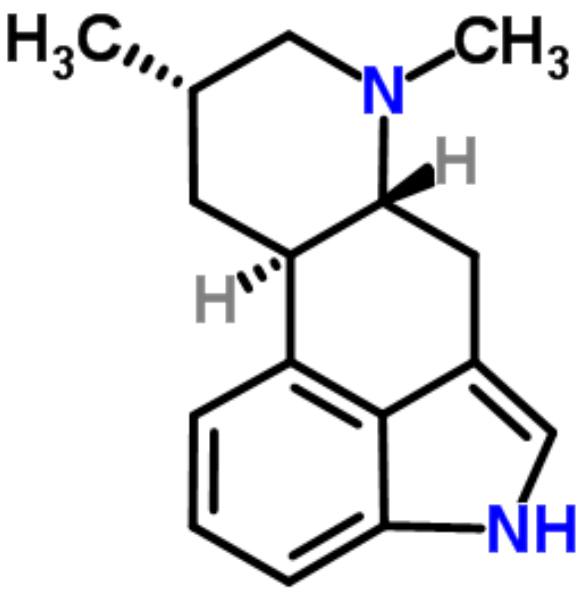
Ergoline Alkaloids

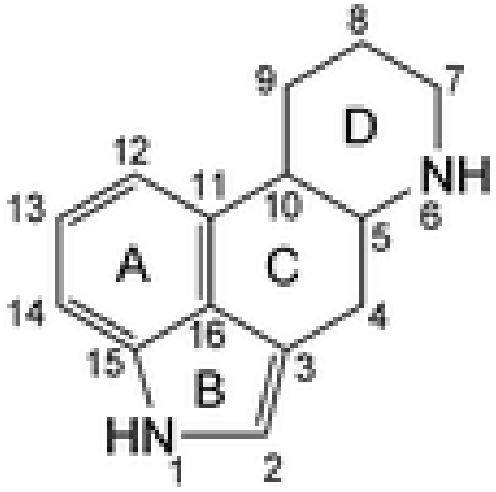
Prof. Dr. Ali H. Meriçli

GENERALITIES

All of the alkaloids in this group are derived from a tetracyclic, octahydroindoloquinoline nucleus, namely ergoline. Although these are commonly classified as clavines, simple lysergic acid derivatives, and ergopeptines, it is also possible, and less ambigous, to classify the various known alkaloids as a function of their basic nucleus.



Ergoline nucleus



tetracyclic ergoline ring system

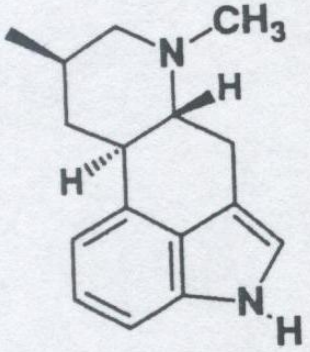
Thus the following are distinguished :

1. **Ergoline Alkaloids** : Ergoline alkaloids can be substituted at C-8, most often by a methyl group (festuclavine), or a hydroxymethyl group (dihydrolysergol), or at C-8 and C-9 in rare cases.
2. **8-Ergolene Alkaloids** . 8-Ergolene Alkaloids can be substituted at C-8 by a methyl group (agroclavine), a hydroxymethyl group (elymoclavine, or a carboxyl group (paspalic acid)

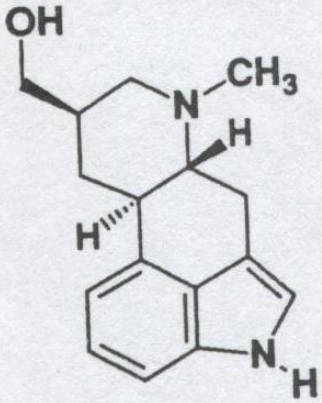
3. **9-Ergolene Alkaloids**. 9-Ergolene alkaloids include the chief alkaloids of the ergot of rye, whether they have an amino acid structure (ergometrine), a peptide structure with a cyclol moiety (ergopeptines), or a peptide structure without a cyclol moiety (ergopeptams)

4. **Secoergoline Alkaloids**. Secoergoline alkaloids have an open D ring (chanoclavine I).

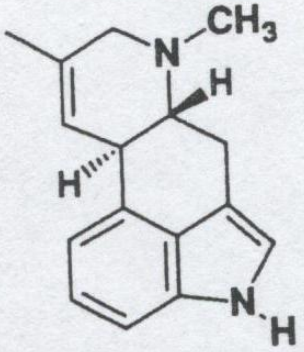
5. **Related Structures**. Related structures sometimes referred to as proergolines, include the precursor of all these compounds, in other words dimethylallyltryptophan, and products such as clavitipic acids.



