

Indole

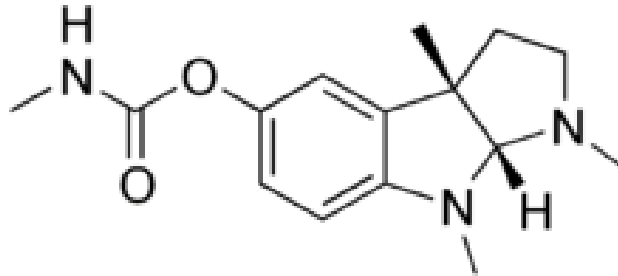
Indole Alkaloids

**Alkaloids Derived from Tryptophane
(Part II)**

1) Physostigma alkaloids (Calabar bean alkaloids)

Physostigmine (Eserine)

- * Present in the seed of *Physostigma venenosum* Fam. Leguminosae.
- * Eserine is a tertiary base, possessing an ester linkage



Uses

A myotic drug (in the treatment of glaucoma). It has a cholinergic effect and stimulates gland secretion.

Being replaced by synthetic anticholinestrase e.g. neostigmine



INTRASTIGMINA[®]

neostigmine methylsulphate 0.5 mg

20 ampoules
of 1 ml for I.M. - I.V. use

Istituto
LUSO FARMACO d'Italia S.p.A.
Milano - Italy



MENARINI INTERNATIONAL

2- Ergot Alkaloids

- **Occurrence:**

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

- Consumption of flour contaminated with Ergot led to many serious intoxications known as (Ergotism).
- Ergot can be detected in flour by using UV light where contaminated flour will show violet spots.



- **Classification of Ergot Alkaloids:**

- **A- Clavine Type Alkaloids:**

Simple water soluble bases with little medicinal value. All end with “clavine: e.g. Agroclavine.

- **B- Lysergic acid Amides:**

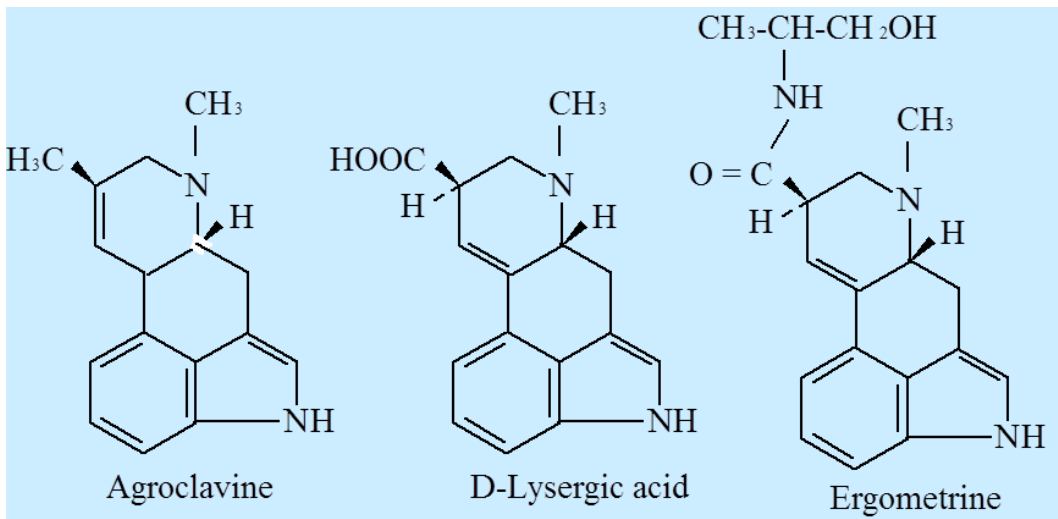
They are all derivatives of (l)-Lysergic acid and subclassified into:

- **1- Simple lysergic acid amides:**

Composed of Lysergic acid and simple amines.

