2016

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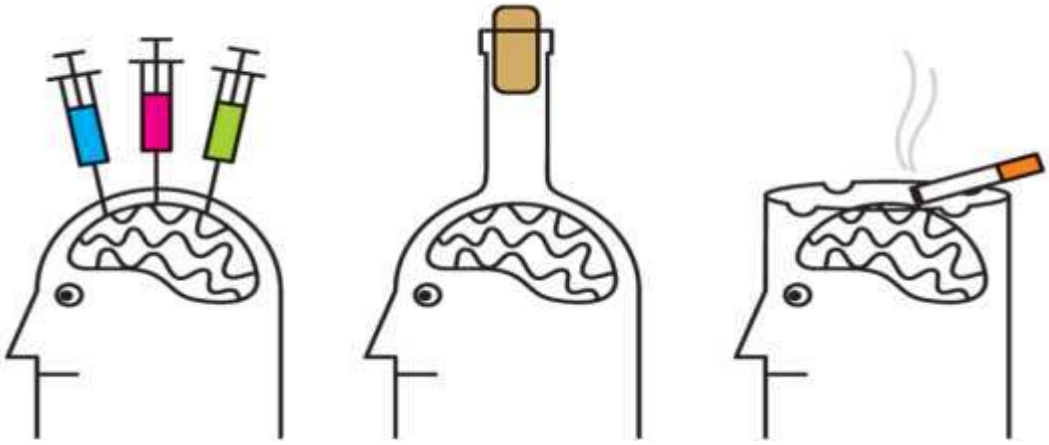


PHYTOCHEMISTRY (3)
ALKALOIDS

Contents

Chapter 1

Generalities of Alkaloids

Definition

The term of alkaloids was introduce by W.Meisner at the beginning of nineteenth century to designate natural substances reacting like bases, in other words like alkalis . There is no simple and precise definition of alkaloids, and it is sometimes difficult to distinguish the thin line between alkaloids and other natural nitrogen containing metabolites.

The alkaloids are **organic nitrogenous bases** found mainly in plants, but also to a lesser extent in microorganisms and animals .One or more **nitrogen atoms** are present, typically as primary, secondary, or tertiary amines, and this **usually confers basicity** to the alkaloid, facilitating their isolation and purification since water-soluble salts can be formed in the presence of mineral acids.

From pharmacological point of view, **the alkaloids are natural compounds with nitrogen in structure which in minimum dose give pharmacological properties.**

Alkaloids containing quaternary amines are also found in nature .The biological activity of many alkaloids is often **dependent on the amine function** being transformed into a quaternary system by protonation at physiological pHs.

The nitrogen atoms in alkaloids originate from an amino acid, and, in general, the carbon skeleton of the particular amino acid precursor is also largely retained intact in the alkaloid structure, though the carboxylic acid carbon is often lost through decarboxylation.

Classification

Different systems of classification may be adopted based on:

1. The **pharmacological action** which lead to biological activity.
2. The **chemical structure type of nitrogen**, heterocyclic or non-heterocyclic and type of ring structure.
3. The **biochemical origin** biosynthetic pathway of production in the plant.
4. The **taxonomical origin** plant families rich in alkaloids.

According to chemical structure, two broad divisions may be recognized:

1. **Non-heterocyclic** or atypical alkaloids that are sometimes called "protoalaklaoids' or biological amines.
2. **Heterocyclic** or atypical alkaloids that are sub-classified into different groups according to their ring structure.

According to **Hegnauer's classification**, which is based on both, the type of nitrogen and the biochemical origin, three main types of alkaloids are distinguished:

1. **True alkaloids** that are derived from amino acids and have nitrogen in a heterocyclic ring.
2. **Proto alkaloids** that are derived from amino acid and do not have nitrogen in heterocyclic ring.
3. **Pseudo alkaloids** that are not derived from amino acids but have nitrogen heterocyclic ring.

Distribution

Alkaloids are distributed in all plant kingdoms, the major source of alkaloids was the flowering plants angiosperms but recently they have been discovered in animals, fungi and marine plants .Due to new technologies, over 1000 alkaloids have been now isolated and identified.

Nomenclature

Alkaloids are named in various ways .By agreement, chemical rules stated that their trivial names **should end by ''ine''**.

These names may refer to:

1. The **genus** of the plant in which they occur generic name, such as Atropine from ***Atropa belladonna***.
2. The **plant species,** specific name, such as **Cocaine** from Erythroxylon coca.
3. The **common name** of the drug, such as **Ergotamine** from ergot.
4. The **name of the discoverer**, such as **Pellerierine** that was discovered Pelletier.
5. The **physiological action** they produce, such as **Emetine** that acts as emetic.
6. A prominent **physical character** they have, such as **Hygrine** that is hygroscopic.

Prefixes and suffixes:

These are, usually, added to the name of the parent alkaloid and are used to designate related alkaloids, generally present in the same plant .Examples are:

1 -Prefixes:

- **''Nor'' -**designates N-emethylation or Ndemethoxylation, e.g . norpseudoephedrine and normicotine.
- **-''Apo''** -designates dehydration e.g .apomorphine.
- **''Iso''-**, **pseudo**-, **neo**-, and **epi**-" indicate different types of isomers.

2 -Suffixes:

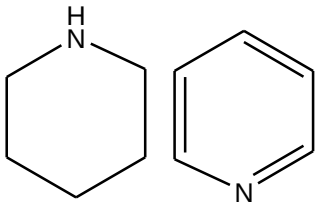
- **''dine''** designates isomerism as in the case of the Cinchona alkaloids, quinidine and cinchonidine are optical isomers of quinine and cinchonine respectively.
- **''ine''** indicates a lower pharmacological activity e.g .ergotamine is less potent than ergometrine.

Basicity

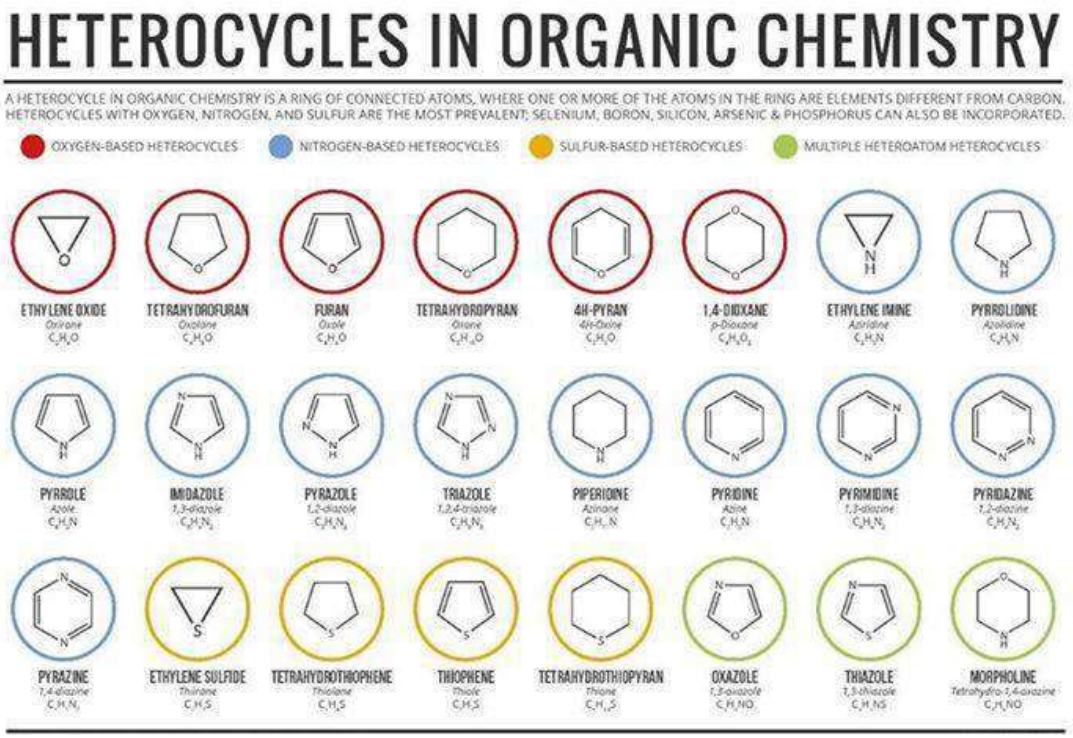
1. The basicity of alkaloids is due to the presence of a lone pair of electrons on the amino nitrogen atom.
2. Amines and, consequently, alkaloids resemble ammonia in chemical they form salts with acids without liberation of water.
3. In plants, alkaloids occur as free bases, salts or N-oxides.

Factors that may influence the degree of basicity

1. The structure of the molecule such as the degree of unsaturation of the heterocyclic ring . **Unsaturation increases the basicity** e.g .**piperidine alkaloids are more basic than pyridine** alkaloids.

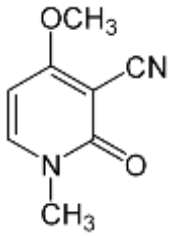


Piperidine pyridine



2. The presence and position of other substituents and functional groups e.g:.
    a. The electron releasing groups, such as alkyl groups, increase the basicity.
    b. The electron withdrawal groups, such as the carbonyl groups, decrease the basicity .

Alkaloids may, therefore, be neutral or slightly acidic, as the electron availability on the amino nitrogen atom decreases .An example of acidic alkaloid is **Ricinine** .



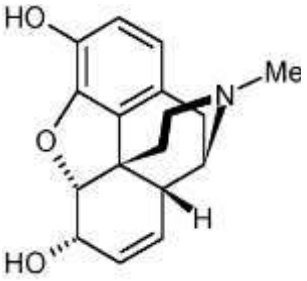
Ricinine

Some alkaloids are amphoteric due to the presence of acidic groups in their molecule.

Examples are:

a. The phenolic alkaloids such as :**morphine**, psycotrine, and cephaline.

b. The alkaloids containing a carboxylic group, such as narceine.



Physical properties

1 -Condition:

Most alkaloids are crystalline solids .Some are liquids that are either.

- volatile e.g .nicotine and coniine, or
- Non-volatile e.g .pilocarpine and hyoscine.

2 -Color:

The majority of alkaloids are colorless but some are colored e.g:.

- Colchicines and berberine are yellow.
- Canadine is orange.
- The salts of sanguinarine are copper-red.

3 -Solubility:

The solubility of alkaloids and their salts is of considerable importance because:

- They are often administrated in solution.
- The differences in solubility between alkaloids and their slats are used as a base for their isolation and purification from non-alkaloidal substances.

- Due to the great variation in their structure the solubility of different alkaloids and salts are variable.