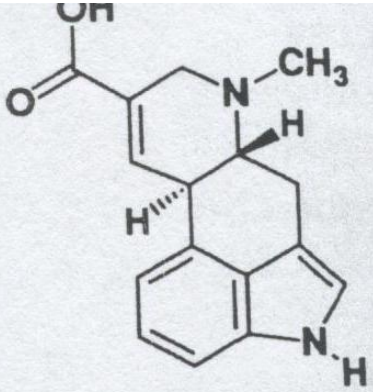
Festuclavine



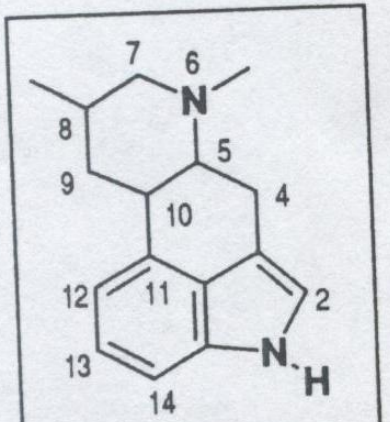
Dihydrolysergol



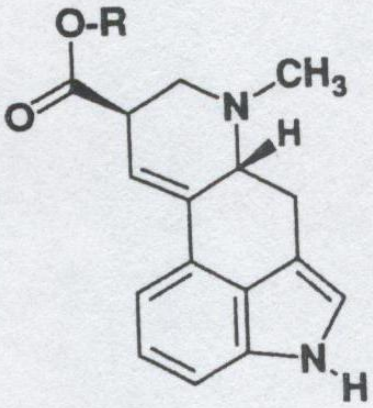
Agroclavine



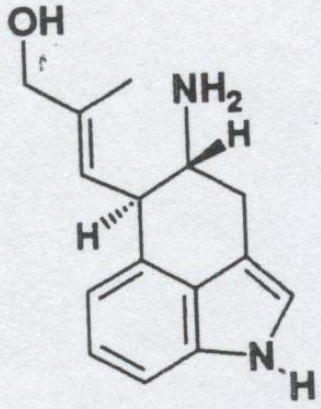
Paspalic acid



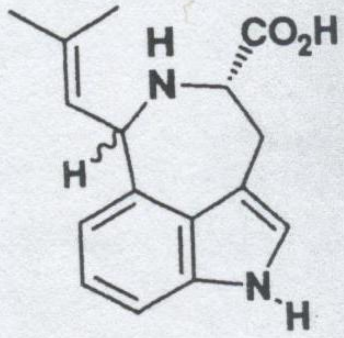
Ergoline nucleus



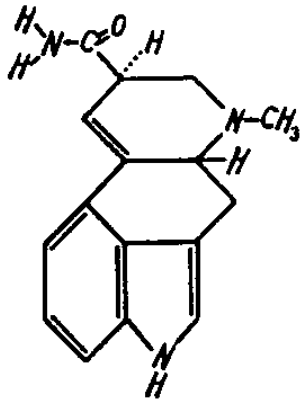
Lysergic acid
and ergopeptines



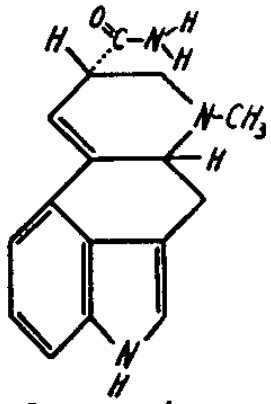
Norchanoclavine I



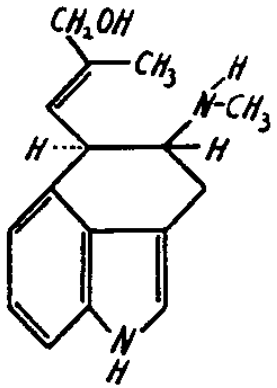
Clavicipitic
acids, I and II



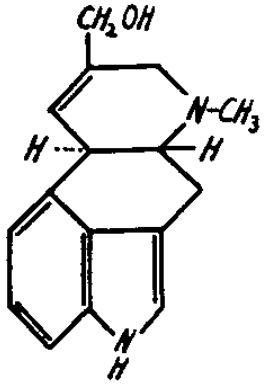
Ergine



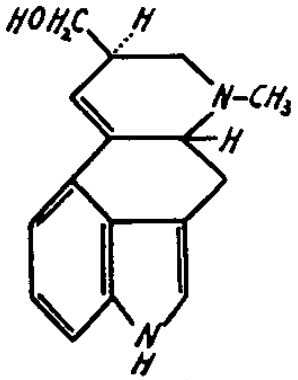
Isoergine



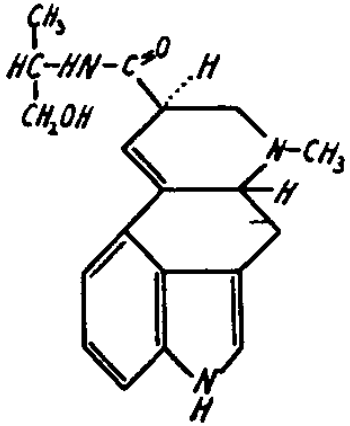
Chanoclavine



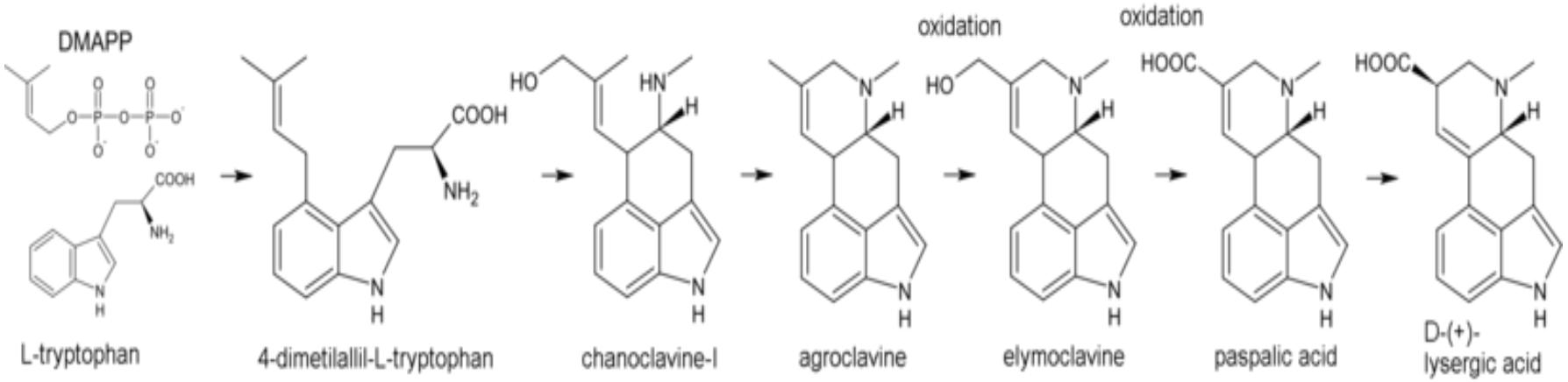
Elymoclavine



Lysergol



Ergometrine
(Ergonovine)



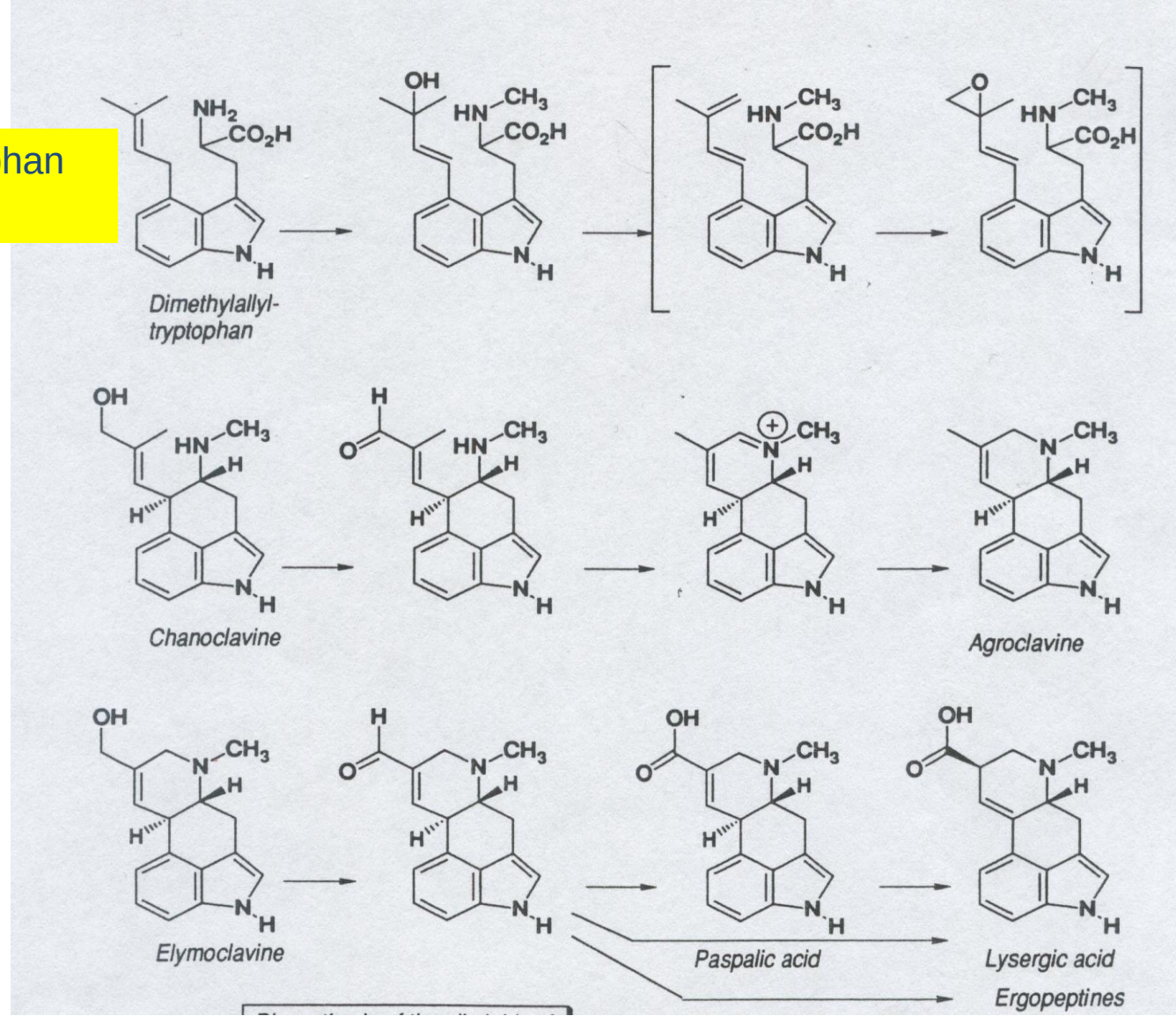
These alkaloids were initially characterized in the ergot of rye, *Claviceps purpurea*.