- **2- Polypeptide Alkaloids:**

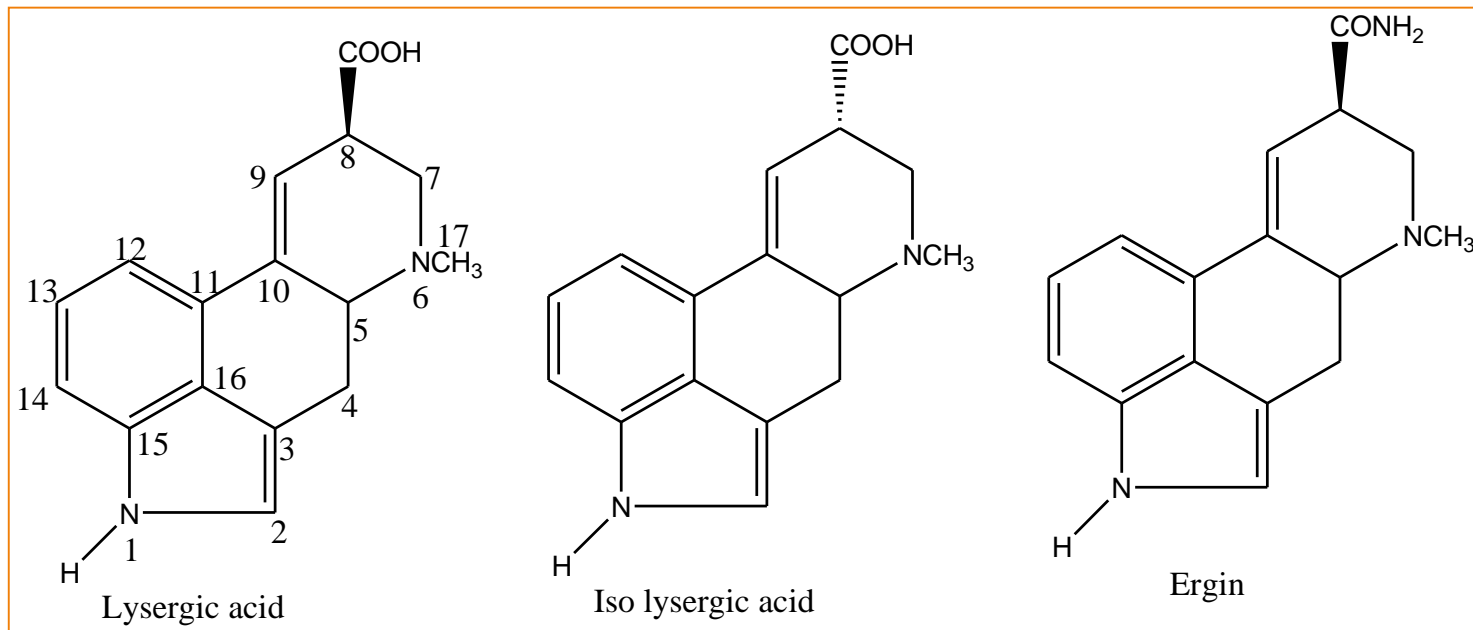
Composed of Lysergic acid and at least 3 amino acids.



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.



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. **ergotamine** and **ergometrine**), are **dextrorotatory, less active** and designated by suffix “**inine**”.

1- SIMPLE LYSERGIC ACID AMIDES

Characters:

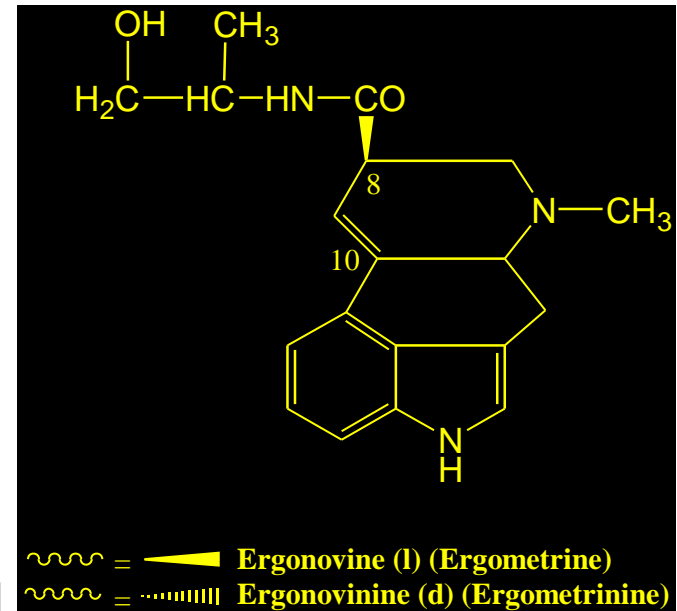
- 1- Composed of Lysergic acid and simple amines.
- 2- Low molecular weight.
- 3- Water Soluble.

Ergonovine (Ergometrine)

- Composed of (*l*)-lysergic acid and 2-aminopropanol.
- Its (*d*) isomer is called Ergometrinine.

Uses:

It causes vigorous contraction of the uterus.
It is mainly used as an oxytocic in order to aid delivery or to prevent postpartum hemorrhage.

