Shape - Cylindrical.

Panama ipecacuanha

- Colour - Greyish-brown to reddish brown
- Odour and taste - Same as in Brazilian variety
- Size - upto 9 mm in thickness.
- Shape - Cylindrical

MICROSCOPY

- **Roots:**
- presence of cork layer with brown contents, which is followed by phelloderm composed of thin walled parenchyma .
- It is full of starch grains and acicular crystals of calcium oxalate.
- Xylem consists of tracheids and small vessel. Secondary medullary ray with starch gains and Size is upto 15 microns.

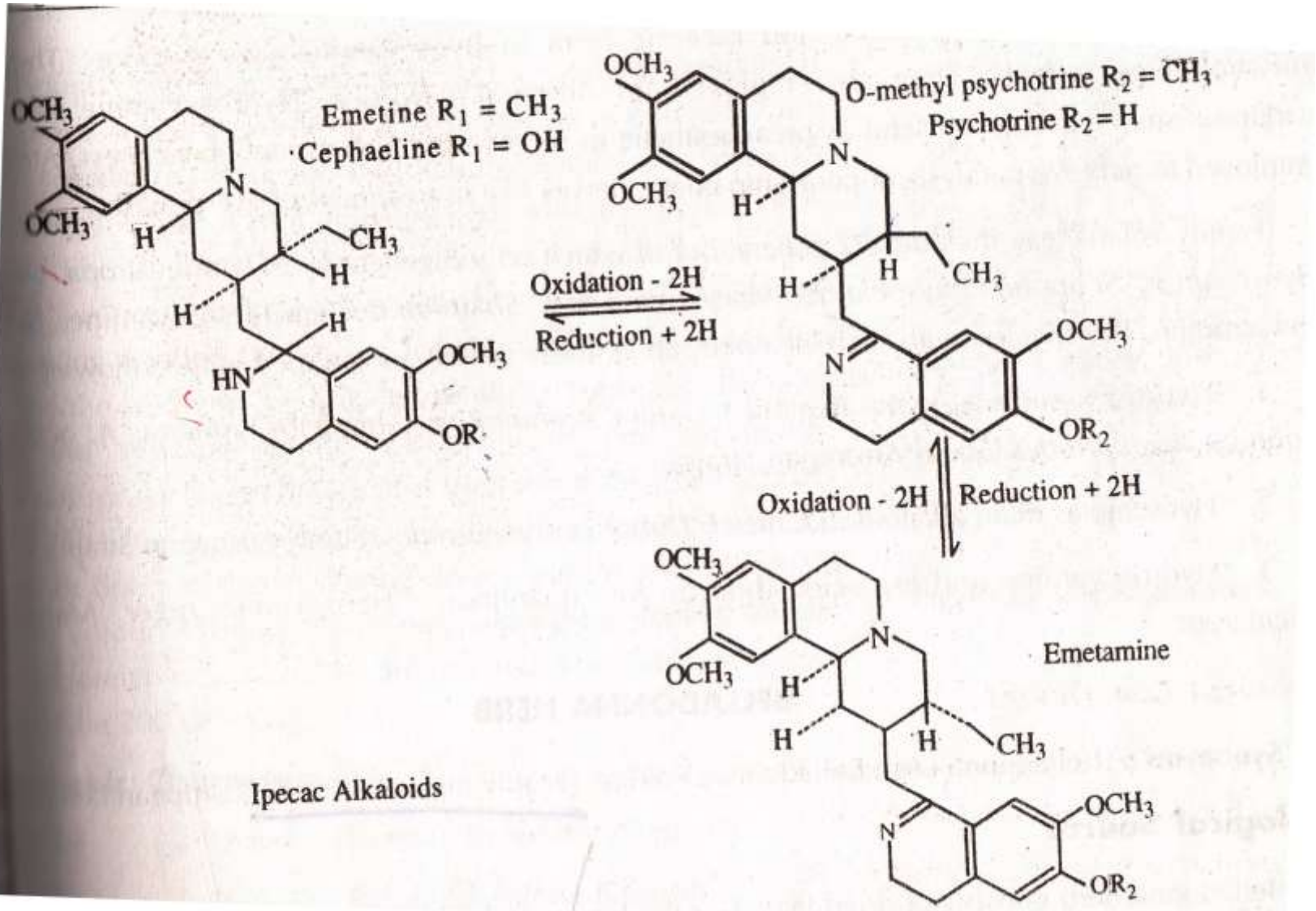

Cork
Phellogen
Phelloderm
Ca-ovalate
Phloem
Cambium
Xylem fibres
Xylem

Contd..

- **Rhizomes:** Pericycle is with thick walled scleried, protoxlyem and spiral vessels. Columbinan variety differs only in one aspect i.e. The starch gains are large and upto 22 microns.

CHEMICAL CONSTITUENT

- Isoquinoline alkaloids which belong to phenolic and non phenolic groups.
- The total alkaloids in Rio-ipecac are upto 2%, and in Panama ipecac, and emetamine.
- The portion of emetine and cephaeline in different varieties is 4:1 (Rio-ipecas), minor bases like phychotrine, emetamine and o-methyl psychotrine


Emetine $R_1 = CH_3$
Cephaeline $R_1 = OH$
O-methyl psychotrine $R_2 = CH_3$
Psychotrine $R_2 = H$
Oxidation - 2H
Reduction + 2H
Oxidation - 2H
Reduction + 2H
Emetamine
Ipecac Alkaloids

- Cephaline is conveted into emetine by methylation of phenolic C (6) hydroxyl group.
- Non phenolic alkaloidal group includes emetine and o-methyl psychotrine, while phenolic alkaloidal group includes cephaeline and psychotrine. Ipecac also cotaines ipecauanhic acid, glycoside ipecacuanhin.

CHEMICAL TESTS

- 2.5 g powdered dug + 20 ml hydrochloric acid + 5 ml ether. Shake well and filter. To the filtrate, add 0.5 g Potassium Chlorate. The presence of yellow colur gradually changing to red, after standing, due to emetine.
- The addition of Sulphuric acid and Sodium Molybdate (Frohde's reagent) to small quantity of emeting gives bright green colour.

USES

- Ipecacuanha is expectorant in small doses and and emetic in higer doses. Cephaeline has more emetic and less expectorant action as compared to emetine.
- Emetine hydrochloride is used as antiprotozoal, as it is highly toxic to amoeba i.e. Entamoeba histolytica, Hence, it is used by administering parentally, in treatement of amoebic dysentery.
- Ipecacuanha is used for isolated of emetine and cephaline.
- emeting has anti-tumour properties.

Adulterants and Substitutes

Opium

- **Raw opium**: is the air dried latex obtained by the incisions from the unripe capsules of ***Papaver somniferum*** Papaveraceae.

- India, Pakisthan, Afganisthan, Turkey, Russia, China, Iran.

Overview

- **Opiates** stneutitsnoc fo sevitavired ro stneutitsnoc era .muipo ni dnuof
- Opiates are narcotic analgesic.
- Narcotic refers to the pain-relieving and sleep-inducing properties of these highly-addictive alkaloids, including morphine, codeine and thebaine .
- Morphine is named after Morpheus the god of sleep, while **(somniferum** .nitaL ni "peels ot" snaem (

History:

- First cultivated in Mediterranean regions and brought by Alexander in 327 B.C to India.
- 1803 Narcotine was first isolated by Derosne.
- 1804 morphine isolated by Segnin.
- 1818 first introduced in medical practice by Magendi and Bally.
- 1833 Codiene isolated by Robiquet.
- 1848 Merck company isolated Papverine.
- 1923 Morphine structure elucidation by Gulland and Robinson.