The following could be mentioned as regards their solubility in water, alcohol and other organic solvents:

- Both alkaloidal bases and their salts are soluble in alcohol.
- Generally, the bases are soluble in organic solvents and insoluble in water Exceptions:
- Bases soluble in water :caffeine, ephedrine, codeine, colchicines, pilocaepine and quaternary ammonium bases.
- Bases insoluble or sparingly soluble in certain organic solvents :morphine and psychotrine ether, therobromine and theophylline in benzene.
- Salts are usually soluble in water and, insoluble or sparingly soluble in organic solvents.

Exceptions:

- Salts insoluble in water :quinine sulphate.
- Salts soluble in organic solvents :lobelline and apoatropine hydrochlorides are soluble in chloroform.
- Salts of weak bases are easily decomposed in solution without alkalinization and release the bases, which extracted with organic solvents.

4 -Optical activity

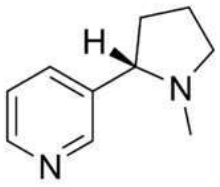
- Many alkaloids are optically active due to the presence of one or more asymmetric carbon atoms in their molecule.
- Optically active isomers shoe different physiological activities .Usually, the 1 (-)isomer is more active than the d (+)isomer, e.g.;
    - L-ephedrine is 3.5 times more active than d-ephedrine and,
    - L-ephedrine is 3.4times more active than d-ergotamine.

Exceptions:

- d-Tubocuranie is more active than the corresponding 1-from.
- Both quinine (-) from and its (d-) isomer quinidine are active.
- The racemic dl-atropine is physiologically active.

Chemical Properties

In addition to carbon, hydrogen and nitrogen, most alkaloids contain oxygen in their molecules .Few alkaloids are oxygen-free such as **nicotine** and coniine.



1 -Salt formation

- Due to their basic character, alkaloids react with acids to from salts.
- Strong bases from salts with very weak acids.
- Weak bases require stronger acids.
- Dibasic alkaloids may form two series of salts.
- Very weak bases form unstable salts, e.g .piperine, papaverine, narcotine and caffeine.
- Amphoteric alkaloids e.g .containing phenolic or carboxylic groups can form salts with both acids and alkalis.
- Alkaloids showing acidic characters do not from salts with acids e.g .Ricinine.

2 -Stability

The influence of different factors such as exposure to light, heat, oxygen, acids and alkalis should be considered during preservation and manipulation of alkaloids .In general, alkaloids are less stable in solution then in the dry state.

- **Effect of heat:**

Alkaloids are decomposed by heat; expect caffeine that sublimes without decomposition.

- **Effect of heat and light in presence of oxygen:**

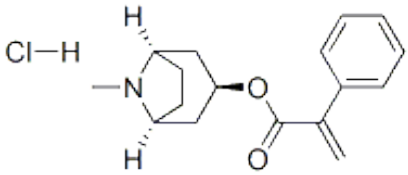
Most tertiary amine alkaloids are easily transformed to the N-oxides when exposed to light and oxygen at elevated temperature.

N-oxides are usually water-soluble; they are characterized by their delayed release properties, low toxicity and low addictive properties as compared to the parent tertiary alkaloids.

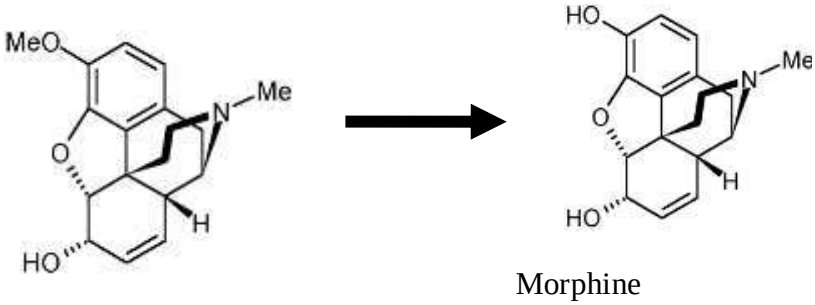
- **Effect of acids:**

Hot dilute acids and concentrated mineral acids may cause:

-Dehydration to produce anhydro-or apo-alkaloids, e.g .dehydration of morphine o produce apomorphine and that of atropine to yield **apoatropine**.



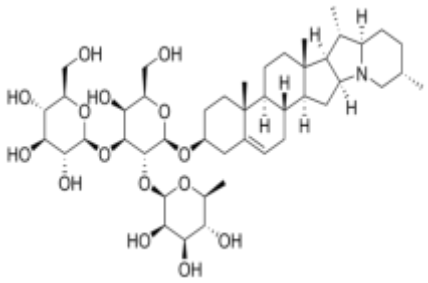
-O-demethylation of certain alkaloids such as quinine, narcotine and codeine to produce phenolic alkaloids by treatment with HI e.g .conversion of codeine to morphine.



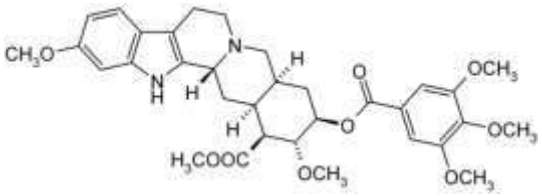
Codeine

Morphine

-Hydrolysis of ester alkaloids, such as atropine and reserpine, and Gluco-alkaloids, such as solanine.



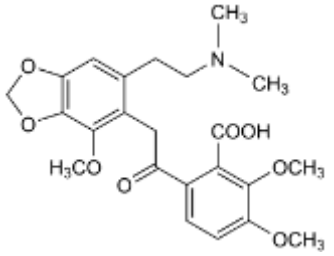
Solanine



Reserpine

- **Effect of alkalis:**

This includes the effect of weak, strong and hot alkalis.



- Weak alkalis liberate most alkaloids from their salts e.g .NH3.

They also can from salts with alkaloids containing a carboxylic group e.g .**narceine**, when treated with NaHCO3, yields the corresponding sodium salt.

- Strong alkalis :such as aqueous NaOH and KOH form salts with phenolic alkaloids.
- Hot alkalis :heating with alkalis results in :hydrolysis ester alkaloids

e.g .atropine, cocaine and physostigmine and cleavage of lactone ring, if present, to produce the corresponding acid, e.g .pilocarpine is transformed to pilocarpic acid.

Tests for detection and identification

Chemical tests commonly performed for detection of alkaloids involve two types of reactions:

1- Precipitation reactions

- These result in the production of amorphous or crystalline precipitates of various colors, in which the precipitating reagent is added to a neutral or slightly acidic aqueous solution of the alkaloidal salts.
- The reagents used contain heavy metals such as Hg, Pt, Bi and from double salts with most alkaloids.

These reactions could be used for extraction and purification.

Care must be taken in the application of these tests as:

- Certain alkaloids such as caffeine and some others do not react.
- False positive response may be obtained in certain cases as most of the reagents used precipitate proteins, tannins, caumarins and certain flavonoids.

2 -Color reactions

These reactions are usually performed by the addition of color reagents to the solid free bases not to their salts to produce characteristic colored solutions.

The reagents used generally contain concentrated sulphuric acid and an oxidizing agent.

- They give colors with most alkaloids, or may be specific for one alkaloid or a group of related alkaloids.

Examples of specific color reaction are:

- Van-Urk's test for ergot alkaloids, these give a blue colour when treated with parar-dimethyl amino-benzaldehyde)PDAB (in concentrated H_2SO_4.
- Vitalis' test for solanaceous alkaloids, these give a violet color when treated with concentrated HNO_3 and alcoholic KOH.

Extraction, purification and separation

Factors affecting the selection of the method of extraction and isolation

1. **Mixtures of related compounds** together with inert constituents, such as tannins, proteins, fats, resins, and pigments, which generally hinder their isolation.
2. **Selection of a suitable method for extraction** alkaloids forms plants which depend on:
    - **A. The scale and purpose of the operation, and**
    - **B. The nature of the raw material.**

Steps:

A -Preparation of the plant sample

B -Extraction and purification

C -Liberation and extraction of alkaloid bases

D -Purification of the crude alkaloidal mixture

E -Separation of individual alkaloids

A -Preparation of the plant sample

The collected plant material is carefully dried, reduced to a suitable size and, if necessary, defatted with petroleum ether e.g .in case of seeds.

B -Extraction and purification

Conform the classic methods for extraction which depend on the nature and physico-chemical properties of the active ingredient (s) needed in investigation (Please see the scheme in your notes).

C -Liberation and extraction of alkaloid bases

The alkaloids ingredients results from extraction, generally liberate the free bases, which are separated by filtration or extraction with organic solvents.

Selection of alkalis

The major factors that limit the selection of the proper alkali are:

1. **The nature of the plant material:**

The use of strong alkali is <u>not recommended</u> in case of fatty drugs e.g .seeds, to avoid saponification, which results in strong emulsions during extraction.

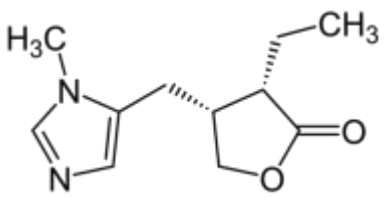
2. **The nature of the alkaloidal salt:**

Salts of strong bases with mineral acids need the use of stronger alkalis than those of weak bases with organic acids.

3. **The chemical nature of the alkaloidal base:**

The use of strong alkali should be avoided in case of ester alkaloids

atropine and cocaine.



Ammonia is the alkali of choice as it is sufficiently basic to liberate most alkaloids, as well as, volatile and completely removed after extraction.

Selection of solvents

Different types of solvents are used during extraction of alkaloids and their salts these include:

1. **Organic water-immiscible solvents**, such as chloroform, ethylene chloride, benzene or ether .These are used to extract most alkaloids except quaternary ammonium bases that insoluble in organic solvents.
2. **Organic water -miscible solvents**, such as methyl or ethyl alcohols.These extract both alkaloids and their salts-
3. **Aqueous acids** that provide a cheap but non-selective mean for extraction of alkaloids are their salts impurities e.g .sugars mucilage, coloring matter proteins and tannins may be extracted.

D -Purification of the crude alkaloidal mixture

This could be affected by either;

1. Dissolution in an organic solvent followed by acid-base or
2. Complex formation with a suitable precipitant followed by decomposition to recover the alkaloids, e.g :.the tannic acid complex is decomposed by treatment with lead hydroxide or lead carbonate.

E -Separation of individual alkaloids

This could be carried by:

1 -Factional precipitation or crystallization:

This is generally performed after derivatization to salts such oxalates, tartrates and picrates.