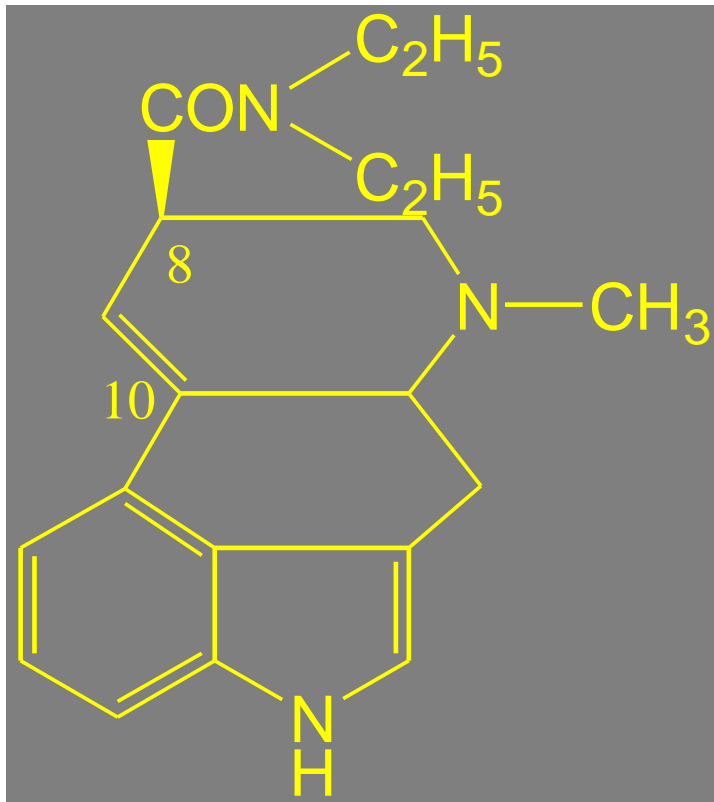


LYSERGIC ACID DIETHYLAMIDE (LSD)

It is a semisynthetic product.

LSD has potent CNS stimulant effect.

LSD is one of the abused drugs.



2- POLYPEPTIDE ALKALOIDS

Characters:

- **They are derivatives of Lysergic acid with a complex polypeptides of at least 3 amino acids.**
- **They have high molecular weight.**
- **They are insoluble in water.**
- **This class include medicinally important members.**

ERGOTAMINE

Characters:

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

α -Hydroxyalanine

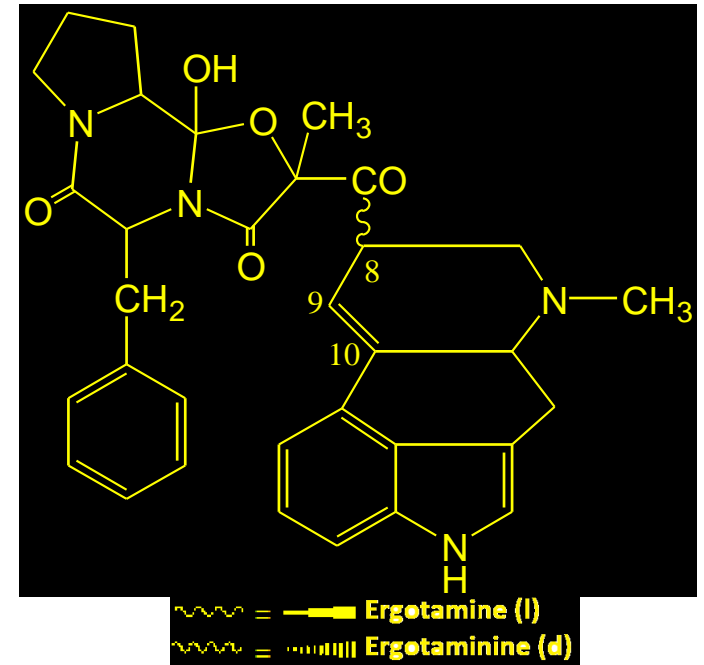
Proline

Phenylalanine

Uses:

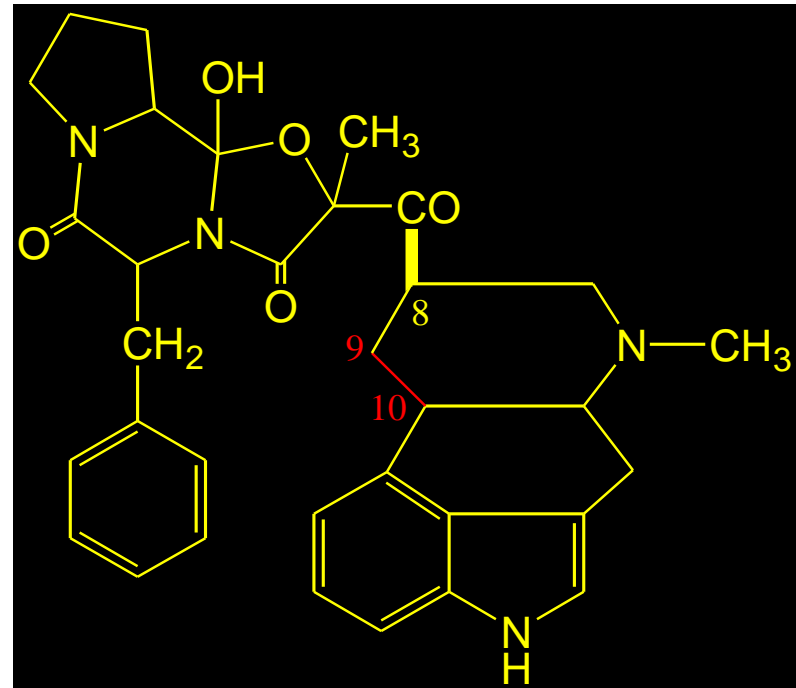
Treatment of migraine as it constricts the peripheral blood vessels.

Has some oxytocic activity.



➤ **STRUCTURE ACTIVITY RELATIONSHIP:**

- Lysergic acid must be in the (*l*) form. The (*d*) isomers are inactive.
- Saturation of the 9- 10 double bond of Ergotamine gives Dihydroergotamine, a compound with **antimigraine** effect but no oxytocic effect.



Chemical Test:

Van-Urk's test

Solution of Ergot alkaloids + Van-Urk's reagent (p-dimethylaminobenzaldehyde in 15% H_2SO_4) containing traces of FeCl_3 \longrightarrow **Deep blue color**



NOVARTIS

Methergin[®]

Methylergometrin.

0,125 mg 30 Dragées/coated tablets/grageas



Metograin

Tablets

For Migraine



REG. NO. IN YEMEN : 0010646

3- *Vinca (Catharanthus)* Alkaloids

Occurrence:

Catharanthus or Vinca is the dried whole plant of *Catharanthus roseus* Fam. Apocynaceae.

It contains about 150 alkaloids, the most important are **vinblastine and vincristine**.

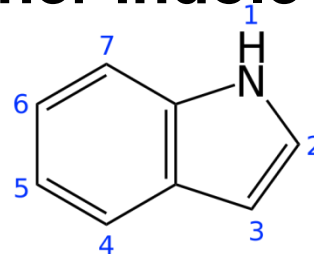


Classification:

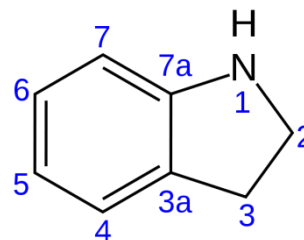
1- Monomeric Alkaloids:

These are alkaloids that contain either indole or indoline:

- Indole monomers e.g. Catharanthine



- Indoline monomers e.g. Vindoline and Vincamine.



2- Dimeric Alkaloids:

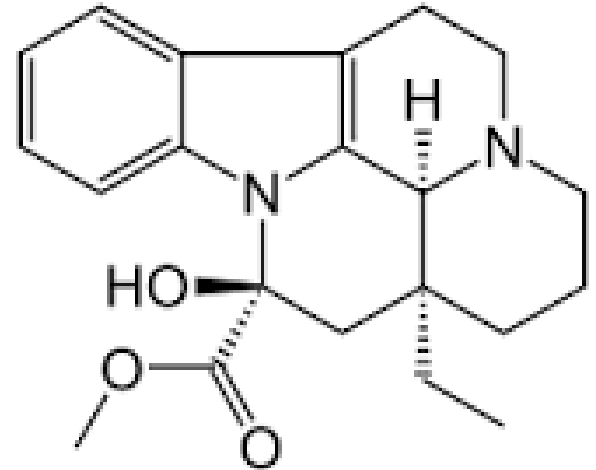
- Homogenic dimmers: Composed of two indole or indoline monomers.
- Mixed dimmers: One indole and one indoline monomers e.g. Vincristine and Vinblastine.