Cultivation, collection and Prepation:

- Poppy is an erect plant attaining 60-120 cm height. It is rarely branched. The leaves are linear, oblong or ovate oblong and have a dentate or serrate margin. It bars bluish white, purple or violet coloured large flowers. Accrodingly, the varienties P. sommniferum var. glabrum, P. someniferum var. album, P. somniferum as only legal source of opium to many countries including United States of America and Britain

- Opium poppy is grown from November to march. Propagation is done by sowing the seed, for wish 3-4 kg of seed per hectare are necessary. The seeds admixed with about 3-4 parts of sand are sown.
- Opium poppy requires, highly fertile, well drained loamy soil with fine sand. The soil should contain organic matter, nitrogen and should have a pH around 7. The distance between two plants maintained is usually 25 cm and the plant reaches maximum height of one meter.

- After sowing within 3-4months the plant bears flowers, which are converted to capsules within few days attain maturity after 15-20days. At maturity the capsule exudes maximum latex. Vertical incision given to capsule upto 2mm. The incision repeats for about 4times on same capsule with 2days interval.

- The average yield of opium is about dried in open areas and further the seeds , it is from 4-5 quintals per hectare .Opium is exported traditionally from India.

Description:

- **Indian Opium**: Dark brown in color . It is found in the form of cubical pieces weighing about 900 g for marketing purposes . It is enclosed in tissue paper and is brittle and plastic in nature. Internally it is homogenous . Depending upon the requirement/the powdered from is available in the pack of 5 to 10 kg

- **Persian Opium** : Dark brown in colour ,found in the form of brick shaped masses , weighing 50 g . It is hygroscopic in nature , granular or nearly smooth with brittle fracture

- **Natural Turkish or European opium:** Brown or dark brown in colour . it is found in conical or rounded and somewhat flattened masses, weighing 250 to 1000g. On keeping, it becomes hard and brittle. It is covered with poppy leaves.

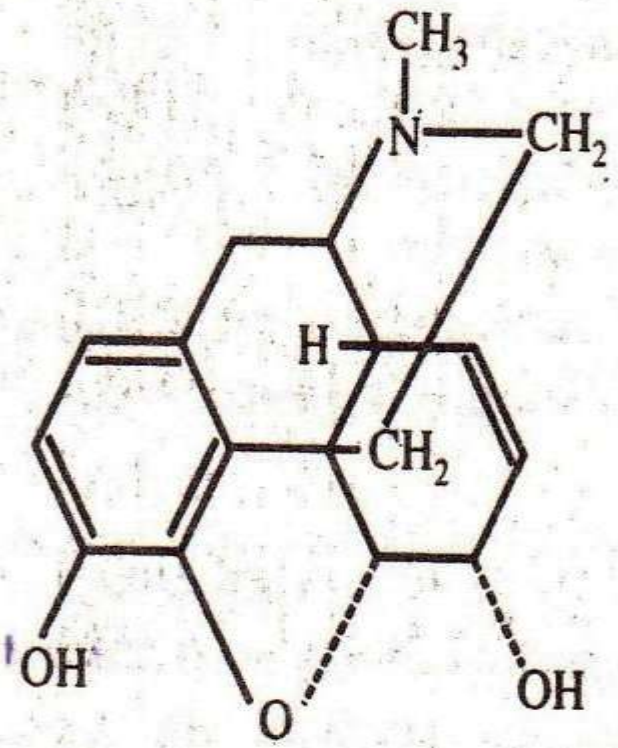
- **Manipulated Turkish opium :** It is chocolate brown or dark brown internally and covered with broken poppy leaves externally. The masses of this type are oval and flattend on upper and lower surface weighing about 200g .It is somewhat plastic or even brittle.

- **Manipulated European opium:** It is dark brown in colour internally and covered with broken leaves. It is found in the form of elongated masses with rounded ends weighing 150 to 500 g. It is firm, plastic and with brittle fracture.

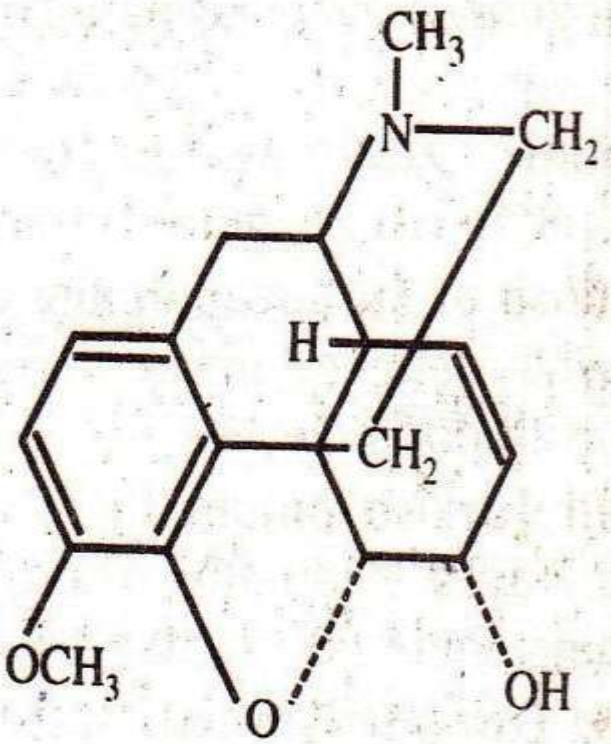
Chemical Constituents:

- The latex conations mainly the alkaloids derived from amino acids Phenylalanine and tyrosine. Chemically ,they are placed under bezylisoquinoline and phenantherene types.

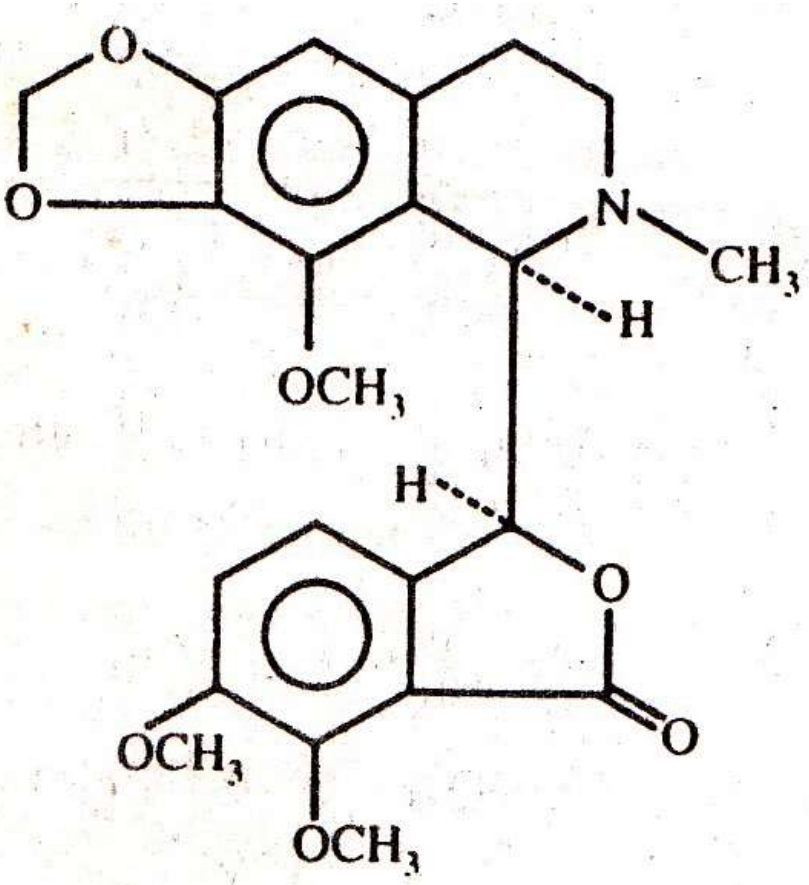
- Morphine is monoacidic ,laevorotatory phenolic alkaloid and also contains an alcoholic hydroxyl group at c(6) position.
- Codeine (methyl morphine) is a strong monoacidic base and inactive optically. It is it is soluble in water and organic solvent.
- Papaverine is a weak monoacidic base and inactive optically. it is slightly soluble in organic solvents, but insoluble in water
- The other important benzylisoquinoline alkaloid narcotine is a weak monoacidic base and is laeavorotatory, while its salt are dextrorotatory.