Biosynthetic origin

Labelling experiments show that the precursor of the ergoline nucleus are tryptophan, mevalonic acid and methionine. Several mechanisms have been proposed to rationalize the first step in the elaboration of ergoline, in other words the formation of dimethylallyltryptophan (= DMAT) : it involves the alkylation of tryptophan by dimethylallyl pyrophosphate, directly at C-4, catalyzed by a specific enzyme, DMAT synthetase.

Ergoline alkaloids.... BIOSYNTHESIS

Dimethylallyltryptophan (**DMAT**)



ERGOT OF RYE ÇAVDAR MAHMUZU
Drug : SECALE CORNUTUM
Claviceps purpurea **Clavicipitaceae**

The fungus exists in two forms : the vegetative form which is a conidiospore-bearing stroma known as sphacelia, and resting form or sclerotium. *Secale cornutum* is the sclerotium form of *Claviceps purpurea* on Poaceae (Graminae) plants especially on rye (*Secale cereale*).

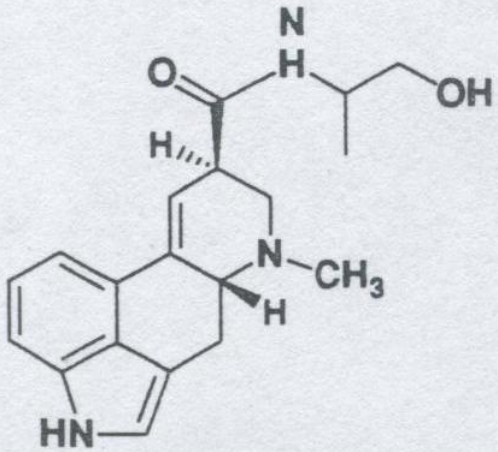
Chemical Composition

Secale cornutum (ergot of rye) is a drug of complex composition. Besides the sugars and a large number of amino acids, the drug contains a high proportion of lipids and also some steroids like ergosterol.

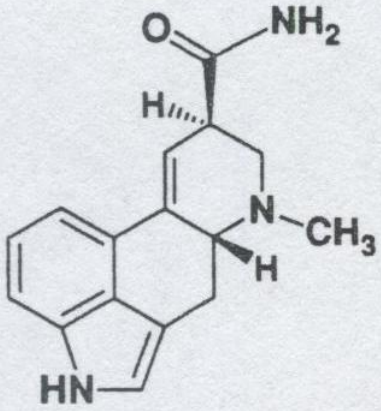
Alkaloids of *Claviceps purpurea*

Alongside traces of clavines, two main groups of alkaloids are distinguished

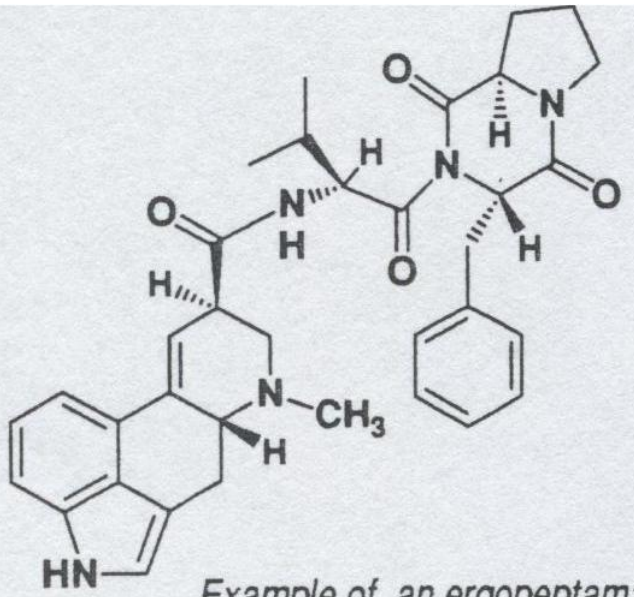
1. **The simple amides of lysergic acid (Lysergic acid derivatives)**: They represent about 20% of the total alkaloids. The chief alkaloid in the group is ergonovine (ergobasine, ergometrine). The drug also contains a small amount of ergine. These compounds are soluble in water.



Ergonovine
(= ergometrine)



Ergine

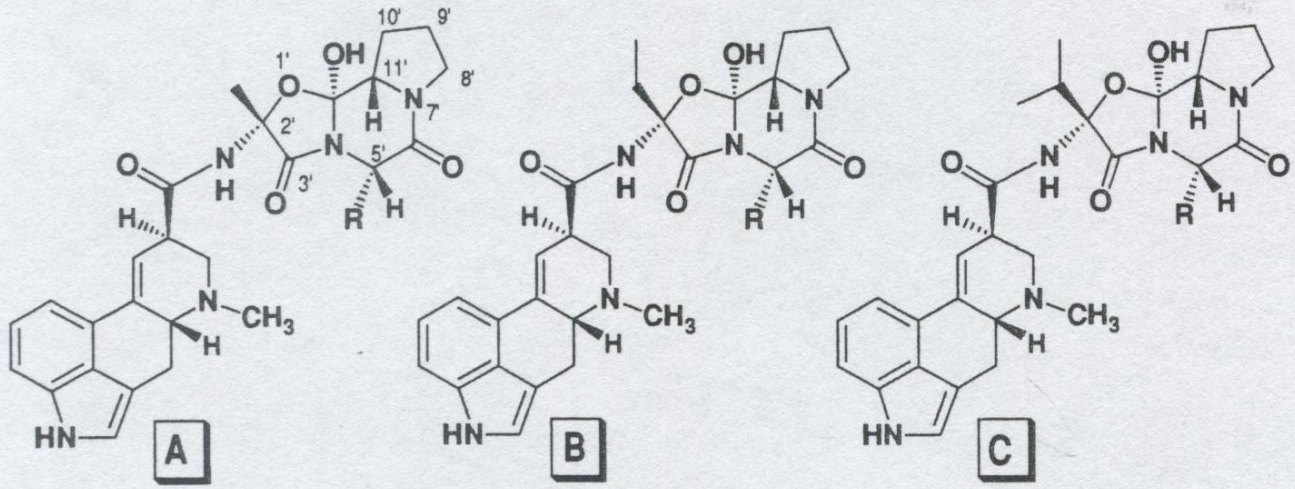


Example of an ergopeptam:
ergocristam

2. The ergopeptines : The ergopeptines are insoluble in water, are by far the principal alkaloid constituents (80% of the total alkaloids).