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.



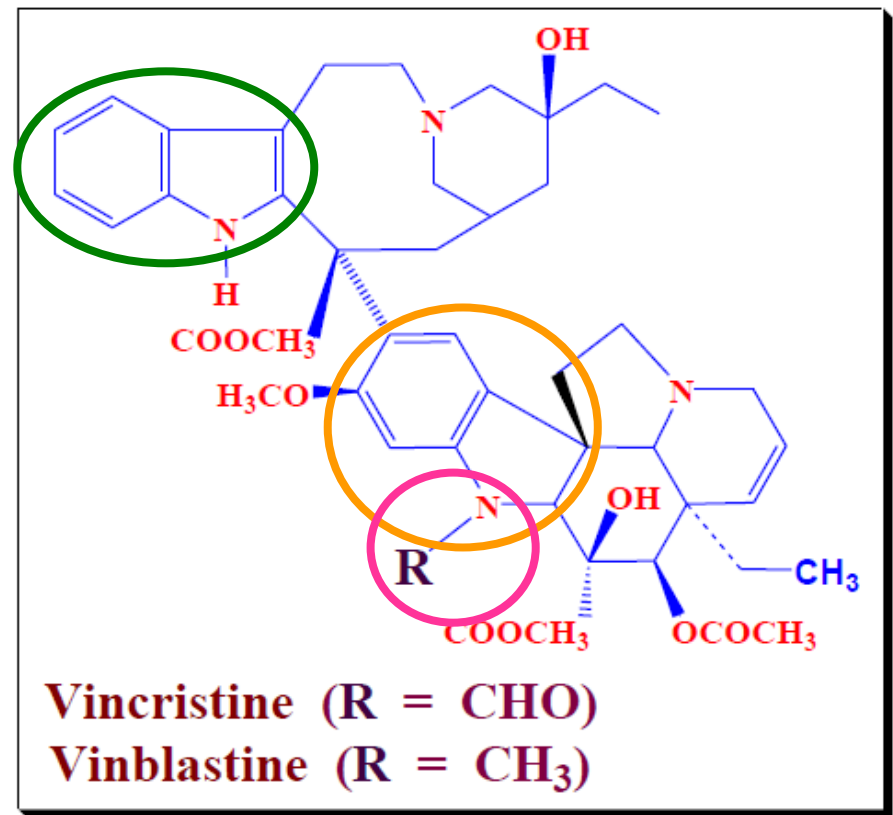
2- Dimeric Alkaloids: Mixed Dimmers

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*.

- **Vincristine** and **Vinblastine** differ only in the substitution on the N-atom of the dihydroindole nucleus.



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.**

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.

4- Nux-vomica Alkaloids

Source:

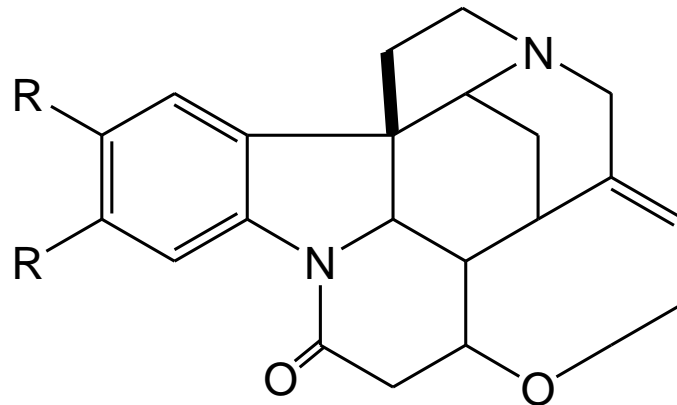
- Seeds of *Strychnose nux vomica* family *Loganiacea* and *Strychnos ignatii* (Ignatius beans).



Constituents: 5% Alkaloids mainly Strychnine and Brucine.

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**.



R= H Strychnine
R= OCH₃ Brucine

Tests for identification:

A- Nitric acid test:

Drops of concentrated nitric + few crystals of the alkaloids:

1. **Strychnine** gives a faint yellow color that on evaporation turns to yellow color

2. **Brucine** gives an intense red color, that on evaporation and addition of SnCl_2 solution turns to violet.

B- Tests for strychnine:

▪ Sulfuric acid-dichromate test:

Few crystals of strychnine + drops concentrated H_2SO_4 + few crystals of $\text{K}_2\text{Cr}_2\text{O}_7 \rightarrow$ deep blue streaks \rightarrow violet \rightarrow purplish red \rightarrow orange \rightarrow yellow.