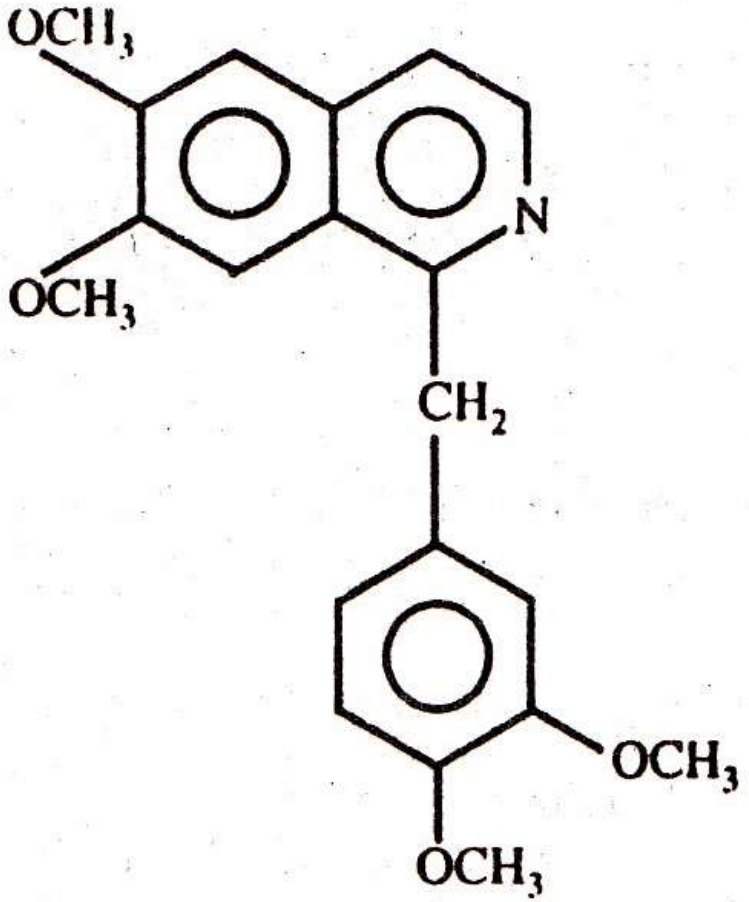
Morphine



Codeine



Narcotine



Papaverine

- The major biologically active alkaloids found in opium are morphine, codeine, thebaine, papaverine and noscapine.
- Papaverine and noscapine, have little to no effect on the human central nervous system, and are not usually considered to be narcotic or opiates, they have have a different mechanism of action.
- papaverine is smooth-muscle relaxant and noscapine is antitussive.

Classification

- **Natural opiates** muipo fo xetal eht ni deniatnoc sdiolakla era: .eniabeht dna ,eniedoc ,enihprom sa
- **Semi-synthetic opioids** ,setaipo larutan eht morf detaerc : morf devired era enodocordyh dna ,enodocyxo ,nioreh sa hcus .eniabeht dna ,eniedoc ,enihprom
- Heroin is diacetylmorphine.

Chemical tests :

- The general test to detect opium is testing presence of meconic acid .The alkaloids are present as the salts of meconic acid.

- (1) Opium is dissolved in water and to the filtrate, ferric chloride solution is added by which deep reddish purple colour is obtained, which persists even on addition of hydrochloric acid.

- **(2)** Morphine when sprinkled on nitric acid give orange red colour codeine does not respond to this test
- **(3)** The treatment of morphine solution with potassium ferricyanide and ferric chloride solutions gives bluish green colour . Codeine does not respond to this test.
- **(4)** Papavering solution in hydrochloric acid gives a lemon yellow colour with potassium ferricyanide solution.

Uses:

- Opium belongs to the category of hypnotic sedative and analgesic in which the action in mainly due to morphine.
- Morphine is a potent analgesic.
- In the medulla ,it sedates the respiratory, centre, emetic centre and the cough reflex.
- Codeine relieves local irritation in the bronchial tact and an antitussive used in various cough medicines.

- Papaverine has relaxant effects on smooth muscles of intestinal and bronchial tract and the blood vessels.
- Diacetyl morphine (heroin) has more narcotic analgesic property than morphine.

- **Fully synthetic opioids**.lodamart ,enodahtem ,enidihtep sa hcus :
- **Endogenous opioid** ,ydob eht ni yllarutan decudorp ,seditpep .snihpromodne dna ,snihpronyd ,snilahpekne ,snihprodne sa hcus

Pharmacological uses

- Opiates and Opioids bind to specific opioid receptors in the central nervous system and other tissues.

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- They have long been used to treat acute pain such as post-operative pain .

- They have also been found to be valuable in palliative care (cancer, and degenerative conditions such as rheumatoid arthritis)

Commercial Varieties of Opium

- Indian Opium: It is bark brown in colour and found in from of cubical pieces weighing 900g. It is brittle and plastic in nature. The powdered form is available as 5 to 10 kg packs. It contains 10 anhydrous morphine.
- **Persian Opium:** It is dark brown in colour and available as brick shaped masses of 450g .it is hygroscopic, granular or smooth.
- **Turkish Opium:** it is commonly called as druggist's opium or opium. It brown or dark brown in color and available as conical rounded or flattened masses.
- **Chinese Opium:** it comes in market in the form of globular cakes and contains 4-11

Adulteration:

- The production of opium is under government control and hence, normally it is not found to be adulterated. The adulterated forms show presence of opium capsules in powdered from, gum and sugary fruits.

Allied Plants:

- The various other species of poppy ,which do not contain morphine are Papaver aremone, P. dubium, P. orientate, P. bracteatum, P. strigosum, P. intermedia, P. paeoniflorum, hybrid of P. somniferum and P.orientate, P. psendo orientale.

Opiate poisoning

- Opiate poisoning can range from discomfort like constipation to death from respiratory depression.

- Alcohol and other sedatives enhance the effect of opiates, especially respiratory depression.

Vinca

B. Source:

Catharanthus or Vinca is the dried whole plant of ***Catharanthus roseus*** G. Don (or ***Vinca rosea*** L), Fam. Apocynaceae.

G. Source: South Africa, India, U.S.A, Europe, Australia.

HISTORY: Known since B.C 50 in European countries as Antidysentric, Antihaemorrhagic, Diuretic, Woundhealing.

Cultivation collection preparation:

- Vinca grows all over india upto 500meters. Rainfall 100cm. Fresh seed are sown in nursery beds or sometimes direct sowing also done.
- 2.5 lag of seeds per hectare are required. When the plants are sufficiently grown up, they are thinned out.
- In february or march they are sown in nursery and transplanted to open fields at 45cm x 30cm distance and about 74,000 plants per hectare is necessary.
- Leaf stripping is done 6 and 9 months after sowing.


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- Stems are cut about 7-8cm above the ground level after one year of growth.
- Leaves, stems and seeds are separated and air dried.
- Seeds are collected from matured fruits for next propagation.
- The yield of dried roots, stems and leaves per hectare in irrigated land is 1 and 3 tonnes respectively.