2 -Gradient pH extraction:

This method is suitable for separating alkaloids of different basicity weakly, moderately and strongly basic. The crude mixture is dissolved in 2 %tartaric acid and extracted with organic solvent .The pH of the aqueous solution is gradually increased to pH 9 and extraction, after each increment with organic solvent.

3 -Chromatographic techniques:

These are the most suitable in case of complex mixtures.

Quantitative analysis

Quantitative determination of alkaloids in crude drugs, galenicals and pharmaceutical formulations is carried with the aim of:

1 -Determination of the genuineness of the raw vegetable material.

2 -Evaluation of the plant material for marketing.

3 -Determination of he site of biosynthesis on the plant.

4 -Selection of the best stage for collection of the plant material.

5 -Evolution of the stability and activity a preparation.

6 -Prevention of overdose and intoxication by potent alkaloids.

7 -Determination of the bioavailability in different oranges and tissues.

Pharmacological activity of Alkaloids

Alkaloids exhibit a wide of pharmacological activities, they can varieties **from tonic to cancer** as follow:

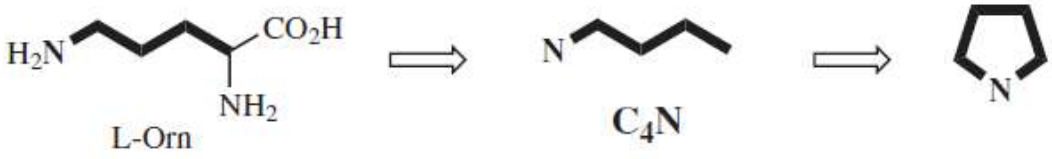
1. Analgesics and narcotics e.g .morphine and codeine
2. CNS stimulants e.g .caffeine and strychnine.
3. Mydriatics e.g .atropine.
4. Anti-asthmatics e.g .ephedrine.
5. Antitussive e.g .codeine.
6. Expectorants e.g .lobeline.
7. Anti-hypertensive e.g .reserpine.
8. Smooth muscle relaxants e.g .atropine and papaverine
9. Skeletal muscle relaxants e.g .d-tubocurarine.
10. Anthelmintics e.g .pelletierine and arecoline.
11. Antiparasitics e.g .quinine and emetine.
12. Anticancers e.g .vincristine, vinblastine and taxol.

Chapter 2

ALKALOIDS DERIVED FROM ORNITHINE

L-Ornithine is a non-protein amino acid forming part of the **urea cycle in animals,** where it is produced from L-arginine in a reaction catalysed by the enzyme arginase . **In plants** it is formed mainly **from L-glutamate.**

Ornithine contains both δ -and α-amino groups, and it is the nitrogen from the former group which is incorporated into alkaloid structures along with the carbon chain, except for the carboxyl group. Thus ornithine supplies a C4N building block to the alkaloid, principally as a pyrrolidine ring system, but also as part of the tropane alkaloids.

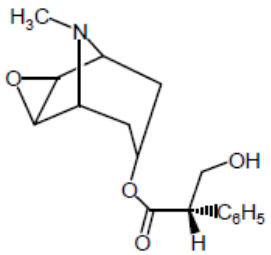


Structure of Tropane Alkaloids

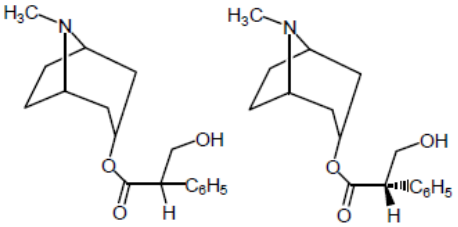
Tropane alkaloids are esters of tropane alcohols and of acids of various structures, either aliphatic or aromatic.

Tropanols

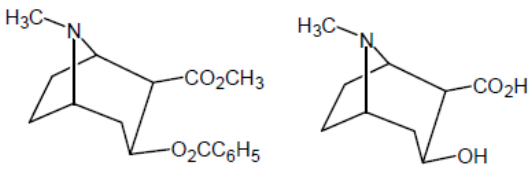
- These alcohols depending on the orientation of the OH in 3 position.
- These can be tropan 3α-ol and tropan 3β-ol.
- Tropan 3α-ol are essentially specific to Solanacea family.
- Tropan 3β-ol are essentially specific to Erytroxylaceae family.
- In the absence of other substituents, the Tropanols are optically inactive.
- The Tropanols are often hydroxylated at C6 or/and C7.
- The Tropanols are often epoxidized at C6 and C7.



(-)-scopolamine



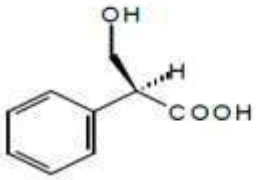
atropine (-)-hyoscyamine



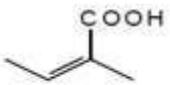
cocaine ecgonine

Acids

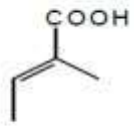
The acids may be aliphatic Tiglic & Angelic acid or aromatic Tropic acid.



Tropic Acid



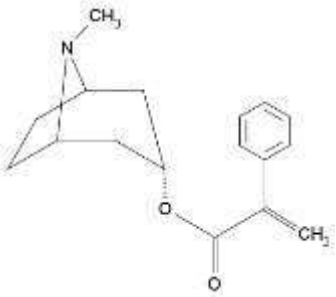
Angelic acid



Tiglic Acid

Alkaloids

The most representative structures are atropine, hyoscyamine, scopolamine, cocaine, apoatropine.



Apoatropine

Pyrrolidine and Tropane Alkaloids

Simple pyrrolidine-containing alkaloid structures are exemplified by hygrine and cuscohygrine, found in those plants of the Solanaceae that accumulate medicinally valuable tropane alkaloids such as hyoscyamine or cocaine .

The pyrrolidine ring system is formed initially as a Δ1-pyrrolinium cation. Pyridoxal 5'-phosphate) PLP-(dependent decarboxylation of ornithine gives putrescine, which is then methylated to N-methyl putrescine .

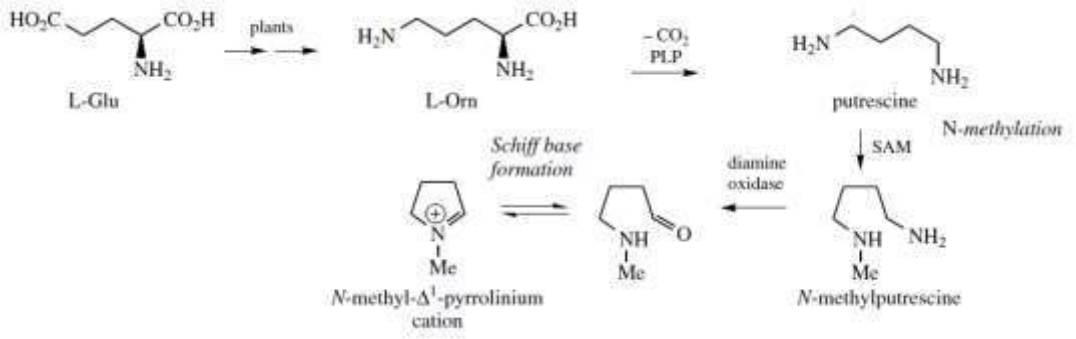
Oxidative deamination of N-methyl putrescine by the action of a diamine oxidase gives the aldehyde, and Schiff base –imine- formation produces the N-methyl-Δ1-pyrrolinium cation.

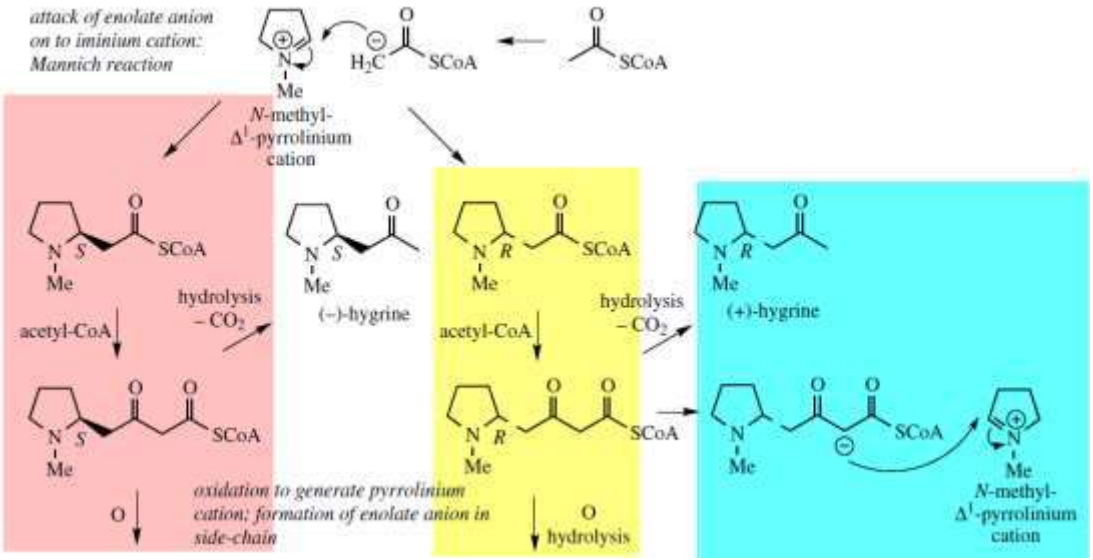
Indeed, the amino aldehyde in aqueous solution is known to exist as an equilibrium mixture with the Schiff base .

An alternative sequence to putrescine starting from arginine also operates concurrently as indicated in.

The arginine pathway also involves decarboxylation, but requires additional hydrolysis reactions to cleave the guanidine portion.

The extra carbon atoms required for hygrine formation are derived from acetate via acetyl-CoA, and the sequence appears to involve stepwise addition of two acetyl-CoA units .