▪ Test with Mandalin's reagent:

Strychnine gives Deep violet blue color, add water \rightarrow red \rightarrow cherry-red.

Uses:

Strychnine is extremely toxic.

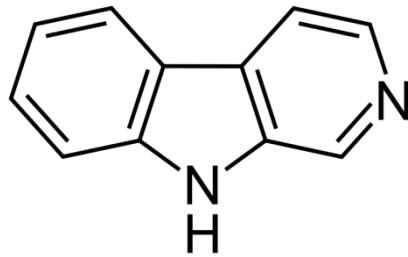
- **It is used in veterinary medicine as CNS stimulant and tonic.**
- **It is used as antidote in barbiturate poisoning.**
- **It is also used as rodenticide.**

Brucine is less toxic than strychnine.

- **It is sometimes used as CNS stimulant,**
- **Commercially it is used as alcohol and oil denaturant**

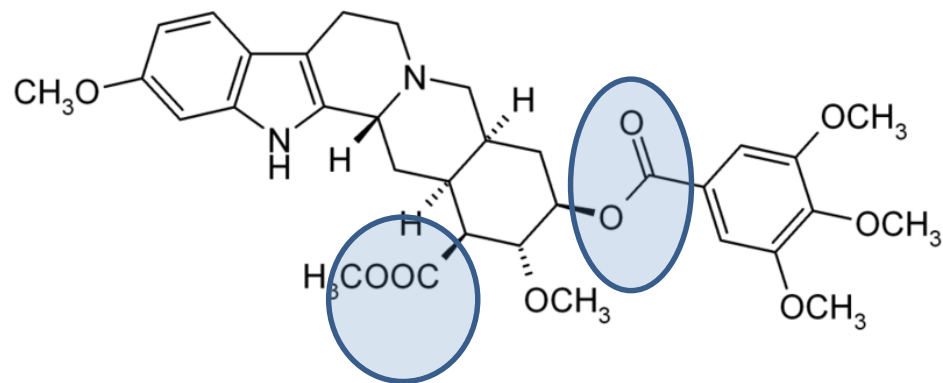
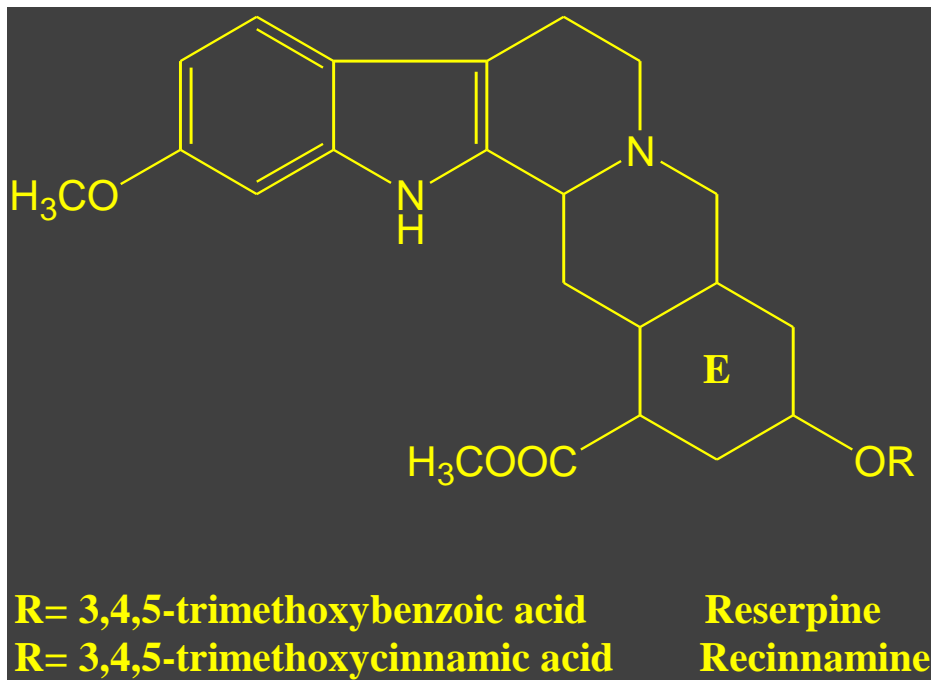
Rauwolfia Alkaloids (carboline alk.)