Description:

C- leaves -> green,

roots-> pale grey

Flowers-> violet pink- white or carmine red

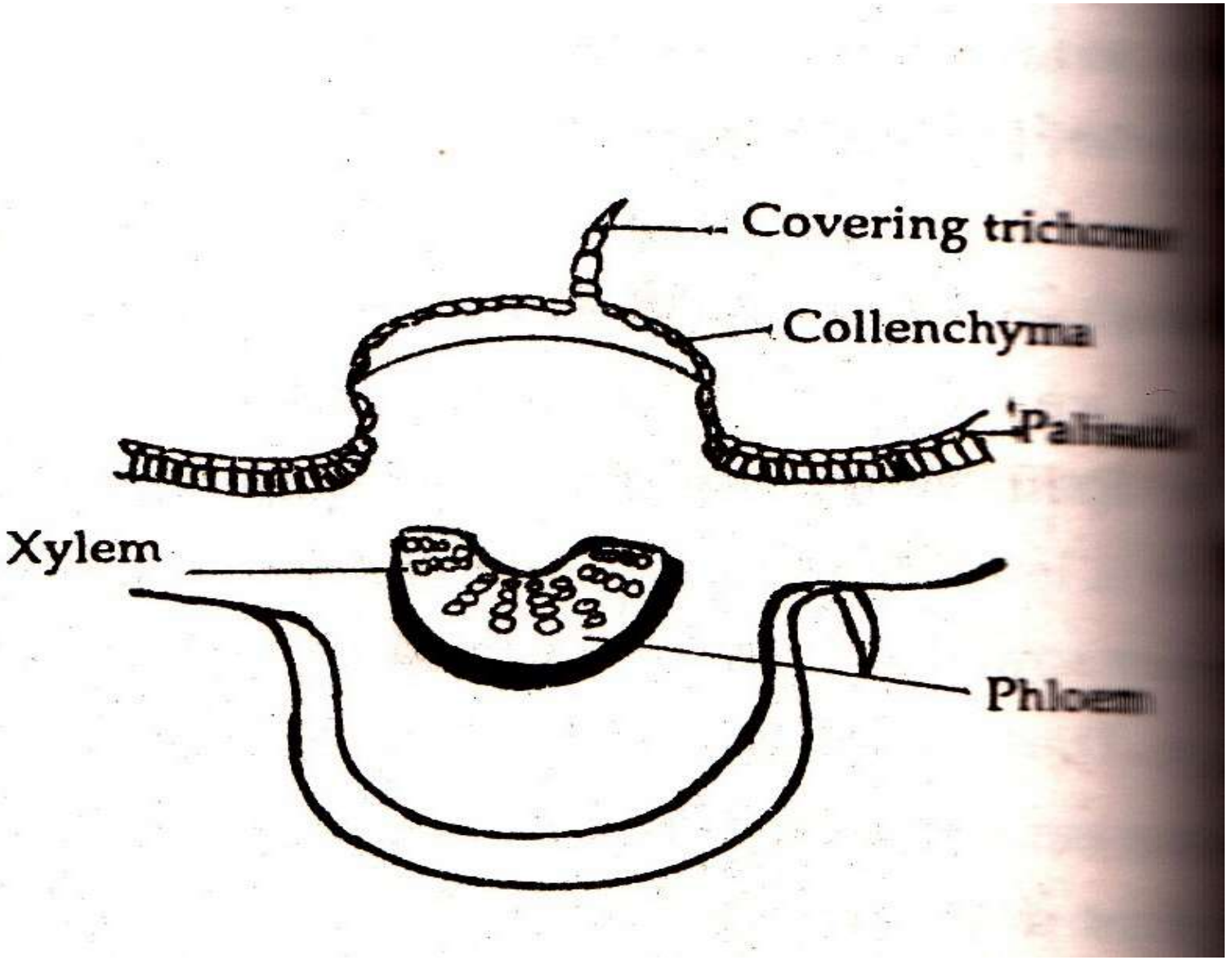
O- characteristic

T- bitter

Sh- vinca is erect, pubescent herb

Microscopic characters:

- Cruciferous stomata
- Upper surface shows presence of single layer of rectangular celled epidermis with unicellular covering trichomes.
- Spongy parenchyma is 5 to 8 layered with intercellular spaces.
- Midrib shows presence of collenchyma.
- Xylem and phloem are present.
- Calcium oxalate crystals absent.


Covering tric
Collenchyma
Pa
Xylem
Phlo

- **Chemical constituents & Classification:**

1- Monomeric Alkaloids:

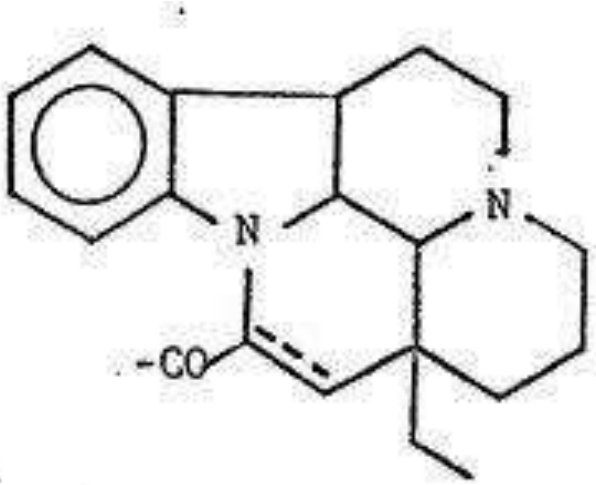
These are alkaloids that contain either indole or indoline:

- **Indole monomers e.g. Catharanthine**
- **Indoline monomers e.g. Vindoline and Vincamine.**

2- Dimeric Alkaloids:

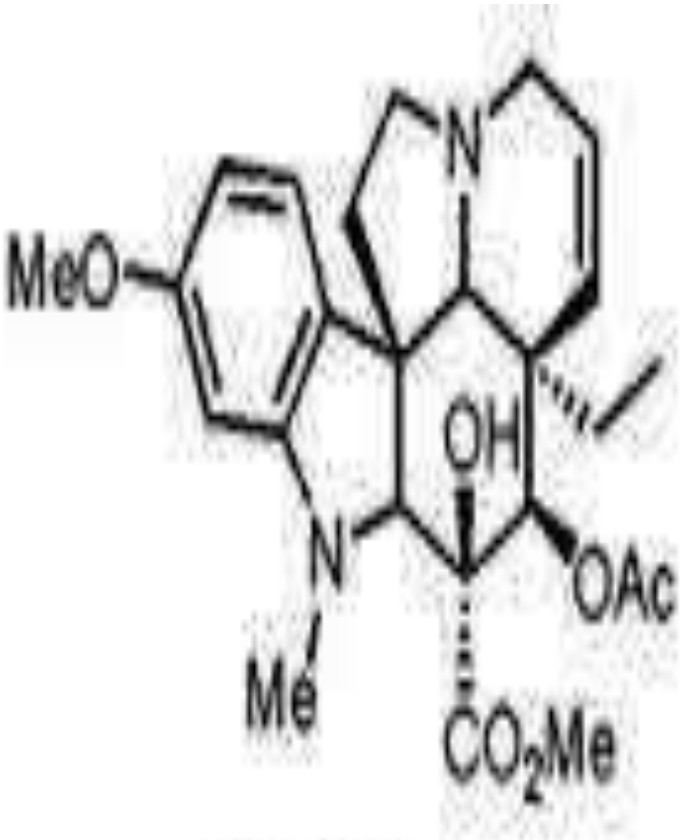
- **Homogenic dimmers: Composed of two indole or indoline monomers.**
- **Mixed dimmers: One indole and one indoline monomers e.g. Vincristine and Vinblastine.**

1- Monomeric Alkaloids:

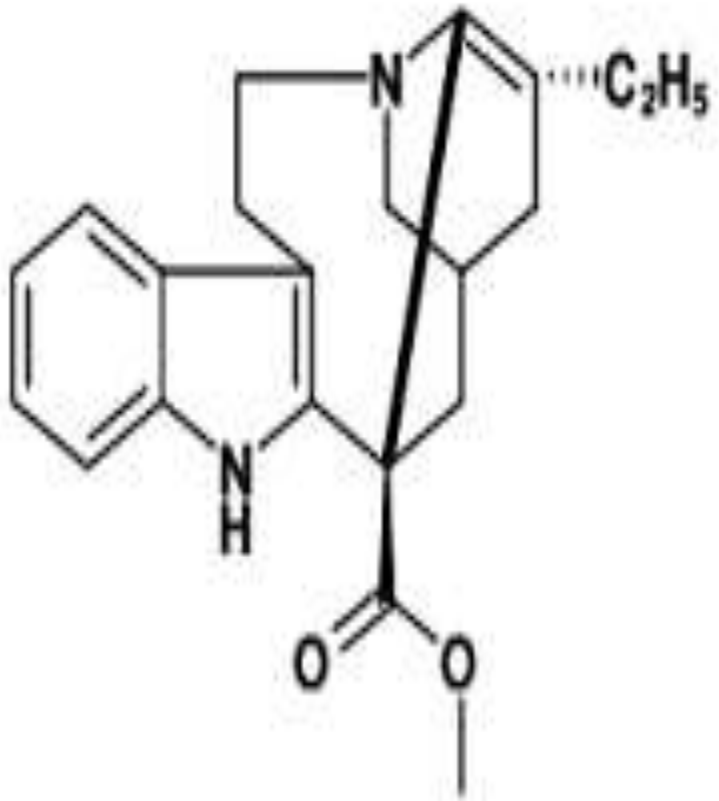


- **Vincamine**

  Enhances the cerebral blood flow, facilitate cerebral circulation metabolism and increase general activity. Vincamine is used in cerebral vascular deficiency and atherosclerosis in elderly patients.



Vindoline



Catharanthine

2- Dimeric Alkaloids:

Mixed dimmers

- *These are dimeric alkaloids having indole and indoline (dihydro-indole) nuclei e.g.* **Vinblastine and Vincristine**

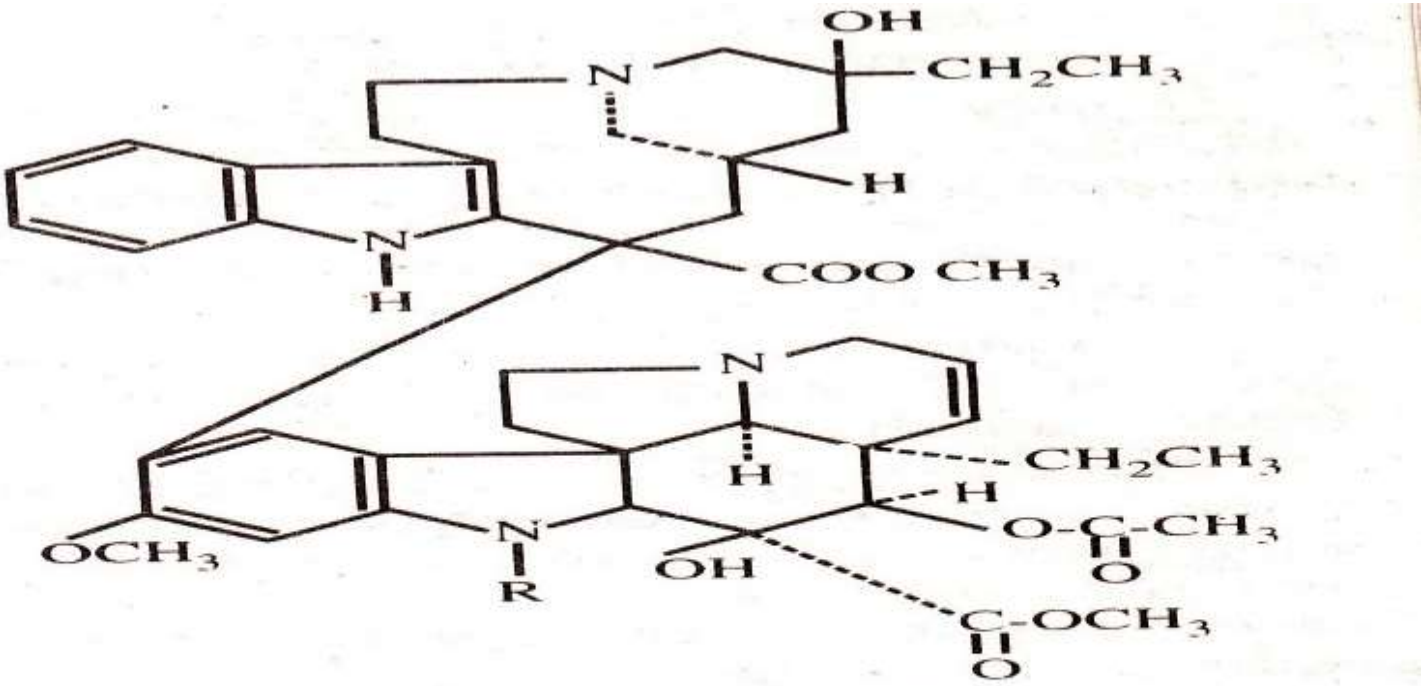
- **Vinblastine and Vincristine**
- **They occur in very minute amounts in *Vinca* (0.003- 0.005); 500 Kg of the plant yield only 1 gm of vincristine.**

- **They are very important for cancer treatment.**

- **Vincristine is more active but isolated in smaller amounts than Vinblastine. Vinblastine can be converted to vincristine chemically or by microbial transformation using *Streptomyces albogriseolu* .**

Vinblastine (Vincaleukoblastine) is produced by coupling of Catharanthine and Vindoline.

Vincristine (leurocristine) has CHO instead of CH_3 in the vindoline part of Vinblastine.



Vinblastine R = CH_3

Vincristine R = CHO

- **Tests for identification:**

- **1-Vanillin /HCl reagent** gives with:

  Vinblastine a **pink** color.

  Vincristine an **orange-yellow** color**.**

- **2-Van-Urk's reagent:**

  → **Reddish-brown color**.

- **Uses :**
- **Vinblastine is used for treatment of Hodgkin's disease (Pseudoleukemia or Lymphatic anaemia) and carcinoma resistant to other therapy.**

- **Vincristine has a cytotoxic effect .It is useful in the treatment of leukemia in children, small cell lung cancer, cervical and vaginal cancers.**

- **Mechanism:**
- Both alkaloids are Antimetabolites interfere with the syntheses of Desoxyribonucleic acids.

Indole Alkaloids

Ergot Alkaloids

Ergot is the dried **sclerotium** of a **fungus**, *Claviceps purpurea* (Fam. Claviceptiaceae) that arise on the ovaries of the **rye plant** (*Secale cereale*, Fam. Gramineae).

- Switzerland, hungary, czech republic.

History:

- "Argot" french word.
- Middle ages toxic effects called st. Anthony's fire.

- Ergotism is due to consuming cereals contaminated with the fungus.
- **Ergotism**.gninosiop togre mret-gnol fo tceffe eht si
- More recently by the action of a number of ergoline-based drugs.
- 1836 Ergot introduced in London Pharmacopoeia.
- History of *Cla viceps purpurea* first coined by Tulsane in 1853.

Ergotism, historical overview

- In middle ages, ergotism is known to have occurred on a large scale in some regions of Europe.
- In 857, for example, there was an epidemic in Germany characterized by necrosis of limbs and culminating in death.
- In 944, some 40,000 people in the south of France died from ergot poisoning.
- Between 837 and 1347, some fifty epidemics were recorded in Central Europe.

Ergotism, historical overview (cont.)