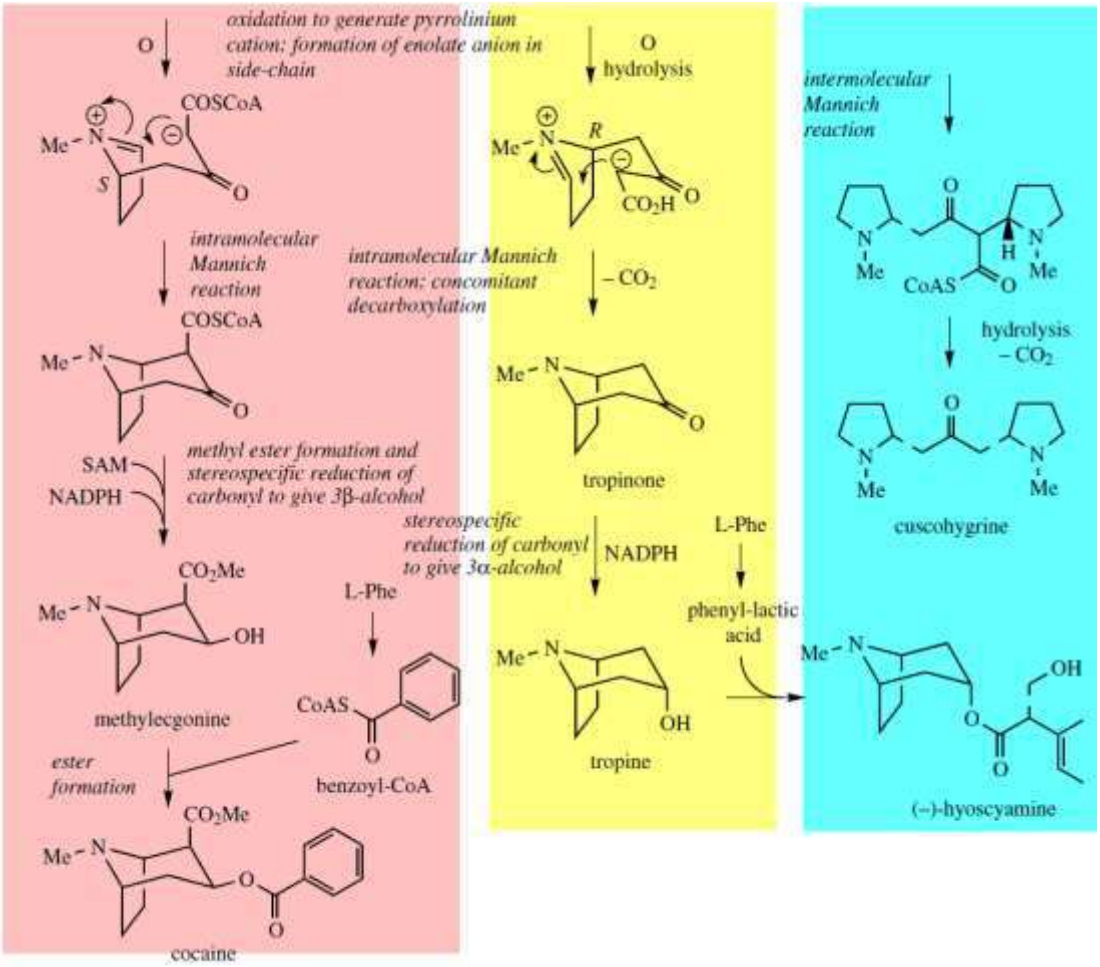
In the first step, the enolate anion from acetyl-CoA acts as nucleophile towards the pyrrolinium ion in a Mannich-like reaction, which could yield products with either R or S stereochemistry .

The second addition is then a Claisen condensation extending the side-chain, and the product is the 2-substituted pyrrolidine, retaining the thioester group of the second acetyl-CoA .

Hygrine and most of the natural tropane alkaloids lack this particular carbon atom, which is lost by suitable hydrolysis/decarboxylation reactions .

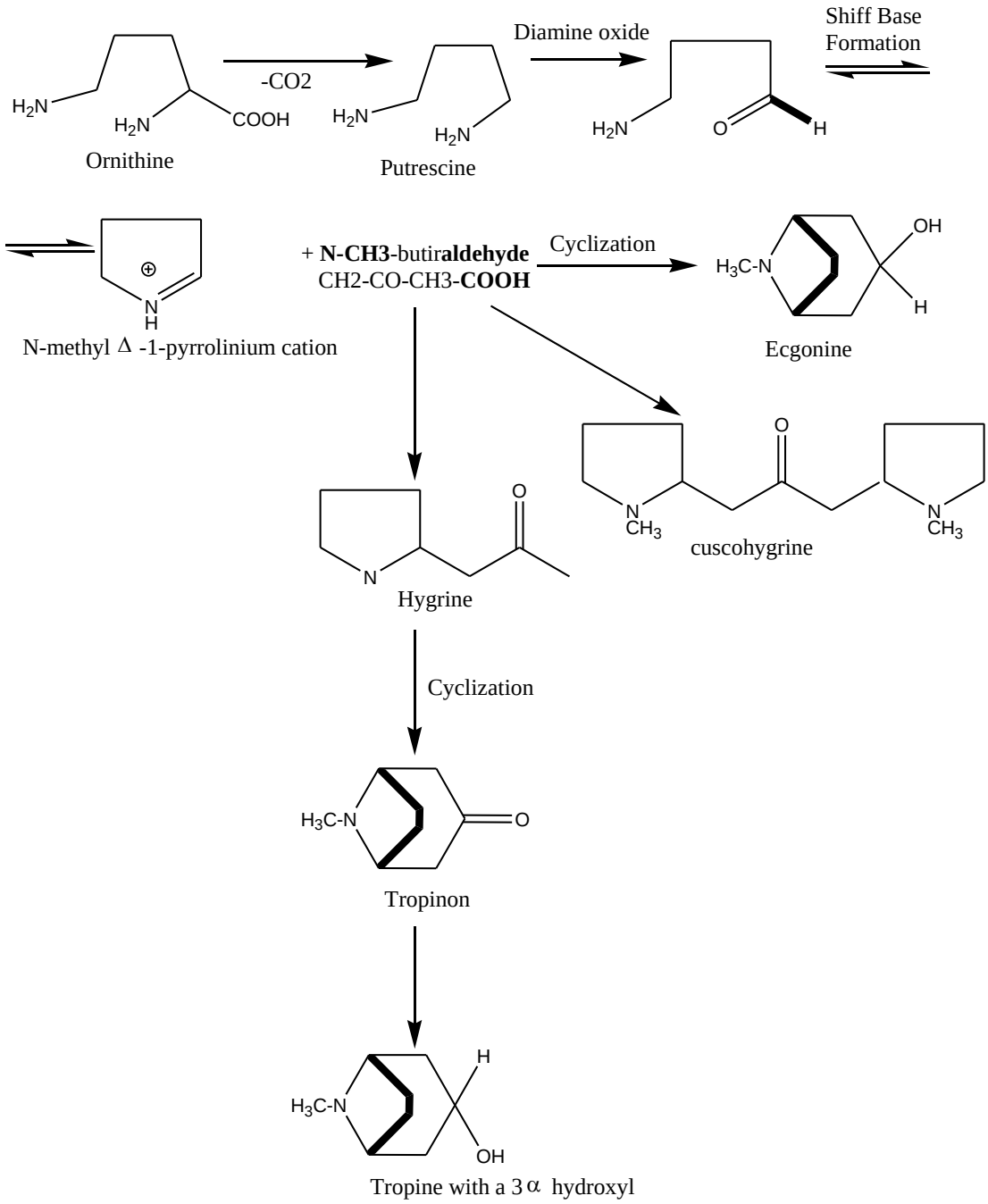
The bicyclic structure of the tropane skeleton in hyoscyamine and cocaine is achieved by a repeat of the Mannich-like reaction just observed .

This requires an oxidation step to generate a new Δ1-pyrrolinium cation, and removal of a proton α to the carbonyl.



The intramolecular Mannich reaction on the R enantiomer accompanied by decarboxylation generates tropinone, and stereospecific reduction of the carbonyl yields tropine with a 3α -hydroxyl .

We can resume all above mention with the following figure:


Diamine oxide
Shiff Base Formation
-CO2
Ornithine
Putrescine
+ N-CH3-butiraldehyde
CH2-CO-CH3-COOH
Cyclization
N-methyl Δ -1-pyrrolinium cation
Ecgonine
cuscohygrine
Hygrine
Cyclization
Tropinon
Tropine with a 3α hydroxyl

Characterization of alkaloids containing tropane alkaloids

Alkaloids that are esters of tropic acid are easy to characterize by the **Vitali-Morin reaction** :the vegetal product is extracted with non polar solvent, and then treated with fuming nitric acid and redissolving the residue with acetone .**A dark purple "violet" color develops in the presence of an alcohol solution of potassium hydroxide.**

Tropane alkaloids are easy to detect by TLC, HPLC & GC.

Official Solanaceae Containing Tropane Alkaloids

Atropa belladonma

Belladona ست الحسن/

Solanaceae Family

Medicinal Parts

The medicinal parts are the leaves and roots.

Phytochemicals

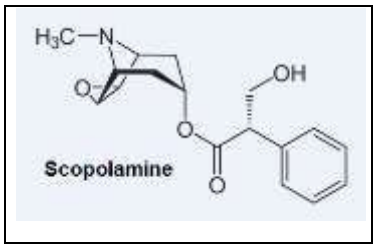
BELLADONNA LEAF

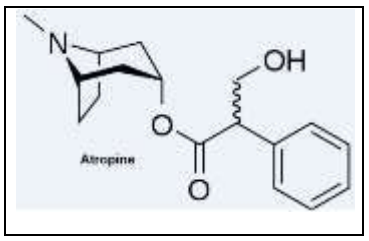
Tropan alkaloids :chief alkaloid -(-)**hyoscyamine**, which during drying transforms to some extent into **atropine**, as well as apoatropine, scopolamine and tropine

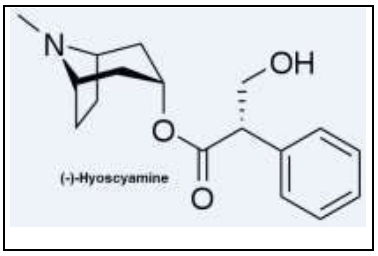
Flavonoids

Hydroxycoumarin: including scopolin, scopoletin

Tannins







BELLADONNA ROOT

Tropan alkaloids :chief alkaloid -(-) hyoscyamine, in drying transformed to some extent during dehydration into atropine as well as apoatropine, 3alpha-phenylacetoxytropane, tropine, cusuhygrine, scopolamine, pseudotropine.

EFFECTS :BELLADONNA LEAF AND ROOT

The tropan alkaloids in the drug atropine, scopolamine, and tropine are responsible for the **anti-cholinergic-parasympatholytic**, spasmolytic, positive, dromotropic and chronotropic effect.

Atropa belladonna preparations **act as a parasympatholytic or anticholinergic via a competitive antagonism of the neuromuscular transmitter acetylcholine.**

This antagonism concerns mainly the muscarine-like effect of acetylcholine and less the nicotine-like effects on the ganglions and the neuromuscular end plate .

Atropa belladonna preparations **release peripheral effects** targeted on the vegetative nervous system and the smooth muscle system, as well as the central nervous system .

Because of the parasympatholytic properties, the drug can cause relaxation of organs with smooth muscles and relieve spastic conditions, especially in the gastrointestinal tract and bile duct.