The principal alkaloids in this group are ergotamine and “ergotoxine”, a mixture of ergocornine, ergocryptine and (α + ß) and ergocristine. The other alkaloids are not abundant and are of no therapeutic interest.

Principal alkaloids of the ergot of rye, Claviceps purpurea



A : Ergotamines **B** : Ergoxines **C** : Ergotoxines

R = CH_2 Ph	*Ergotamine*	*Ergostine*	*Ergocristine*
R = CH_2 $CH(CH_3)_2$	*α-Ergosine*	*α-Ergoptine*	*α-Ergocryptine*
R = $CH(CH_3)CH_2CH_3$	*	*	*β-Ergocryptine*
R = $CH(CH_3)_2$	*Ergovaline*	*Ergonine*	*Ergocornine*
R = CH_2CH_3	*Ergobine*	*Ergobutine*	*Ergobutyrine*

* not known

Tests :

The alkaloids can be detected by color reactions. The ergot alkaloids react with 4-dimethylaminobenzaldehyde under acidic conditions to give a blue color (Van Urk reaction).

Pharmacological Activity :

- **Ergonovine** : This alkaloid is a potent oxytocic : it increases basal tone, and the frequency and strenght of the uterine contractions; the more advanced the pregnancy, the stronger the effect is. This activity is thought to the stimulation of the α-adrenergic receptors in the myothelium.

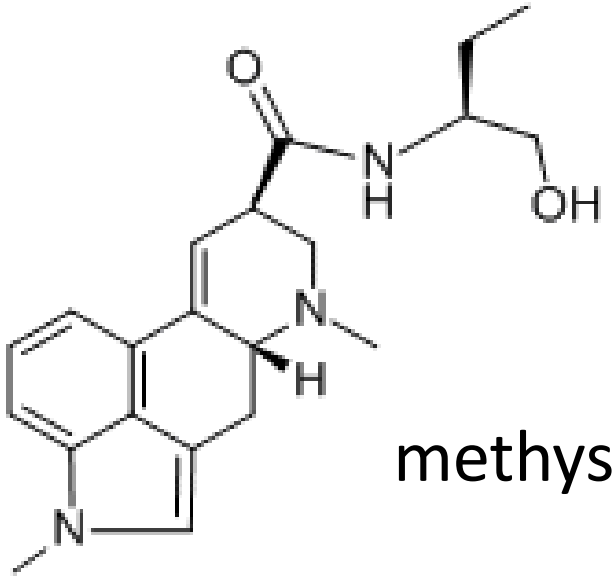
• **Ergotamine** : At low doses ergotamine is a potent vasoconstrictor acting by stimulation of the α-adrenergic receptors (or of the serotonergic receptors in the case of the cranial blood vessels). The change in vascular tone is particularly marked peripherally and in the branches of the external carotid; this reaction is accompanied by thr closure of the arterio-venous shunts.

- **Hydrogenated Derivatives of Naturally-occuring Alkaloids :**They result from the hydrogeneration of the 9,10 double bond which decreases the agonist activity at the α-adrenergic receptors and reinforces the potency of the adrenergic and and serotonergic antagonist activity
- **9,10-Dihydroergotamine.** It is more active on veins than arteries; it is a vasoregulator which stabilizes vascular tone.
- **9,10-Dihydroergotoxine.** It has a complex pharmacology (stimulation of central receptors, peripheral vasodilatation, ergulating activity on the neuronal metabolism).

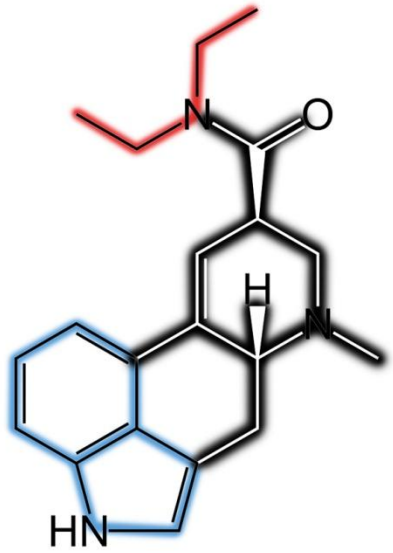
- **Other Semisynthetic or Synthetic Derivatives**

- **Methysergide .** It results from the methylation of the indole nitrogen atom of methylergonovine. This is a potent serotogenic antagonist, devoid of intrinsic vasoconstricting effect.

- **Lysergic acid Diethylamide = LSD.** LSD is a semisynthetic derivative, of no use in therapeutics, and is a potent psychedelic.



methysergide



Lysergic Acid Diethylamide

Uses of Ergot Alkaloids

Methylergometrine. Methylergometrine maleate is indicated for obstetric emergencies: afterbirth delivery and post-partum hemorrhages, after cesarean sections, after curettage, after abortion by suction or curettage, and for uterine atony after giving birth. For these indications, it is administerd by IM injection (0.2 mg). It is contraindicated during pregnancy; in case of severe arterial hypertension, occlusive vascular disease, or severe infectious disease.

Ergotamine. Ergotamine tartarate provides a specific treatment of the acute attack of migraine headache and related vascular headaches; it must not be considered a basic treatment of the patient with migraines. Its mode of action (vasoconstricton) explains why its efficasy is maximal at the beginning of the attach, when it is administered as soon as the prodomal symptoms of the acute attack of migraine and the attack felt. In the majority of cases, the administration of 2 mg is is sufficient (in adults). If ischemic symptoms appear the treatment must be discontinued immediately.

Dihydroergotamine.

Dihydroergotamine has the folowing indications : for the treatment of migraines and vascular headaches; to improve the symptoms of venous and lyphatic vessel insuffiency. It is also proposed for the treatment of orthostatic hypotension.

Dihydroergotoxine- dihydroergocristine. Both alkaloids used as mesylate salts have similar indications : they are proposed for oral administration (2-5 mg per day) as a corrective treatment of senile cerebral insuffiency (lack of attention, memory loss), to treat the sequelae of cerebrovascular accidents, dizziness in the elderly and retinal disorders of vascular origin. In administration on an empty stomach is avoided.

Methysergide. Methysergide maleate is used orally, only in adults (1 mg/day) for the following indications : basic treatment of migraines and facial pain of vascular origin. It is not a treatment for permanent migraine. It is contraindicated in cases of severe hypertension, coronary insuffiency, peripheral vascular symptoms, serious hepatic or renal insuffiency, pregnancy, and breast-feeding.