- **Source:** *Rauwolfia* roots (*Rauwolfia serpentina*, Fam. Apocynaceae)



Carboline skeleton

- **Constituents:** The most important are Reserpine, Deserpine and Rescinnamine.
- **Properties:**
 - Reserpine and related alkaloids are weakly basic diester, tertiary alkaloids and possess a carboxylic group on ring "E".

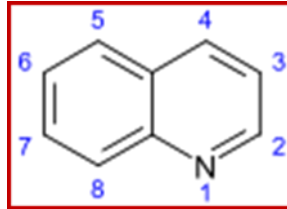


- **Tests for reserpine:**

- Vanillin /HCl reagent: → violet color.
- Sodium molybdate in H_2SO_4 → Yellow → Blue in two minutes.

- **Uses:**

- Reserpine and the related alkaloid rescinnamine are mainly used as antihypertensives (250-500 mg daily) and as tranquilizers (0.1- 1mg or more daily).



Quinoline Alkaloids

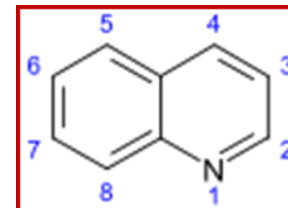
Alkaloids Derived from Tryptophane

Quinoline Alkaloids

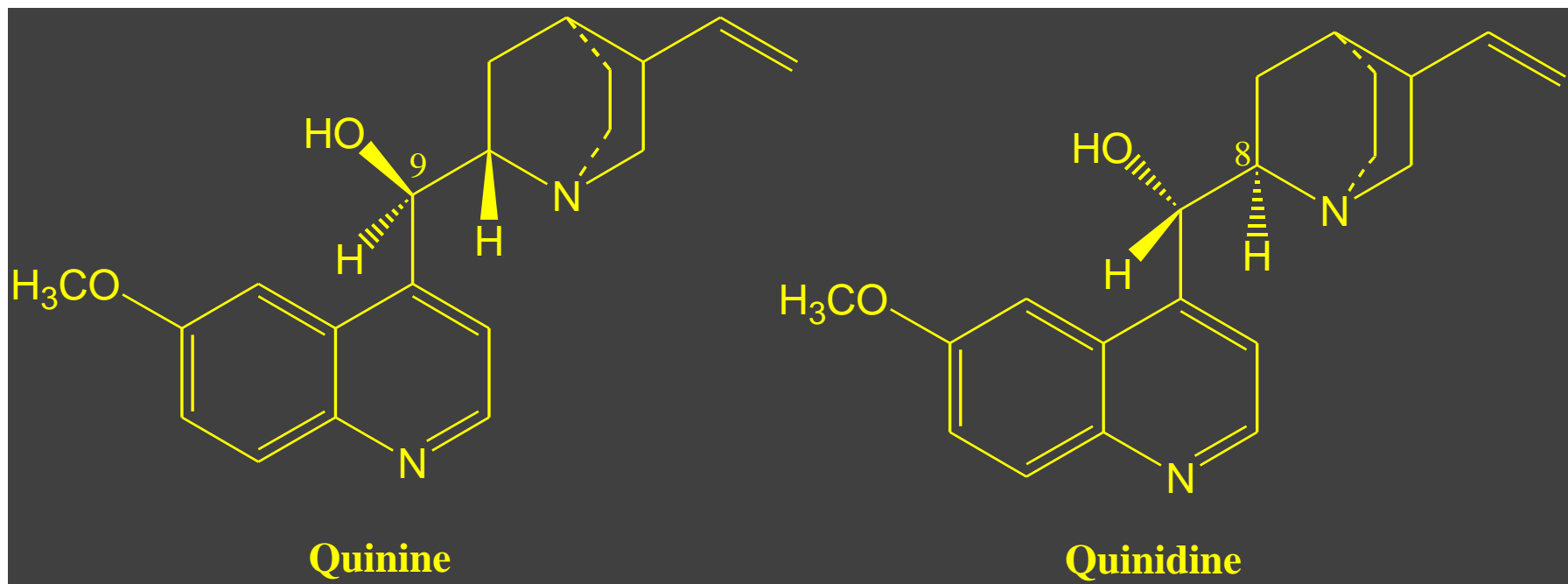
Alkaloids containing quinoline as their principle nucleus include those obtained from cinchona (quinine, quinidine, cinchonine and cinchonidine).

Cinchona

- bark of *C. pubescens* (*C. succirubra*) or of its varieties (**Fam. Rubiaceae**).
- **7-15% alkaloids** which occur in combination with special organic acids chiefly quinic acid and cinchotannic acid.
- used in the treatment of **malaria fever** for many years.
- Over doses of cinchona products results in **temporary loss of hearing and in impaired sight**. Ringing in the ears is a symptom of toxicity (**Cinchonism**).