Additionally, Belladonna use may result in **muscular tremor or rigidity** due to effects on the central nervous system .

Atropa belladonna preparations have a **positive dromotropic** as well as a **positive chronotropic** effect on the heart .

The drug has always been important in folk medicine for its **hallucinogenic effect.**

Antidote for organophosphate poisoning

By blocking the action of acetylcholine at muscarinic receptors, atropine also serves as an **antidote for poisoning by organophosphate insecticides and nerve gases**.

Some of the nerve gases attack and destroy acetyl cholinesterase, so the action of acetylcholine becomes prolonged .Therefore, atropine can be used to reduce the effect of ACh.

INDICATIONS AND USAGE

Atropine lowers the "**relax and assimilate** "activity of all muscles and glands regulated by the parasympathetic nervous system .

This occurs because atropine is a competitive antagonist of the muscarinic acetylcholine receptors) . Acetylcholine is the neurotransmitter used by the

parasympathetic nervous system (.Therefore, it may cause swallowing difficulties and reduced secretions .Topical atropine is used as midriatic to dilate the pupils.
Belladonna extract provide peripheral anticholinergic/antispasmodic action and **mild sedation** .
According to its labeling, it is possibly effective for use as adjunctive therapy in the treatment of irritable bowel syndrome irritable colon, spastic colon, mucous colitis and acute enterocolitis.

Emergency

Injections of atropine are used in the treatment of bradycardia an extremely low heart rate, asystole and **p**ulseless **e**lectrical **a**ctivity PEA in cardiac arrest.

Contraindication

Atropine is contraindicated in patients predisposed to narrow angle glaucoma.

Side effects and overdoses

Adverse reactions to atropine include ventricular fibrillation, supraventricular or ventricular tachycardia, giddiness, nausea, blurred vision, loss of balance, dilated pupils, photophobia, and possibly, notably in the elderly, confusion, hallucinations and excitation .These latter effects are due to the fact that atropine is able to cross the blood-brain barrier .Because of the hallucinogenic properties, some have used the drug recreationally, though this is very dangerous.
In overdoses, atropine is poisonous .Atropine is sometimes added to other potentially addictive drugs; abuse of those drugs is then prevented by the unpleasant effects of atropine overdose .The antidote to atropine itself is physostigmine or pilocarpine.

Toxicity

Belladonna is one of the most toxic plants. Children have been poisoned by eating as few as three berries. Ingestion of a leaf of the Belladonna can be fatal to an adult . The root is often the most toxic part, though this can vary from one specimen to another.

All parts of the plant contain tropane alkaloids.

Symptoms of belladonna poisoning are :dilated pupils, tachycardia, hallucinations, blurred vision, loss of balance, a feeling of flight, staggering, a sense of suffocation, paleness followed by a red rash, flushing, husky voice, extremely dry throat, constipation, urinary retention, and confusion .The skin can completely dry out and slough off .Fatal cases have a rapid pulse that turns feeble.

Antidote

The antidote is physostigmine or pilocarpine.

Drugs in Pharmacy

<u>Please go personally to the pharmacy and ask the pharmacist about drugs containing one of ingredient)s (above mention.</u>

Hyoscyamus niger

Henbane

Solanaceae Family

Medicinal Parts

The medicinal parts are the dried leaves or the dried leaves with the flowering branches, the dried seeds and the whole fresh flowering plant.

Characteristics

Henbane has a strong, distinctive odor .The plant is poisonous.

In folk medicine

Henebane was formerly used as a fumigant for asthma and toothache.

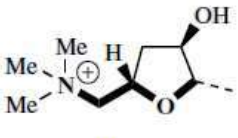
Phytochemicals

Tropane alkaloids 0.05 -0.28 :%chief alkaloid -(-)hyoscyamine, under storage conditions changing over to some extent into atropine, and scopolamine

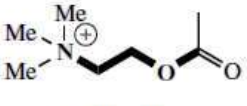
Flavonoids :including, among others, rutin

EFFECTS

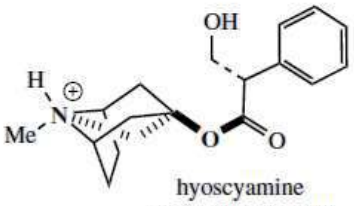
Main active agents :Alkaloids, flavonids .Henbane preparations produce a parasympatholytic or anticholinergic effect by competitive inhibition of acetylcholine . This inhibition affects the muscarinic action of acetylcholine but not its nicotine-like effects on ganglia and motor end plates.



muscarine



acetylcholine



hyoscyamine
(as conjugate acid)

Henbane preparations exert peripheral actions on the autonomic nervous system and on smooth muscle, as well as the central nervous system .Because of their parasympatholytic properties, they cause relaxation of organs containing smooth muscle, particularly in the region of the gastrointestinal tract .Furthermore, they relieve muscular tremors of central nervous origin.

The spectrum of actions of *Hyoscyamus niger* additionally includes a sedative effect.

INDICATIONS AND USAGE

Dyspeptic complaints

CONTRAINDICATIONS

Tachycardiac arrhythmias, prostatic adenoma, angle-closure glaucoma, acute pulmonary edema, mechanical stenoses in the area of the gastrointestinal tract, megacolon.

Drug Interactions

Enhancement of anticholinergic action by tricyclic antidepressants, amantadine, antihistamines, phenothiazines, procainamide and quinidine.

Solanaceae that are Industrial Sources of Tropane Alkaloids

It is leaves, which can be used for the extraction of alkaloids, contain more than 1 % total alkaloids, with the hyoscyamine-atropine group dominating.

Datura stramonium

Characteristics

The foliage has an unpleasant smell)narcotic smell(; the flowers are fragrant and poisonous.

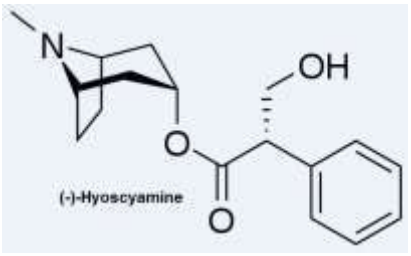
Medicinal Parts

The medicinal parts are the dried leaves or the dried leaves with the tips of the flowering branches.

Occasionally the fruit, the ripe seeds and the fresh, aerial parts of the plant are used . Parts of the plant are regarded as poisonous.

Phytochemicals

Tropane alkaloids) 0.1-0.65(% in the leaves and)0.4-0.6(% in the seeds :chief alkaloids in both leaves and seeds is -(-)hyoscyamine, under drying conditions changing over to some extent into atropine and scopolamine)ratio 4:1(, furthermore including, among others, apoatropine, belladonnine, tigloylmeteloidin



Flavonoids

Hydroxycoumarins: including, among others, umbelliferone, scopolin, scopoletin

Withanolide: including, among others, withastramonolide

EFFECTS

The drug contains alkaloids)hyoscyamine, scopolamine (in extremely varying concentrations .The effect is anticholinergic and parasympatholytic)see Belladonna(; the scopolamine fraction is more responsible for this effect.

Datura stramonium was first used for epileptic fits, and it was also used for hallucinogenic effect in magic and witch potions.

CONTRAINDICATIONS

Glaucoma, suspicion of glaucoma, paralytic ileus, pyloric stenosis, enlarged prostate, tachycardic arrhythmias, acute pulmonary edema.

Daily Dosage

Stabilized leaf powder :0.05 to 0.1 gm drug as a single dose up to 3 times a day.

ALKALOIDS CONTAINING ERYTHROXYLACEAE

Erythroxylum coca

History

- The Coca leaf has been cultivated, at the first time, by Indian peoples to avoid starvation.
- The cocaine alkaloid "**erythroxyline**", was first isolated by the German chemist Friedrich Gaedcke in **1855** .
- In **1860**, Albert Niemann, a Ph.D .student at the University of Göttingen in Germany, who then developed an improved **purification process of cocaine**.
- In **1879** cocaine began to be **used to treat morphine addiction**.
- In **1884** cocaine was introduced into clinical use as a **local anesthetic** in Germany.

- In **1886** John Pemberton **introduced in Atlanta, a beverage consisting of coca leaf extracts**, African kola nuts, and sweet carbonated syrup .The product was named **Coca-Cola.**

- **Coca-Cola was sold in bottles for the first time on March 12, 1894**
- The **first synthesis** and **elucidation of the structure of the cocaine** molecule was by Richard Willstätter in **1898**
- Originally intended as **a patent medicine** when it was invented in the late 19th century by John Pemberton
- In the **19th century**, **cocaine** was available only in the form of a **botanical product** or a botanical product in solution.
- **Patterns of coca consumption changed dramatically in the 20th century.**

- In **1923**, Richard Willstatter was able to synthesize a **mixture** of D-cocaine, Lcocaine, D-pseudococaine, and L-pseudococaine.
- A registered **trademark** of The **Coca-Cola** Company in the United States **since March 27, 1944.**
- **In 1955, first can of coca-cola.**

Addiction terms

- **Controlled substance**" is a drug or substance of which the use, sale, or distribution is regulated by a state government entity.
- **Addiction <u>is a brain disease able to relapse</u>**, characterized by **<u>compulsive use</u>**, **<u>loss of control</u>** of over use, and **<u>continued use</u>** one or more psychoactive drugs, in spite of adverse consequences.
- **Drug addiction** is considered **a pathological state** .The disorder of addiction involves the progression of **acute drug use** to the development of drug-**seeking behavior**, **the vulnerability to relapse**, and the **decreased ability to respond to naturally rewarding stimuli.**
- **Habituation** is a condition resulting from the repeated consumption of a drug.

Drug addiction has two components:

- *Physical dependency, and*
- *Psychological dependency.*

- **Physical dependence** :occurs when **a drug** has been **used habitually** and the **<u>body</u>** has **become accustomed to its effects** .The person must then continue to use the drug in order to feel normal, or its absence will trigger the symptoms of withdrawal.
- **Psychological dependency**: occurs when **a drug** has been **used habitually** and the **<u>mind</u>** has become **emotionally reliant of its effects**, either to elicit pleasure or relieve pain, and does not feel capable of functioning without it .Its absence produces intense cravings, which are often brought on or magnified by stress.
- **Tolerance** :Is **a state of adaptation** in which **<u>exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over</u>** time.

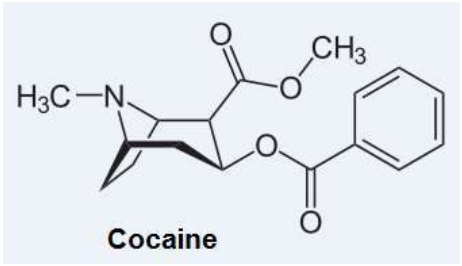
<u>Many prescription or over the counter drugs can become addictive if abused.</u>

Medicinal Parts

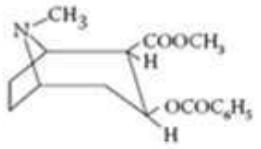
The medicinal parts are the leaves of the coca bush.