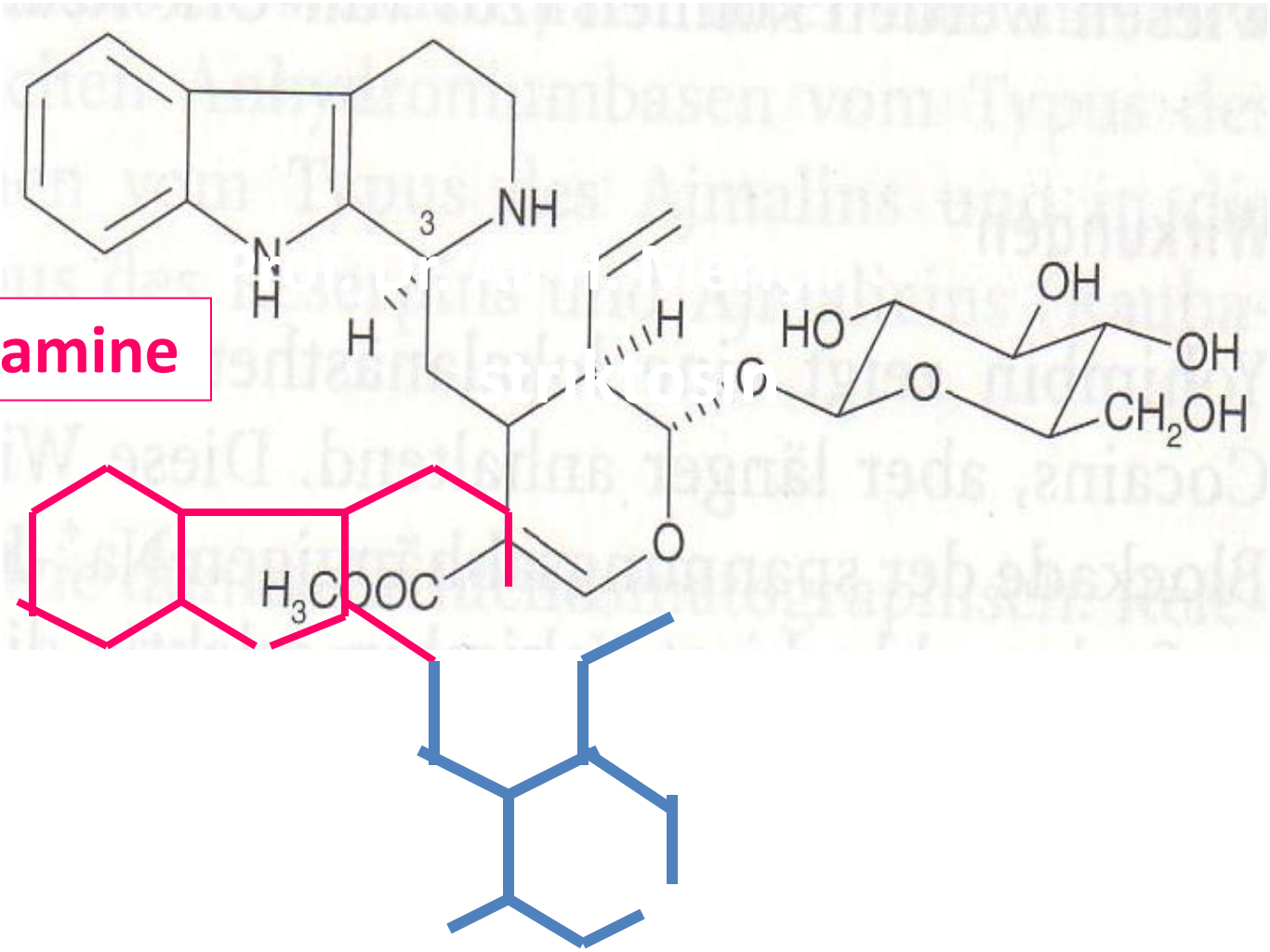
Monoterpenoid Indole Alkaloids

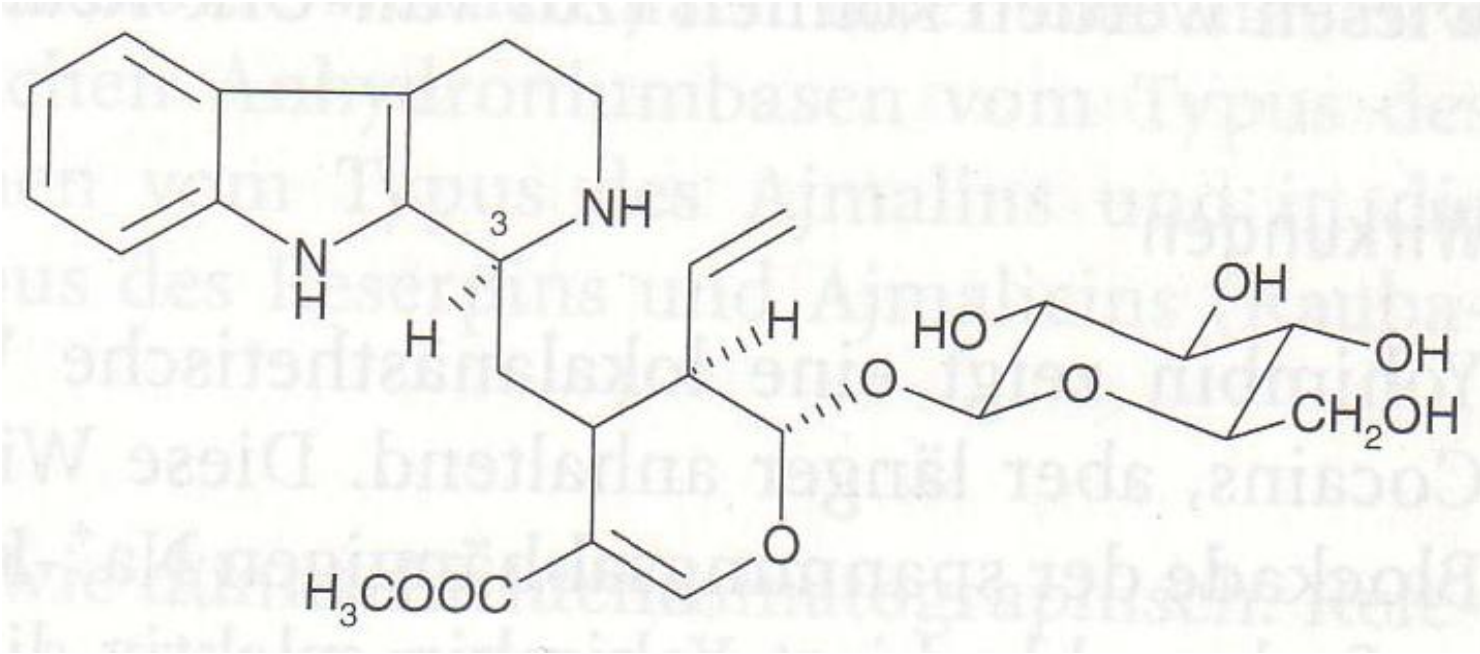
Prof. Dr. Ali H. Meriçli

INTRODUCTION

As stated in the general introduction to alkaloids derived from tryptophan, the distribution of this very vast group of alkaloids is practically limited to three families : Apocynaceae, Loganiaceae and Rubiaceae. Apocynaceae contains the majority of the alkaloids that have been isolated or marketed, and mostly have pharmacological applications.