- In 1670, a French physician, Dr Thuillier, suggested that food could play a role in this disorder.
- Later, others showed that when ergot was fed to animals, they died.
- All the victims had eaten rye bread.
- In August 1951, in France more than a hundred people were poisoned and several died as a result.
- During the 1st half of the twenty century an intoxication have been reported in Egypt and was owed to ergot-contaminated wheat flour.
-

Collection and preparation:

- Rye plant is the host and ergot is a parasite. 600 plants from different families of wild and cultivated plants act as host for ergot fungus. Other species of ergot are C. microcephala, C. nigricans, C. paspali
- Scleroital stage or a dormant stage contains the maximum amount of drug.

Life cycle

- An ergot fo terolf fo yravo eht nehw spoleved *muitorelcs* eht fo seiceps lagnuf a fo serops yb detcefni si laerec ro ssarg suneg *Claviceps* .

- The proliferating fungus destroys the plant ovary and connects with the vascular tissue of the plant .

- The first stage of ergot infection is a white soft tissue (known as *sphacelia stage* wedyenoh yragus gnicudorp (eht fo tuo spord netfo hcihw ,(ecnatsbus ykcits hcir-ragus) .seiravo detcefni
- This honeydew contains millions of spores which are dispersed to other florets by insects .
- Later, the sphacelia convert into a hard dry **sclerotium** .seiravo eht edisni
- At this stage, alkaloids (mycotoxins) accumulate in the sclerotium .

- When a mature sclerotium drops to the ground, the fungus remains dormant until proper conditions (onset of spring, rain period, climate etc).
- It germinates, forming one or several fruiting bodies with head and stalk.
- In the head, spores are formed, which are ejected simultaneously (at the same time).

Ergot fungus on wheat

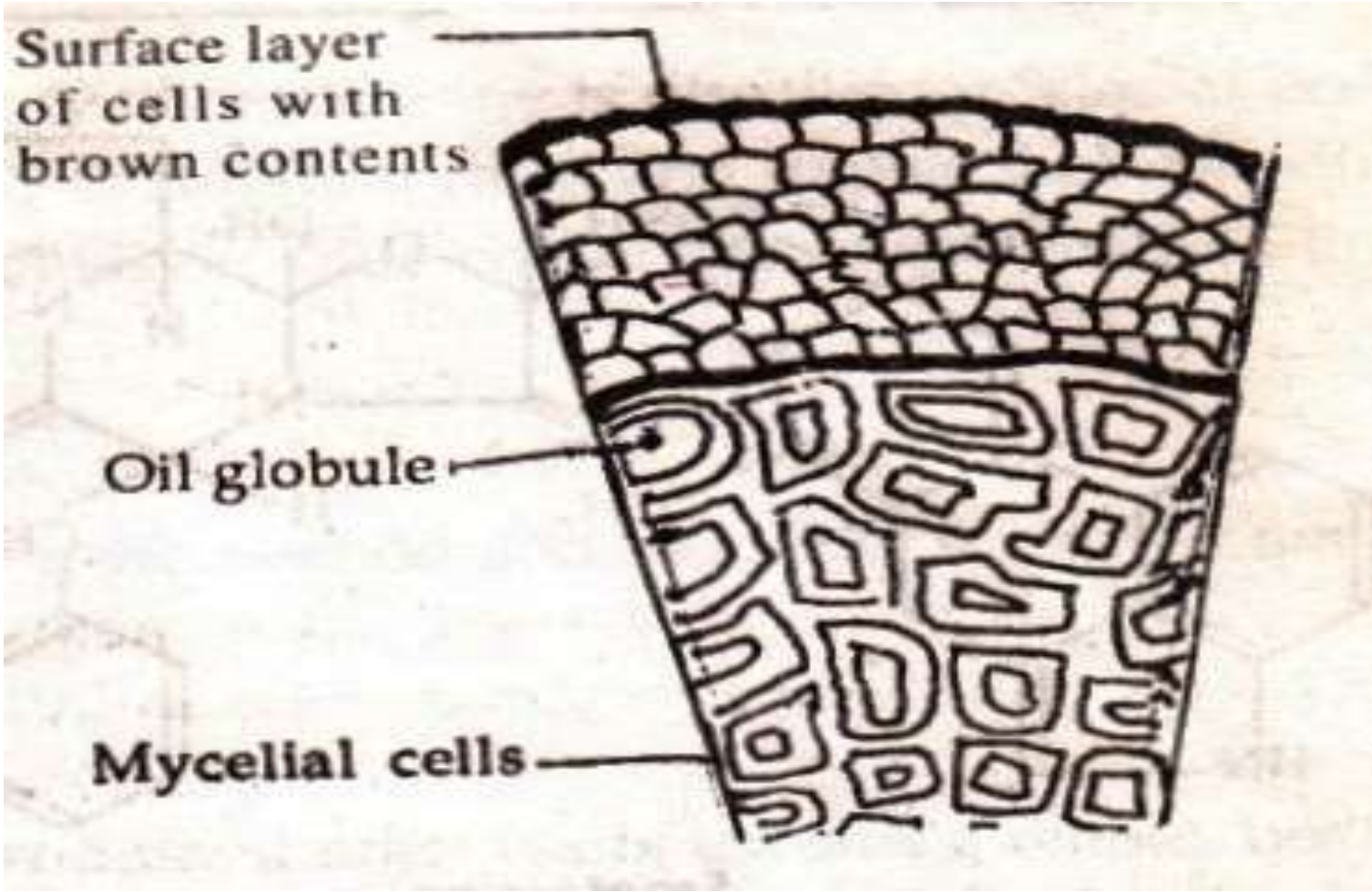
Macroscopy:

- Color- externally dark violet to black, internally pinkish white.
- Odour- disagreeable and faint.
- Taste- unpleasant.
- Size- sclerotia are 1-3cm in length 1-5mm in width.
- Shape- sclerotia are fusiform, triangular.

Microscopy:

- Outermost layer of the sclerotium is made up of few thin, flattened, polygonal cells of puple to dark brown color.
- Inner part is made up of dense pseudo parenchymatous cells composed of chitin.
- Mycelial cells are round or oval, thick with high refractive walls.
- Fixed oils.
- Sclerotium does not contain starch, calcium oxalate or any of the lignified tissue.

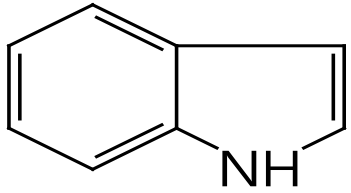
T.S. of Sclerotium of Ergot:



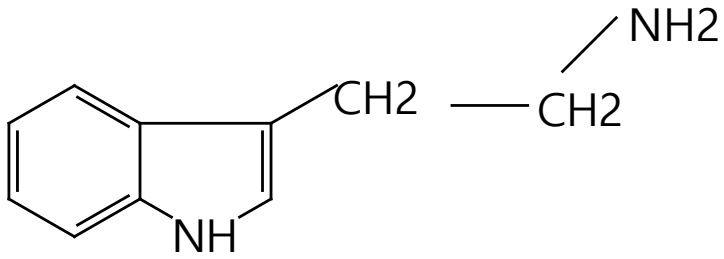
Chemical constituents:

- They are medicinally important indole alkaloids (0.1-0.25%) which are derivatives of lysergic acid.
- Biogenetically they are derived from the amino acid tryptophan.