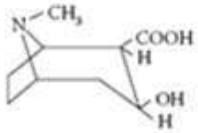
Phytochemicals

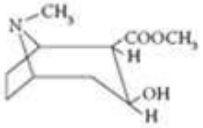
Coca contains several alkaloids 0.75 -2%, tropanic alkaloids from cis serial as ecgonine and pseudotropine ester)tropococaine.(Tropane alkaloids :main alkaloid -(-) cocaine, including, among others, cis-cinnamoyl cocaine, trans-cinnamoyl cocaine, also including alpha-truxillin, beta-truxillin, benzoylecgonin.

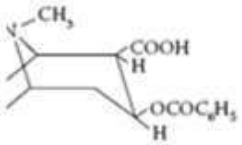


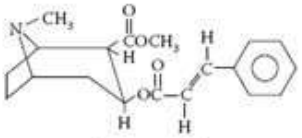
Cocaine

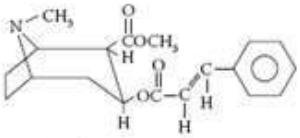

Cocaine

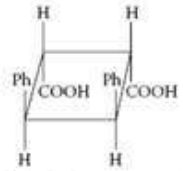

Ecgonine


Methylecgonine

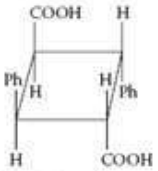

Benzoylecgonine


trans-Cinnamoylcocaine

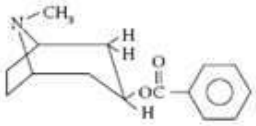

cis-Cinnamoylcocaine

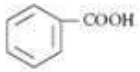


beta-Truxinic Acid

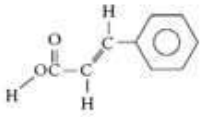


alpha-Truxillic Acid


Tropacocaine



Benzoic Acid


trans-Cinnamic Acid

EFFECTS

Cocaine is a powerfully addictive CNS stimulant that is snorted, injected, or smoked. Crack is cocaine HCl powder has been processed to form a rock crystal that is then usually smoked.

Cocaine usually makes the user feel euphoric and energetic, but also increase body temperature, blood pressure and heart rate.

Users risk heart attack, respiratory failure, stroke, seizures, abdominal pain, and nausea. In rare cases sudden death!

Cocaine, **in any form**, is a powerfully addictive drug, and addiction seems to develop more quickly when the drug is smoked--as crack is--than snorted--as powdered cocaine typically is.

Thus, all types or methods of administration of cocaine can lead to addiction and other severe health problems, including HIV/AIDS, hepatitis and other infectious diseases.

The faster cocaine is absorbed into the bloodstream and delivered to the brain. Injecting or smoking cocaine produces a quicker, stronger high than snorting.

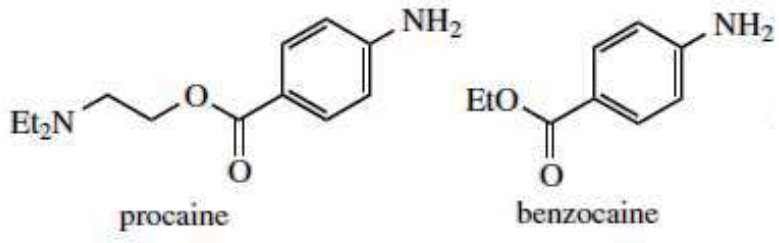
Users take cocaine in "overdoes," during which the cocaine is used repeatedly and at increasingly higher doses. This can lead to increased irritability, restlessness, panic attacks, and paranoia—even a full-blown psychosis, in which the individual loses touch with reality and experiences auditory hallucinations. With increasing dosages or frequency of use, the risk of adverse psychological or physiological effects increases.

Mechanism of action:

Cocaine is a strong CNS stimulant that increases levels of dopamine, associated with pleasure and movement, in the brain's reward circuit.. Certain brain cells, or neurons, use dopamine to communicate, but cocaine acts by preventing the dopamine from being recycled, causing excessive amounts of the neurotransmitter to build-up, amplifying the message to and response of receiving neuron, and finally disrupting normal communication.

Tolerance may develop—this means that higher doses and/or more frequent use of cocaine is needed to register the same level of pleasure experienced during initial use. At the same time, users can also become more sensitive (sensitization) to cocaine's anxiety-producing, convulsant, and other toxic effects.

Cocaine Hydrochloride acts as a local anesthetic and stimulates the central nervous system .In high doses, the drug causes paralysis of motor neuron fibers .



The **LD50** of cocaine when administered to mice is **95.1 mg/kg**.
There is no specific antidote for cocaine overdose.

Cocaine stays in your system for 12-72 hours depending on the dose. But it's metabolite takes much longer to get eliminated. After this period it is usually not detected in urine. However, there is an exception. If a large quantity of alcohol has also been consumed with cocaine, it takes even longer to eliminate- 5 days approximately. It also leads to the formation of a metabolite called Cocaethylene.

Benzoylecgonine is the main metabolite of cocaine, which is used in drug screening test. Many factors determine how quickly it gets cleared from the body. Therefore, in cocaine users, **benzoylecgonine testing in urine is commoner than testing of cocaine itself.**

How much time a drug takes to get eliminated out of the system would depend upon:

- The amount of drug taken.
- How frequently or regularly you are taking it?
- Individual body weight and height.
- Your overall rate of metabolism, which depends on your levels of activity and health status.

Types of Drug Screening

Saliva test– Cocaine is detectable in saliva after 5 to 10 minutes of taking the drug. It may be detected in saliva till 2 to 4 days.

Urine test– Detectable after 2 to 5 hours of use, till a period of 3 to 4 days.

Blood testing is more specific. The drug is detected after 5 to 6 hours till around 5 to 7 days or even more.

Hair test: The drug starts showing in hair after 5 to 7 days till around 80 to 90 days. Urine testing is most popular because it is painless, easy and inexpensive. Home kits available in the market are also based on urine testing.

Scott test: It is best known for the cobalt thiocyanate test (or Scott test), which is a proven screening test for the presence of cocaine.

Procedure

The cobalt thiocyanate test is performed by placing approximately 2 to 4 milligrams of a target substance in a glass test tube, then 5 drops of cobalt thiocyanate reagent. After shaking, 1 or 2 drops of concentrated hydrochloric acid are added, and the tube is again shaken. Ten drops of chloroform are then added, and the tube is vortexed (vortexer is a simple device used commonly in laboratories to mix small vials of liquid), and then allowed to settle and separate into two layers. The final color of the chloroform (organic) layer is recorded.

Addition of the cobalt thiocyanate reagent to cocaine hydrochloride results in the surface of the particles turning a bright blue (faint blue for cocaine base). The solution changes back to pink upon adding one or two drops of hydrochloric acid and mixing. Addition of 10 drops of chloroform, vortexing, and allowing the solution to settle results in a blue organic layer for both cocaine hydrochloride and cocaine base. Diphenhydramine and lidocaine also give blue organic layers. These compounds are known false positives for cocaine.

USAGE

Just in stomatology the plant is used in the manufacture of the local anesthetic as cocaine hydrochloride.

PRECAUTIONS AND ADVERSE REACTIONS

Chewing an excessively large quantity of the leaves can cause psychic disturbances and hallucinations.

Chronic use can lead to poor nutritional states and disinterest in work, due to the suppression of feelings of hunger and the resulting reduction in food intake .

The enhanced vulnerability to illness and the reduced life expectancy are also conditioned by the immunosuppressive effect of the drug .Beyond that, the drug is probably carcinogenic in effect. Embryo toxic and sensitizing .The observed dependence on the drug cocoaism (is mainly psychically conditioned. Although withdrawal symptoms are also known)need for sleep, bulimia, anxiety, irritability, tremor .

Pregnancy

Cocaine passes into the embryo or fetus and is embryo toxic.

Nursing Mothers

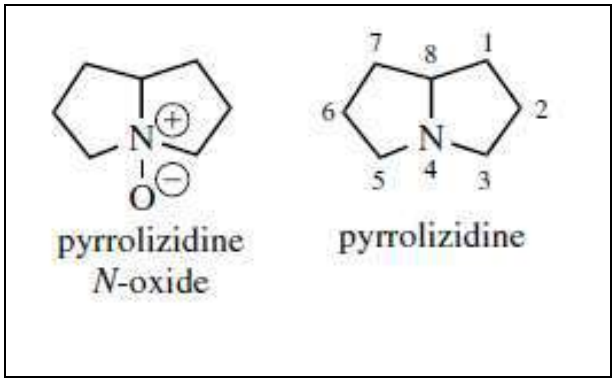
Cocaine passes into the mother's milk.

Addiction treatment option:

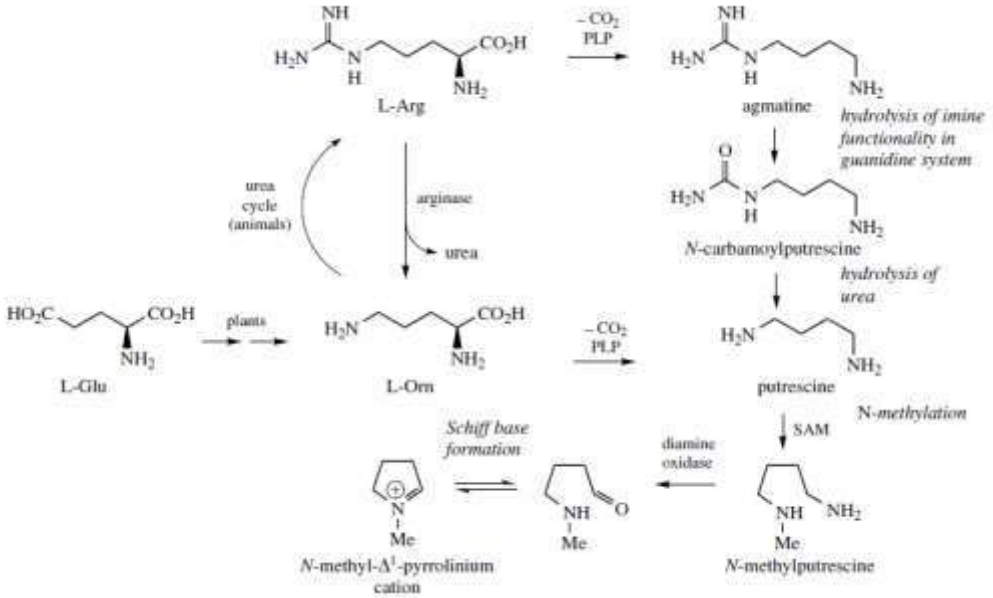
- Withdrawal
- Behavioral intervention (particular cognitive behavior therapy)
- Drugs: to relieve withdrawal symptoms