The most remerkable characteristic of the alkaloids in this group is probably their common biosynthetic origin : all of the known compounds arise from a unique precursor, namely strictosidine. This is a glycoside. It is formed by the condensation of the molecule of tryptamine with a monoterpenoid aldehyde, namely secologanin =secologanoside, an iridoid.


tryptamine
NH
3
N
H
H
H
HO
OH
OH
O
CH_2OH
O
H_3COOC
secologanoside



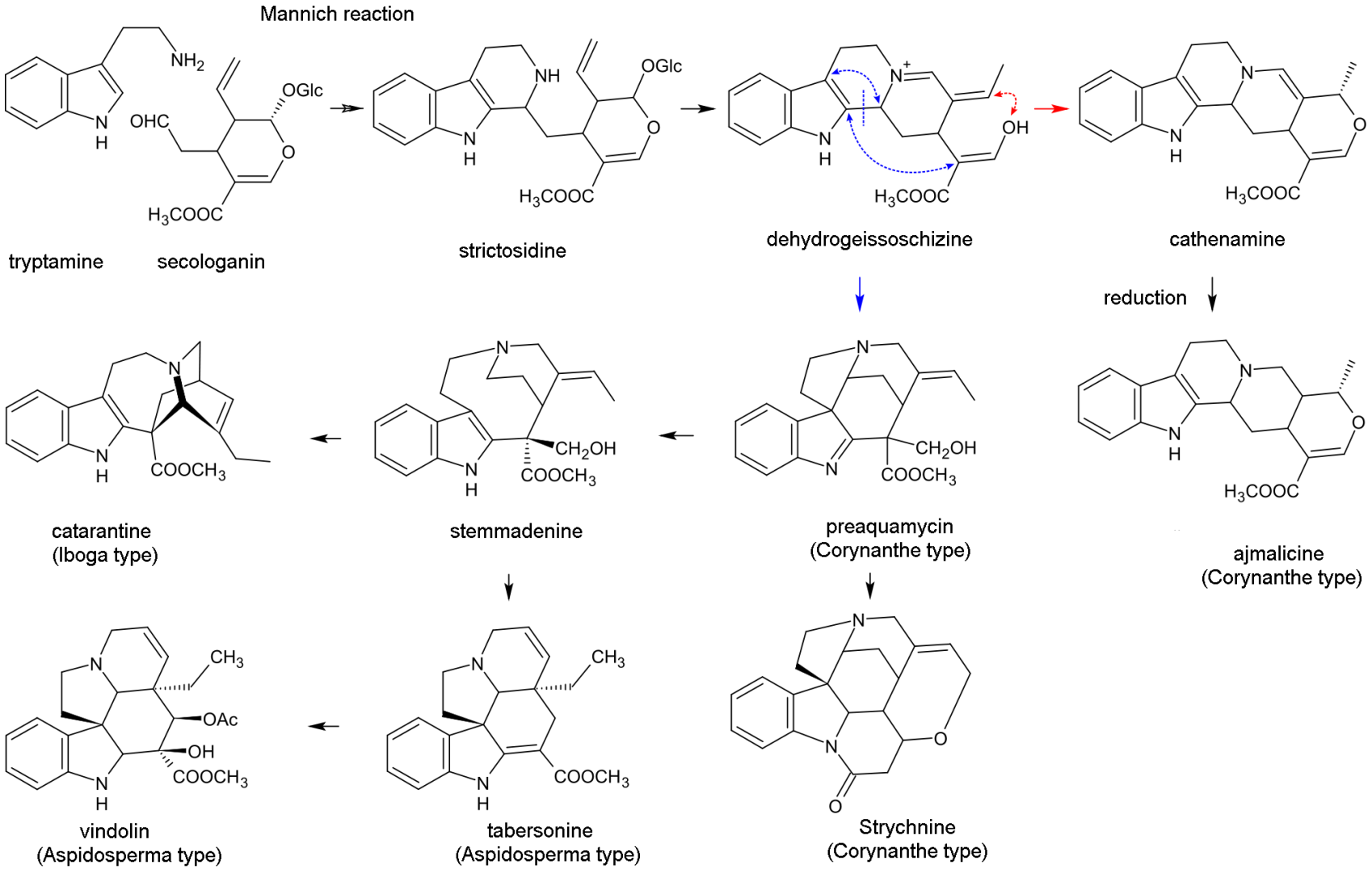
strictosidine

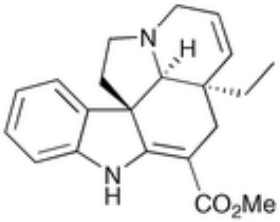
There are several biosynthesis types of indole alkaloids

Type Ia : corynentheans
Type Ib : strychnans
Type II : ibogans
Type III : aspidospermans

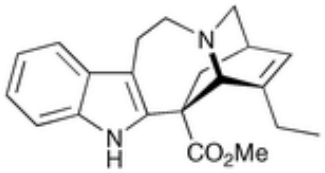
Special cases :

1. Binary alkaloids from *Catharanthus*
2. Quinoline alkaloids from *Cinchona* ssp.

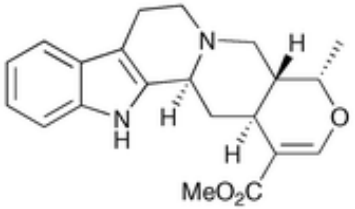

Mannich reaction
tryptamine
secologanin
strictosidine
dehydrogeissoschizine
cathenamine
reduction
catarantine
(Iboga type)
stemmadenine
preaquamycin
(Corynanthe type)
ajmalicine
(Corynanthe type)
vindolin
(Aspidosperma type)
tabersonine
(Aspidosperma type)
Strychnine
(Corynanthe type)



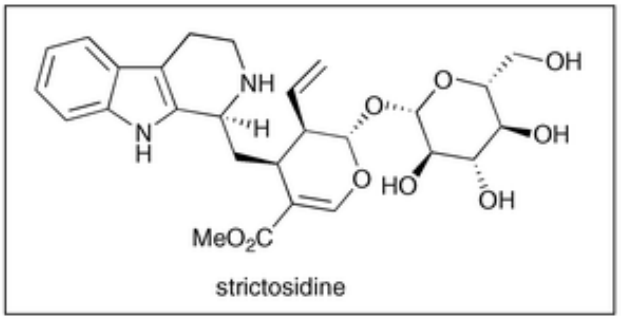
aspidosperma
(tabersonine)



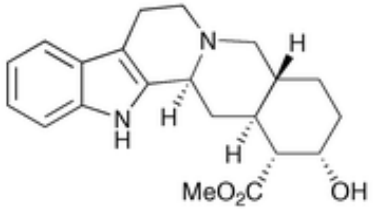
iboga
(catharanthine)



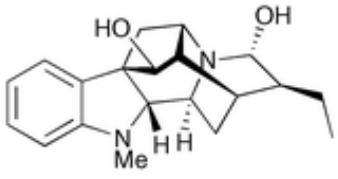
corynanthe
(ajmalicine)