Both Quinine and Quinidine, Cinchonine and Cinchonidine are Diastereoisomers. Each pair differs in the stereochemistry at C-8 and C-9.



❑ Quinine:

- a diastereoisomer of quinidine, occurs as white, odorless, bitter crystals.
- Quinine (l) gives Quinidine (d) among other products when warmed with KOH in amyl alcohol
- Quinine is **antimalaria agent**.

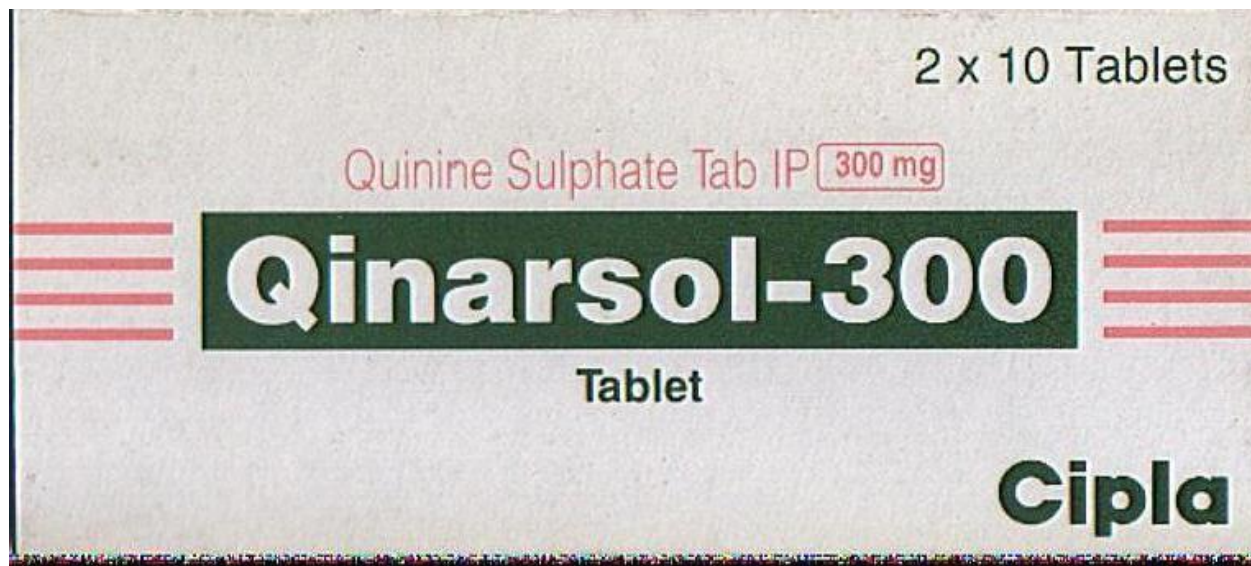
❑ Quinidine:

- an **antiarrhythmic class I** (sodium channel blockade).
- inhibits the rapid sodium influx, decreases the rate of depolarization, contractility, and the atrial and intraventricular conduction velocity.
- used for treating various cardiac arrhythmias

❑ Cinchonine and cinchonidine are used as anti-inflammatory.

The current indications of quinine include the following:

- 1- treating of pernicious malaria and of cases of malaria resistant to 4-aminoquinolines.
- 2- The symptomatic treatment of fevers, aches and flu-like states.
- 3- Quinine ascorbate, combined with vitamins, used in programs to quit smoking (60-80mg/day in four doses).
- 4- in combination with thiamine, to relieve muscle cramps.



Identification:

1- With oxygenated acids (e.g. sulphuric and acetic acid)

Quinine and quinidine produce a strong **blue fluorescence** when dissolved in these acids.

2- Thalleioquin reaction

Quinine and quinidine in solution in **dilute H_2SO_4** can be treated by **Br_2** until the fluorescence disappears.

The addition of aqueous **NH_3** causes the development of an emerald **green color**, which can be extracted with chloroform.

3- The addition of $K[Fe_3(CN)_6]$ -solution in alkaline medium leads to a **purplish red** color that can also be extracted with chloroform.

Structure activity relationship:

For antimalarial activity (Quinine):

Removal of vinyl group \longrightarrow loss of activity

Replacement of CHOH by CH₂ or Co \longrightarrow decrease of activity