Pyrrolizidine alkaloids

- Borago
- Comfrey

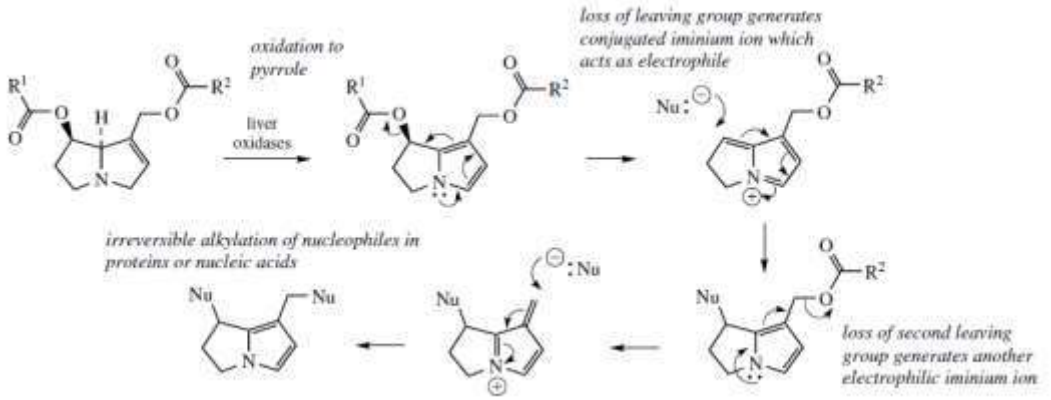


Two molecules of ornithine are utilized in formation of the bicyclic pyrrolizidine skeleton, the pathway proceeding via the intermediate putrescine. Because plants synthesizing pyrrolizidine alkaloids appear to lack the decarboxylase enzyme transforming ornithine into putrescine, ornithine is actually incorporated by way of arginine.



The pyrrolizidine skeleton is formed from homospermidine by a sequence of oxidative deamination, imine formation, and an intermolecular Mannich reaction, which exploits the enolate anion generated from the aldehyde.

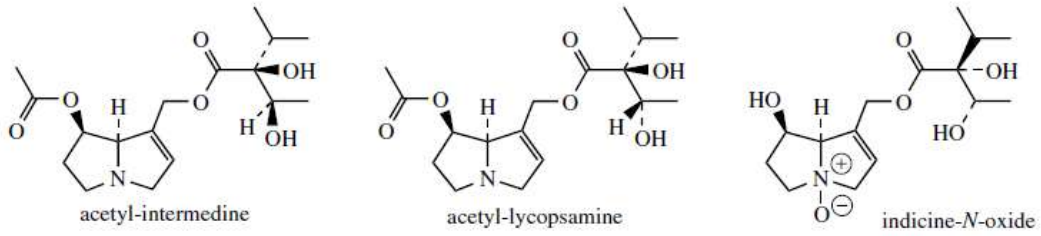
Many pyrrolizidine alkaloids are known to produce pronounced hepatic toxicity and there are many recorded cases of livestock poisoning .Potentially toxic structures have 1,2-unsaturation in the pyrrolizidine ring and an ester function on the side-chain . Although themselves non-toxic, these alkaloids are transformed by mammalian liver oxidases into reactive pyrrole structures, which are potent alkylating agents and react with suitable cell nucleophiles, e.g .nucleic acids and proteins



N-oxides are not transformed by these oxidases, only the free bases .The presence of pyrrolizidine alkaloids, e.g .acetyl-intermedine and acetyl-lycopsamine in medicinal comfrey *Symphytum officinale*; Boraginaceae (has emphasized potential dangers of using this traditional herbal drug as a remedy for inflammatory, rheumatic, and gastrointestinal disorders.

Prolonged usage may lead to liver damage .

Indicine-N-oxide from *Heliotropium indicum* (Boraginaceae) demonstrated significant antileukaemic activity in clinical trials but undesirable hepatotoxicity prevented any further development.



The tobacco alkaloids, especially nicotine, are derived from nicotinic acid **but also contain a pyrrolidine ring system derived from ornithine** as a portion of their structure.

Drugs Containing Pyrrolizidine alkaloids

Borago officinalis

Boraginaceae

Synonym: Star flower

Medicinal Parts

The medicinal parts are the dried Borage flowers and the dried or fresh foliage, stems and leaves.

Characteristics

Borage has a taste similar to cucumber.

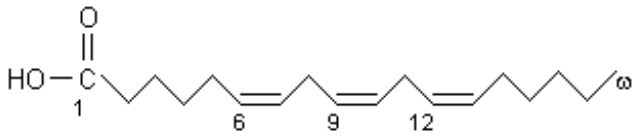
Traditional Medicine

Borage is used as a sequestering and mucilaginous agent for coughs and throat illnesses and as a bronchial treatment .It is also used as an anti-inflammatory agent for kidney and bladder disorders, as an astringent and to treat rheumatism.

Phytochemicals :

BORAGE OIL

Borage seed oil contains 17-28% of **gamma-linolenic acid (GLA)** and is the **richest** known source. The seed oil content is between 26-38% and in addition to GLA contains the fatty acids **palmitic acid** (10-11%), **stearic acid** (3.5-4.5%), **oleic acid** (16-20%), **linoleic acid** (35-38%), **eicosenoic acid** (3.5-5.5%), **erucic acid** (1.5-3.5%), and **nervonic acid** (1.5%). The oil is often marketed as "starflower oil" or "borage oil" for uses as a GLA supplement, although healthy adults will typically produce ample GLA through dietary linoleic acid.



EFFECTS:

Traditionally, *Borago officinalis* has been used

in hyperactive gastrointestinal, respiratory and cardiovascular disorders, such as gastrointestinal (colic, cramps, diarrhea), airways (asthma, bronchitis), cardiovascular,

(cardiotonic, antihypertensive and blood purifier),urinary (diuretic and kidney/bladder disorders).

Medically, use borage for regulation of metabolism and the hormonal system, and consider it to be a good remedy for PMS and menopause symptoms such as the hot flash

INDICATIONS AND USAGE

Borage oil is used for neurodermatitis, Pre Menstrual Syndrome (PMS) and as a food supplement.

PRECAUTIONS AND ADVERSE REACTIONS

BORAGE OIL

No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages.

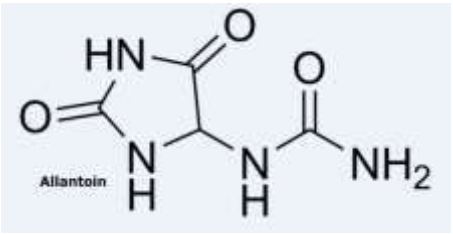
Symphytum officinalis

Comfrey

Boraginaceae

Medicinal Parts

The medicinal parts are the fresh root and the leaves.



Phytochemicals

Allantoin

Mucilages, Fructans

Triterpene saponins: including symphytoxide A

Tannins

Pyrrolizidine alkaloids 0.03 %in the leaves: including echinatine, lycopsamine, 7-acetyl lycoposamine, echimidine, lasiocarpine, symphytine, intermedine, symveridine.

EFFECTS

Anti-inflammatory Effect—Comfrey suppresses leukocyte infiltration during the inflammation process.

Demultant Effect: The mucilages act as demultants for a soothing and irritation reduction effect.

Comfrey is used **as a tea** for upset stomach, ulcers, heavy menstrual periods, diarrhea, bloody urine, persistent cough, painful breathing (pleuritis), bronchitis, cancer, and chest pain (angina). It is also used as a gargle for gum disease and sore throat.

INDICATIONS AND USAGE

• Anti-inflammatory agent

Externally, Comfrey is used for bruises, sprains and promotion of bone healing & in cosmetics.

CONTRAINDICATIONS

Comfrey is contraindicated in pregnancy and in nursing mothers.

Tussilago farfara

Coltsfoot

Asteraceae

Medicinal Parts

The medicinal parts are the dried inflorescences, the dried leaves and the fresh leaves.

Characteristics

The taste and texture is slimy-sweet and the leaves have a honey-like smell when they are rubbed.

Phytochemicals :

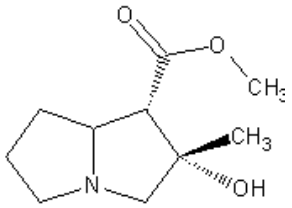
Mucilages)7 :(%acidic polysaccharides

Tannins

Triterpenes :including beta-amyrin, arnidiol .faradiol

Steroids :including beta-sitosterol

Pyrrolizidine alkaloids) traces, not in plants from all places of origin :(**tussilagin**, isotussilagine, senkirkine . senecionine



Tussilagin

Flavonoids

EFFECTS: COLT'S FOOT FLOWER, HERB, AND ROOT

The plant has found particular use in Chinese herbal medicine for the treatment of respiratory diseases, including cough, asthma, and acute and chronic bronchitis. It also is a component of numerous European commercial herbal preparations for the treatment of respiratory disorders. Coltsfoot preparations long have been used to

soothe sore throats. The mucilage most likely is responsible for the demulcent effect of the plant.

The pyrrolizidine alkaloids are antibacterial, carcinogenic, and hepatotoxic .The mucin polysaccharides cause a demulcent, sequestering, and anti-inflammatory effect.

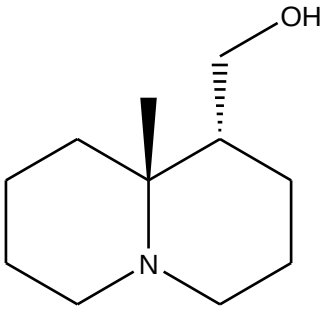
INDICATIONS AND USAGE

- Cough
- Bronchitis
- Inflammation of the mouth and pharynx

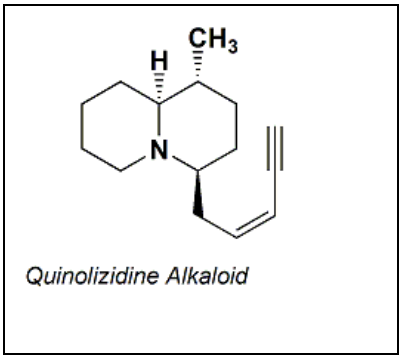
CONTRAINDICATIONS

Administration during pregnancy and nursing is contraindicated.