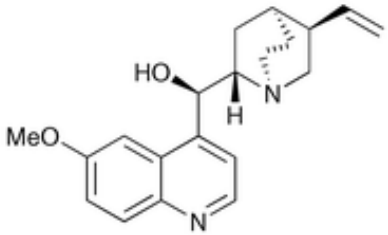
strictosidine



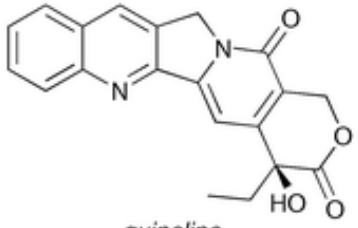
corynanthe
(yohimbine)



ajmalan
(ajmaline)



quinoline
(quinine)



quinoline
(camptothecin)

Tryptophan

Tryptamin

Geraniol

Secologanin

Strictosidine

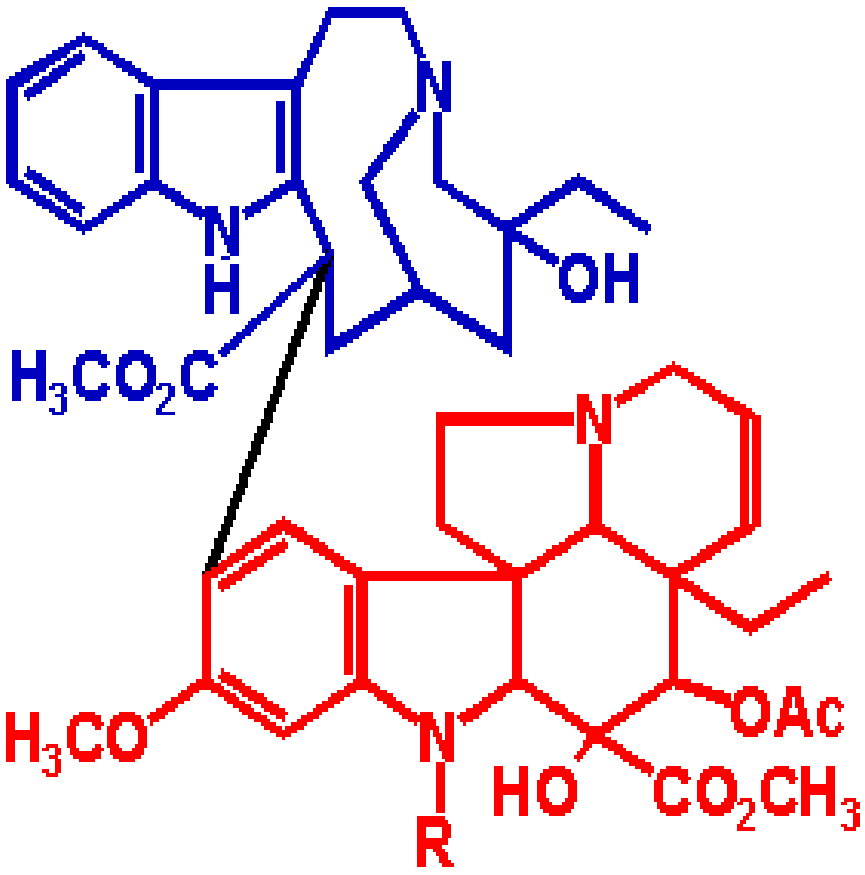
Tabersonine

Catharanthine

Vindoline

3,4-anhydrovinblastine

(bisindol)



Vinblastine R = CH_3

Vinchristine = CHO

DRUGS CONTAINING INDOLE ALKALOIDS

LOGANIACEAE

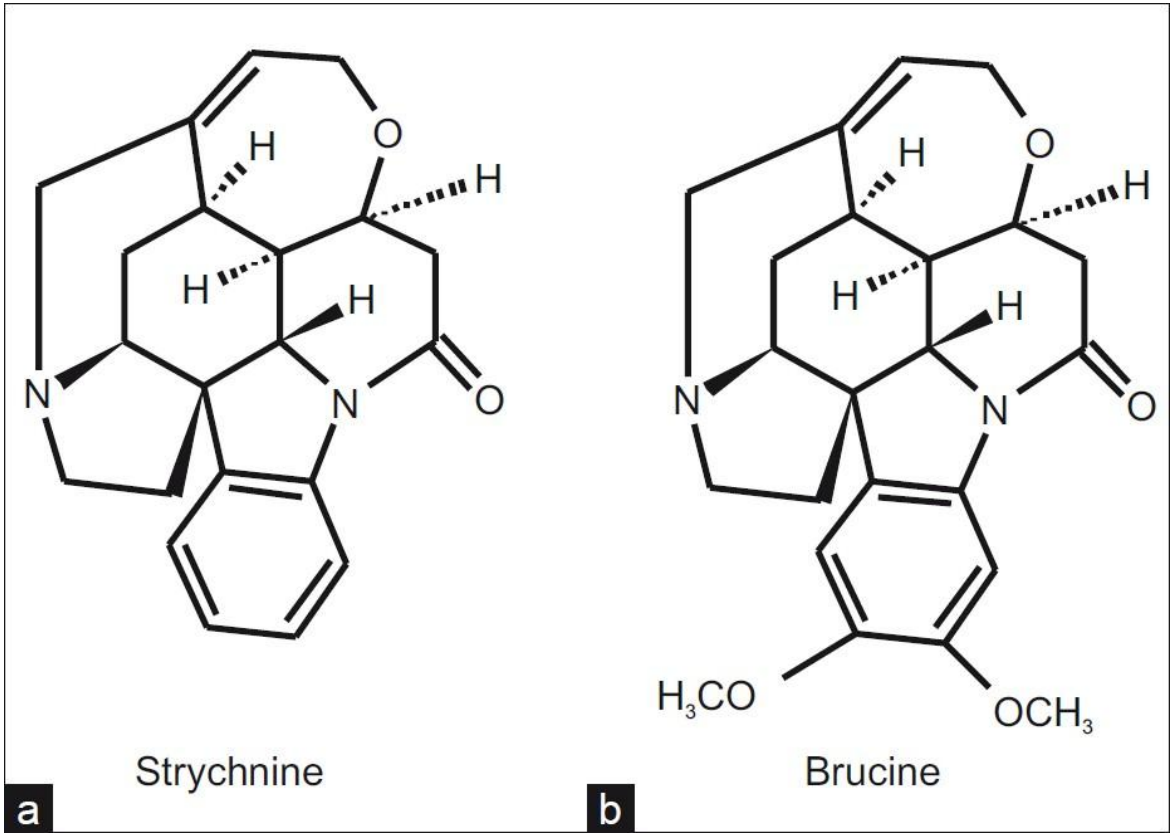
Nux Vomica

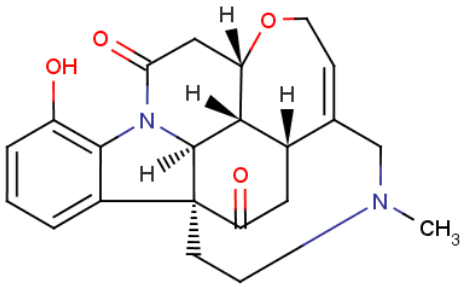
Strychnos nux-vomica

Strychni semen

Kargabüken tohumu

The nux vomica tree is a species from the south of Asia. The drug contains from 1 to 3% total alkaloids chiefly represented by strychnine and its dimethoxylated derivative, brucine. The minor alkaloids have a similar structures: colubrine, vomicine, novacine ect.