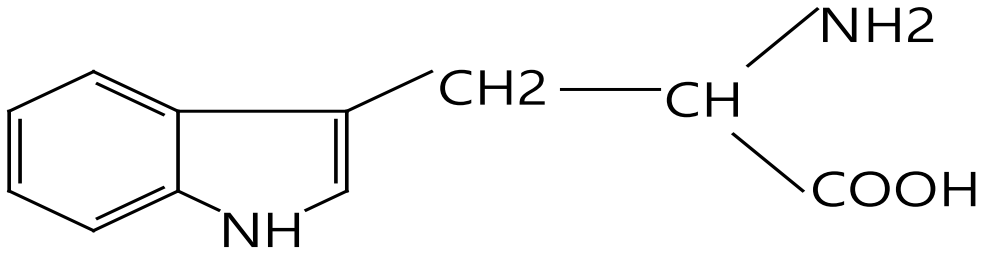
- Indole



- Tryptamine

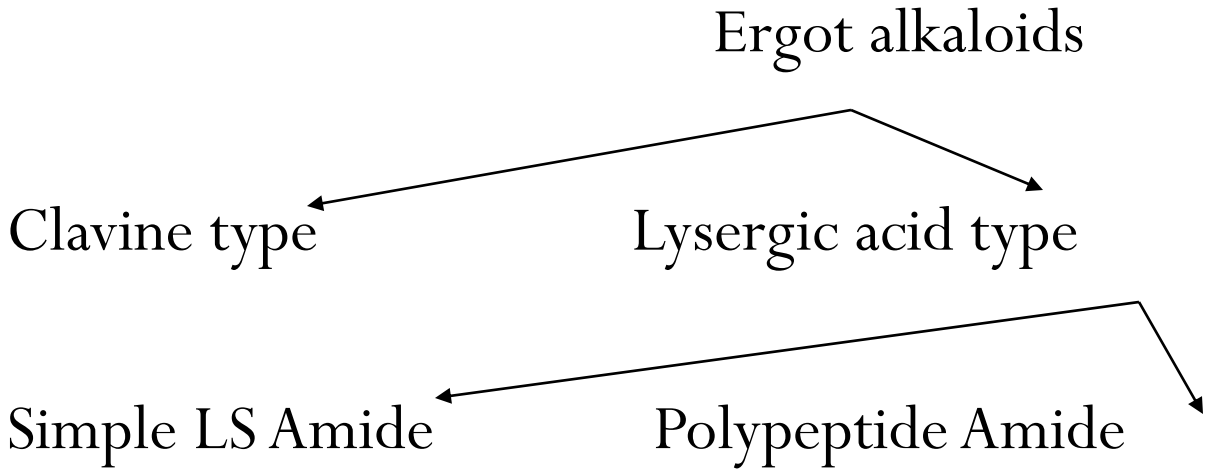


- Tryptophan



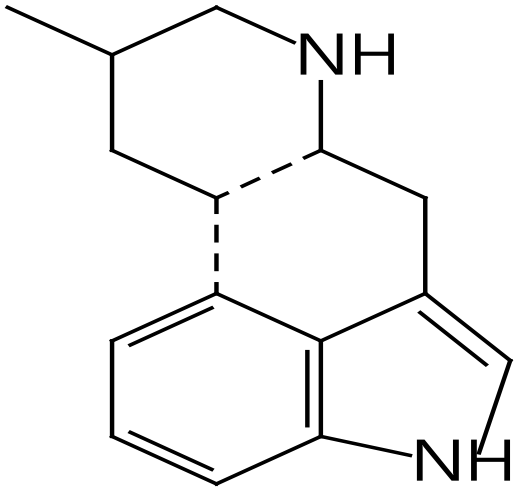
Classification

- There are two main groups of ergot alkaloids :
- A-The clavine type .
- B-The lysergic acid derivatives type.


Ergot alkaloids
Clavine type
Lysergic acid type
Simple LS Amide
Polypeptide Amide

Ergot alkaloids

- The clavine type alkaloids as well as the lysergic acid derivative alkaloids are product of condensation of tryptophan (or tryptamine) with isoprenyl moiety (5 Carbons)
- Ergot alkaloids

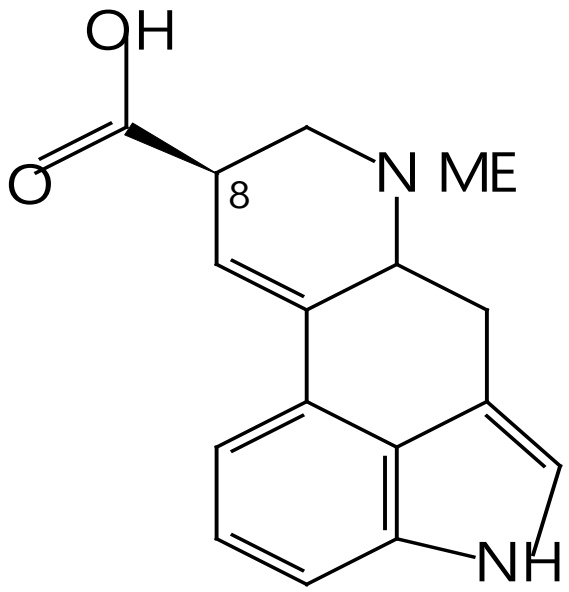


A-The clavine type alkaloids

- Alkaloids of this class all end with the suffix (-clavine) e.g. agroclavine, elemoclavine…..
- They are all simple water soluble bases.
- Not physiologically active as the lysergic acid derivatives.
- Recently few examples show significant oxytocic activity.
- Agroclavine is a powerful uterine stimulant.

B-The lysergic acid derivatives
i-The simple lysergic acid amides

- All are water soluble alkaloids.
- Low molecular weight.
- All are amides of lysergic acid with simple amines.



General Characters:

- Ergot alkaloids are N-monosubstituted amide derivatives of both lysergic acid and its isomer isolysergic acid that differ only in configuration at C-8.
- On treatment with **ammonia lysergic** and **isolysergic acids** give the corresponding amides **ergine** and **isoergine** respectively.

Lysergic acid

Isolysergic acid

Ergine

- Members related to **lysergic acid** (e.g. **ergotamine** and **ergometrine**) are **levorotatory**, **more active** and designated by suffix **"ine"**.
- Members related to **isolysergic acid** (e.g. **ergotaminine** and **ergometrinine)**, are **dextrorotatory, less active** and designated by suffix **"inine"**.

- The simplest naturally existing is ergine (lysergic acid amide, LSA) and erginine (isolysergic acid amide).
- Ergine is a psychoactive component, it is known as natural LSD.
- The semithynthetic LSD is more potent than ergine as a psychedelics drug.
- Psychedelics are part of a wider class of psychoactive drugs known as hallucinogens .

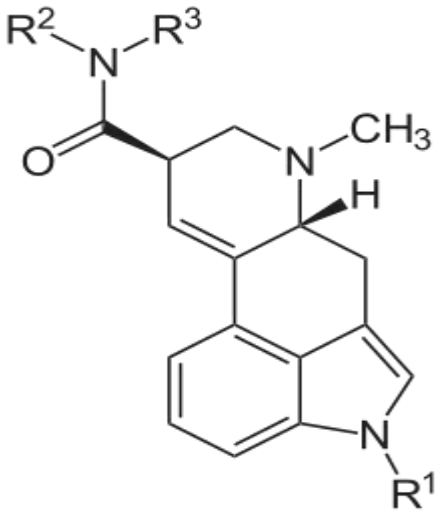
i-The simple lysergic acid amides (cont.)

- The most important members of this group is the potent oxytocic alkaloid ergometrine.
- Ergometrine is the amide of lysergic acid with 2-amino propanol.
- And the famous hallucinogen (LSD) lysergic acid diethylamide.
- LSD is a semisynthetic drug with a very potent action on the CNS in extremely small doses.

LSD

- LSD was first semi-synthesized by Albert Hofmann in 1938 from ergot .
- The short form LSD comes from its early code name *LSD-* -eruäS gresyL" namreG eht rof noitaiverbba na si hcihw ,*25* .rebmun laitneuqes a yb dewollof "dimalyhteid
- It is commonly semi-synthesised by:
- reacting diethylamine with lysergic acid .
- or from ergine (lysergic acid amide).