H
O
H
H
H
N
N
O
Strychnine
a
H
O
H
H
H
N
N
O
H3CO
OCH3
Brucine
b


H
O
O
OH
H
H
N
H
O
N
CH3

Vomicine

Strychnine produces excitation of all portions of the CNS. Strychnine intoxication is reminiscent of tetanus; symptoms include anxiety, increased sensitivity to noise and light, and periodic convulsive attacks, triggered by some noise of light contact. Death occurs by asphyxia following the contraction of the diaphragm.

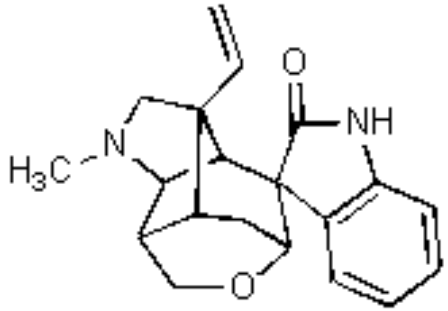
Strychnine was formerly used mainly to poison rodents, and the galenicals obtained from the drug were ingredients of replenishing and invigorating "tonic" preparations. It is a barbiturate antagonist which is no longer used in therapy.

Yellow Jassamine Gelsemii radix

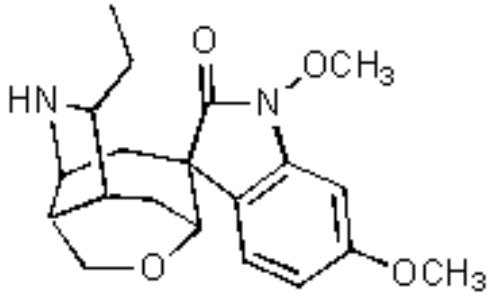
Gelsemium sempervirens

This species is a shrub with indiciduous leaves and yellow flowers, which grows wild in the dump woods of the south eastern United States. The alkaloids of the roots (0.5%) have a complex, oxindole structure : gelsemine, gelsemicine, gelsedine, sempervirine and their hydroxylated derivatives.

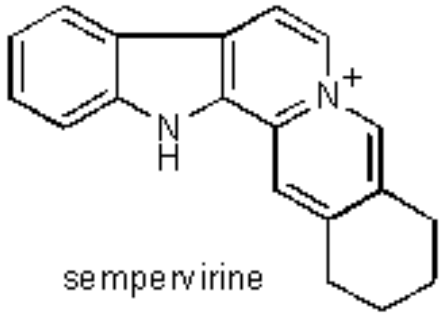
Gelsemine and the preparations based on *Gelsemium* were formerly used to treat neuralgia, pain, and spasms. As an antispasmodic, the tincture and extract of *Gelsemium* are still used as ingredients of some cough.



Gelsemine



gelsemicine



sempervirine

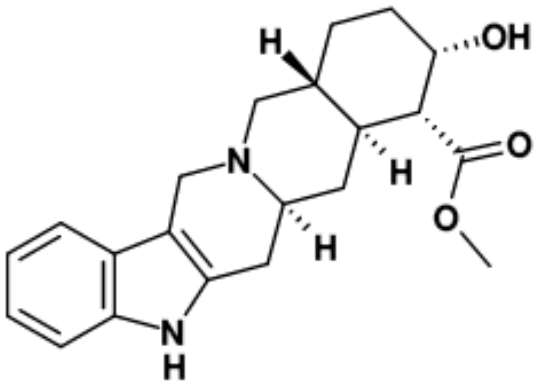
DRUGS CONTAINING INDOLE ALKALOIDS

RUBIACEA

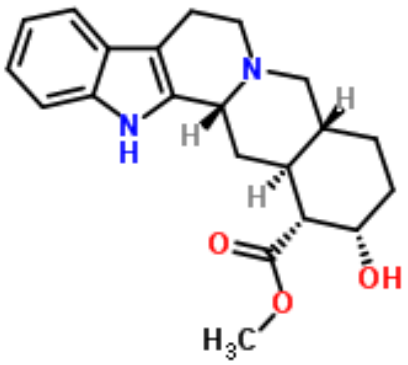
Yohimbe **Yohimbe cortex**

Pausinystalia yohimbe

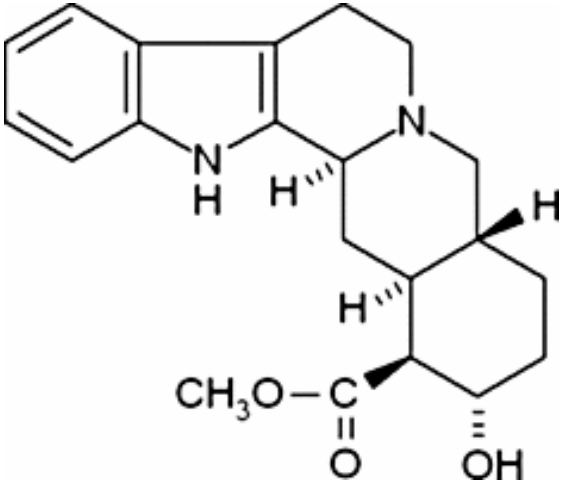
Yohimbe is a tall tree, widespresd in the forests of Cameroon, Gabon, and Congo. The majority of the 1 to 6% indole alkaloids contained in the trunk bark is of the yohimbane type. Alongside yohimbine, which is the chief constituent, in the same series (corynanthine, the 16-epimer) or in other series pseudo-yohimbine (the 3-epimer), allo-yohimbine (the 20-epimer) and more. The drug also contains heteroyohimbanes such as ajmalicine and tetracyclic derivatives (corynanthine and related structures).



Yohimbine



Pseudo-yohimbine



Corinanthine

Yohimbine is a selective inhibitor of the presynaptic α -2-adrenergic receptors and is symphatolytic. At low doses, it is hypertensive, and at higher doses, it is hypotensive and it is a peripheral vasodilator: it is the vasodilatation of the corpus cavernosum which is behind the reputation of yohimbe as an aphrodisiac. Its activity on smooth muscle results in an increase in intestinal tone and motility.

Reference Books :

Main Book

Bruneton, J., Pharmacognosy, Phytochemistry, Medicinal Plants, TEC & DOC Editions, Paris 1999

Other Books

- Hänsel, R., Sticher, O., Pharmakognosie – Phytopaharmazie, Springer Medizin Verlag, Heidelberg 2010
- Evans, W.C., Trease and Evans Pharmacognosy, Elsevier Limited, Edinburgh, London 2002
- Baytop, T., Farmakognozi I-II, İstanbul Üniv. Yay. No. 2783, Eczacılık Fak. No.29, İstanbul 1980
- Tanker, M., Tanker N., Farmakognozi I-II, Ankara Üniv. Eczacılık Fak. Yay. No. 63, Ankara 1990