General structure of lysergic acid amides



Name	R1	R2	R3
Ergine	H	H	H
Ergometrine	H	CH(CH3)CH2OH	H
Methergine	H	CH(CH2CH3)CH2OH	H
Methysergide	CH3	CH(CH2CH3)CH2OH	H
LSD	H	CH2-CH3	CH2-CH3

(–) Laevorotatory alkaloids		(+) Dextrorotatory alkaloids
Ergometrine	Water-Soluble	Ergometrinine
Ergotamine	Water insoluble	Ergotaminine
Ergosine		Ergosinine
Ergocristine		Ergocristinine
Ergocryptine		Ergocryptinine
Ergocornine		Ergocorninine

Ergotamine

- **Characters:**
- Its (d) isomer is called Ergotaminine.
- The peptide moiety is composed of 3 amino acids:

  α-Hydroxyalanine

  Proline

  Phenylalanine

- **Uses:**

  Treatment of migraine as it constricts the peripheral blood vessels.

  Has some oxytocic (ecobolic) activity.

Ergometrine

- Is a potent oxytocic alkaloid.
- Contraction of uterus.
- Facilitate labour.
- Prevent postpartum hemorrhage.

Chemical tests:

- 1) Ergot powder + p-dimethylaminobenzaldehyde ----→ blue.
- 2) Ergot + solvent ether + sulphuric acid→ Filtrate obtained shows red violet color in its aqueous layer, when treated with saturated sol of sodium bicarbonate.
- 3) Ergometrine gives blue fluorescence in water.

Uses:

- Ergot alkaloids have a wide range of biological activities.
- 1- Ergotamine is used in the treatment of migraine.
- It has the ability to constrict dilated blood vessels in the cerebral membranes.
- Hypertension is a side effect.
- 2- Ergometrine is used during childbirth to enhance labour pains in delivery cases. –after expulsion of the placenta– to stimulate uterine contractions and to prevent postpartum hemorrhage.

Rauwolfia

- Synonyms: Rauwolfia root, Serpentina root, Chhotachand. Source: Dried roots of Rauwolfia serpentina
- Family: Apocynaceae. It contains NLT 0.15% of reserpine and ajmalcine.
- GS: Tropical regions of Asia, America and Africa. Commercially, In India, Sri lanka, Myanmar, Thailand and America. In India UP, Bihar, Orissa, Tamil Nadu, West Bengal, Karnataka, Maharashtra and Gujarat.

Cultivation

- Climate: wide range of, best suited humid, shade
- Soil: wide range of with large amount of sand makes plants more susceptible for disease Clay: loamy soil,
- pH: acidic up to 4 Temperature: 10-38 degree C,
- Rainfall: 250-500 cm
- Propagation: seeds, roots, cutting, root stumps Initially seeds are sown into the nursery beds.
- Sowing period: May or breakdown of monsoon Implanting seedling: August, at a distance of 16-30 cm Various fertilizer, manures: ammonium sulphate, urea, bone meal. Collection: when plants are 3-4 year old. Uprooting, roots are cut properly, washed as to remove earthy matter & dried in air.

Morphology

- Color: bark: greyish yellow, Wood: pale yellow Odor: odorless Taste: bitter Size: 10-18 cm long; 1-3 cm in diameter Shape: sub-cylindrical, slightly tapering & tortuous
- Microscopy:
- Cork: striated Phelloderm (few layers of parenchyma) Narrow phloem: small scattered sieve tubes Secondary phloem: Calcium oxalate crystals Xylem: Vessels, tracheids, wood parenchyma, wood parenchyma & wood fibre

Constituents:

- About 30 indole alkaloids; range from 0.7-3% on GS
- Mostly in bark, root Indole, Indoline, Indolenine ,Oxyindole, Pseudo indoxyl alkaloids Reserpine Oleo-resin, phytosterol, fatty acid, alcohol, sugar .
- Ajmalicine, ajmaline, rauwolfinine, rescinnamine, reserpinine, yohimbine, serpentine, serpentinine Reserpine: ester of trimethoxy benzoic acid Rescinnamine: ester of trimethoxycinnamic acid
- Chemical test :With conc. HNO_3 → red coloration of medullary rays
- Reserpine: with vanillin in acetic acid → violet red color alkaloids: powdered rauwolfia + H_2SO_4 + p-dimethyl amino benzaldehyde → violet-red color

- USES: Reserpine: lowers BP by depleting store of catecholamine at nerve ending, prevent re-uptake of nor-epinephrine at storage sites, allowing enzymatic destruction of neuronal transmitter. Neuropsychiatric disorder Rescinnamine: anti hypertensive but Higher dose □ depression Dereserpine: anti hypertensive & tranquiliser Ajmalicine: treatment of circulatory diseases, relief of obstruction of normal cerebral blood flow. Syrosingopine: same as above but milder
- Allied Species: Rauwolfia vomitoria R. obscura R. Rosea

Nux-Vomica:

- Synonyms: Crow fig, Semen Strychni
- Source: Dried ripe seeds of Strychnous nuxvomica Linn.
- Family: Loganiaceae.
- Contain NLT 1.2 % of total alkaloids calculated as strychinine.
- GS: East India, Sri lanka, Northern Australia, and India. Abundantly in South India i.e. Tamil nadu, Kerala and on Malabar coast. Also available in Bihar, Orrisa, Konkan, Mysore and Gorakhpur.

Collection & Preparation

- Found throughout the tropical area, 1300 m above sea level. -Plant height: 10-12 m, crooked trunk, several branches. -Leaves are orange, oppositely arrange, oval shape, entire margin and acute apex. -Flowers are greenish white and the bark is greyish to yellow. -Fruit are orange yellow, consists a berry about the size of a small orange. -When ripe it has a hard orange-yellow pericarp and a white, pulpy interior – containing 4-5 seeds & Seeds are washed to remove pulp and dried. -Unripen seeds are separated by the floating test in water. -Seeds are dried on mat and packed in gunny bags for marketing. -Collection of fruit and seeds is carried out from NovemberFebruary. -Exported in small sacks known as pockets.

- Morphology: Hilum, ridge on testa and micropyle Color: greenish brown Taste: bitter
- Microscopic Characters: Lignified Trichomes, layer of collapsed cells and endosperm
- Chemical Constituents: 1.5-5% bitter Indole alkaloids, Strychnine and Brucine -Vomicine, α-colubrine, pseudostrychnine, Isostrychnine, N-oxystrychnine, protostrychnine, β-colubrine and novacine. Glycosides: loganin, chlorogenic acid and fixed oil
- Chemical test s:Thin sections of nux vomica seeds are defatted and following test are performed. 1. Stain the TS of nux vomica with conc. HNO3 → endospermic cells take yellow color due to presence of brucine.
- 2. Stain the TS of nux vomica with ammoium vandate & H2SO4 → Manddin's reagent →endospermic cells become purple due to strychine
- 3. Strychnine + H2SO4 + Potassium dichromate → violet color red → finally yellow

- Properties: Brucine is the dimethoxy derivative of Strychnine. Both alkaloids contains 2 Nitrogen atoms. Hemitoxiferine is a degradation product of strychnine. Dimerization of hemitoxiferine produces a valuable skeletal muscle relaxant Toxiferine
- USE -Bitter stomachic, tonic, CNS stimulant, increases BP, certain forms of cardiac failure, stimulant for respiratory & CVS -Brucine: very less physiological action, 1/6 th potency as compared to strychine, 4 times bitter than strychine. Brucine: denaturinng alcohol, inedible fats, dog poison.
- Allied specids: Strychnos nuxblanda, S. potatorum