Quinolizidine Alkaloids



Lupinine



Lupines

Fabaceae

Lupinus albus (Lupinus termis)

Traditional name: ترمس

Lupine plants was used especially seeds, after boiling and prolong steeping in water to get ride of their bitter and poisonous alkaloids, are used as stock feed and for human consumption as important source of protein. One germ meal of termis contained about 44% crude protein and the quality of protein is similar with soybean protein, one of the best sources of protein. The medical value resume in treatment of stomach ulcer, as anti-inflammatory agent, and anthelminthic, diuretic, emmenagogue. Recently lupine extract **(NOT AQUEOUS EXTRACT)** used for the recovery of diabetes mellitus.

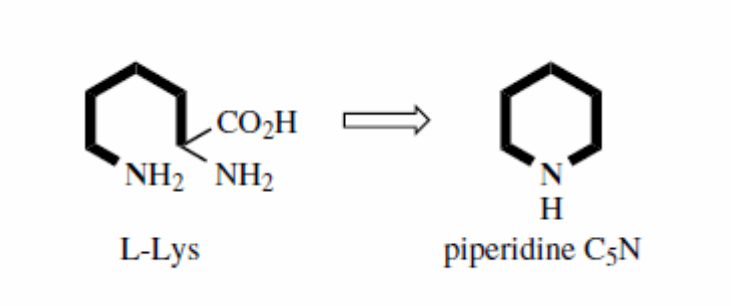
Aqueous extract of termis contain poisonous quinolizidine alkaloids

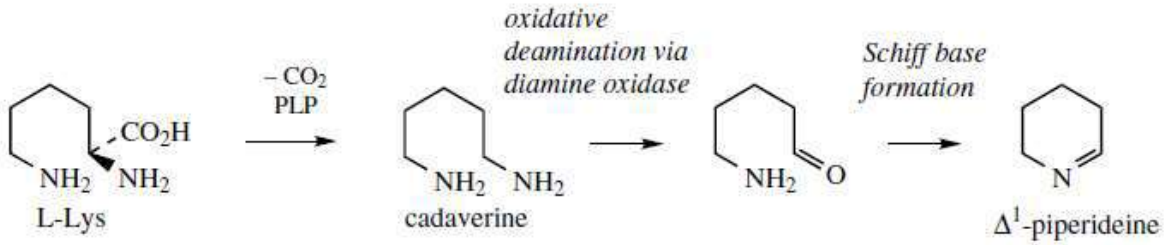
Chapter 3

ALKALOIDS DERIVED FROM LYSINE

L-Lysine is the homologue of L-ornithine, and it too functions as an alkaloid precursor, using pathways analogous to those noted for ornithine.

The extra methylene group in lysine means this amino acid participates in forming six-membered piperidine rings, just as ornithine provided five membered pyrrolidine rings .As with ornithine, the carboxyl group is lost, the ε-amino nitrogen rather than the α-amino nitrogen is retained, and lysine thus supplies a C5N building block.





Lobelia inflate

Lobiliaceae

Indian Tobacco, eyebright

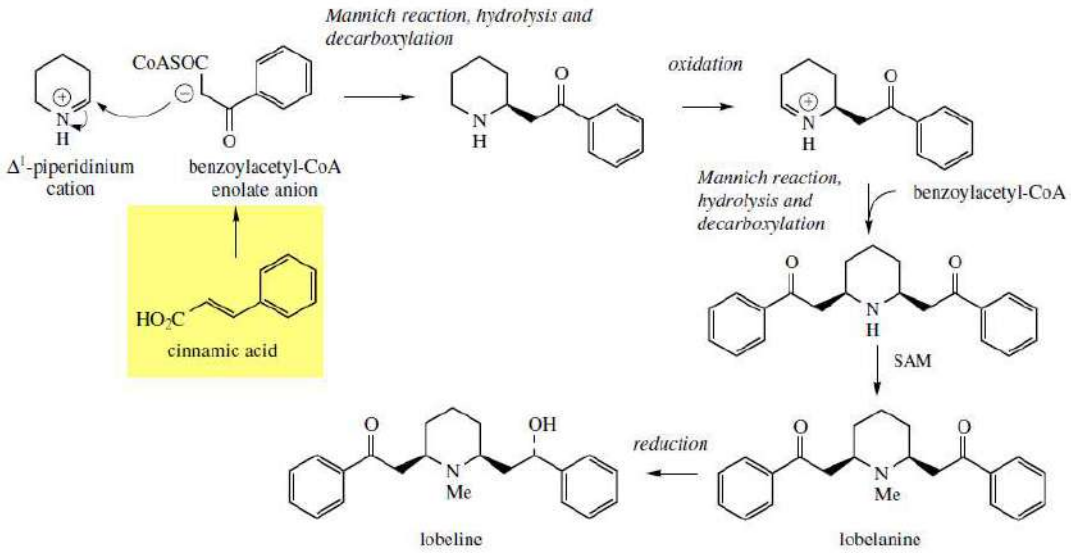
Medicinal Parts

The medicinal parts are the fresh and dried herb

Characteristics

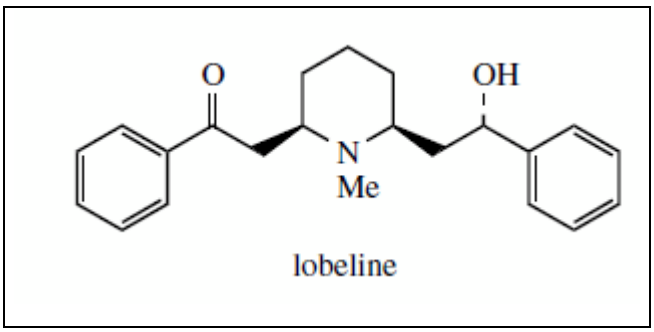
After chewing the leaves the taste is similar to tobacco .The taste 'is' acrid, the odor faintly irritant.

Biosynthesis of Lobeline



Phytochemicals

*Piperidine alkaloids: 6 %*chief alkaloids L-lobeline alphalobeline; companion alkaloids including among others lobelanine, lobelanidine, norlobelanine, and **isolobinine.**



Another constituent of lobelia, beta-amyrin palmitate, has been studied for its antidepressant effects.

EFFECTS

The main active principle is lobelin .The drug has a stimulating effect on the respiratory center but it is broken down too quickly in the body to be used as a respiratory analeptic. Some people take lobelia as a sedative to help them relax. Other people use it to increase sweating. Lobelia is applied to the skin for muscle pain, joint lumps associated with rheumatoid arthritis (rheumatic nodules), bruises, sprains, insect bites, poison ivy, and ringworm.

How does it work?

Lobelia contains chemicals that might thin mucus (phlegm) to make it easier to cough up (expectorate) and help breathing, especially in people with asthma. One chemical in lobelia has actions similar to nicotine.

INDICATIONS AND USAGE

*Homeopathic Uses :*Lobelia inflata is used only in homeopathy as an asthma treatment and also as an aid in curing addiction to smoking isolobinine.

OVERDOSAGE

Over dosage leads to dryness of the mouth, nausea, vomiting, diarrhea, abdominal pain, burning in the urinary passages, feelings of anxiety, dizziness, headache, shivering, respiratory difficulties, paraesthesias, outbreak of sweating, bradycardia, cardiac arrhythmias, somnolence and muscle twitching; death can occur through respiratory failure, accompanied by convulsions .Dose of 0.6 to 1 gm from the leaves are said to be toxic, 4 gm fatal.

Punica granatum

Punicaceae Family

Pomegranate

Medicinal Parts:

The medicinal parts are the root, the bark, the fruits, the peel of the fruit and the flowers.

Phytochemicals :

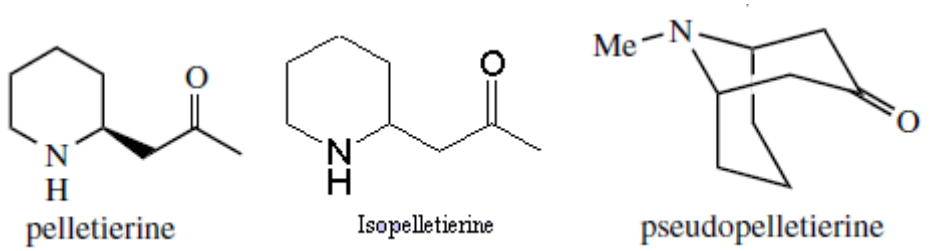
POMEGRANATE FRUIT PEEL

Tannins 25 to 28%; gallo tannins: including punicalin, granatine D, punicalagin granatine C, granatine A, granatine B

POMEGRANATE STEMS AND ROOT

*Tannins 20 to 25 %gallo tannins :(*including punicalagin, punicacortein C, casuarin

Piperidine alkaloids*) 0.4 %in the rind of the stem, up to 0.8 %in the rind of the root :(*chief alkaloids **isopelletierine**, N-methylisopelletierine, pseudopelletierine



pelletierine Isopelletierine pseudopelletierine

Fruit (Dry weight)

- **Calories** per 100g: 362Kcal
- **Water** : 0%
- **Protein**: 5g; Fat: 2.2g; Carbohydrate: 90.5g; Fibre: 12g; Ash: 2.6g;
- **Minerals** - Calcium: 40mg; Phosphorus: 180mg; Iron: 3mg; Magnesium: 0mg; Sodium: 4.35mg; Potassium: 1250mg; Zinc: 0mg;
- **Vitamins** - A: 90mg; Thiamine (B1): 0.27mg; Riboflavin (B2): 0.25mg; Niacin: 3.2mg; B6: 0mg; C: 43mg;

EFFECTS

The drug, which contains tannins and alkaloids, is anthelmintic and amoeboid . Pelletierin triggers, like strychnine, a raised stimulant reflex, which can escalate to tetanus and is effective against diverse tapeworms, ring worms and nematodes.
The tannins in the drug makes it useful as an astringent for sore throats, diarrhea and dysentery.
Recent studies proved the antioxidant, anticarcinogenic, and anti-inflammatory properties of pomegranate constituents have been published, focusing on treatment and prevention of cancer, cardiovascular disease, diabetes, dental conditions, erectile dysfunction, bacterial infections and antibiotic resistance, and ultraviolet radiation-induced skin damage. Other potential applications include infant brain ischemia, male infertility, Alzheimer's disease, arthritis, and obesity.

INDICATIONS AND USAGE

As in folk medicine Pomegranate is used for infestation with tapeworm and other worms, for diarrhea and dysentery, as an abortifacient and astringent; externally used for hemorrhoids and as a gargle in cases of sore throat.

Piperidine Amides : Piperaceae

Piper nigrum

Piperaceae

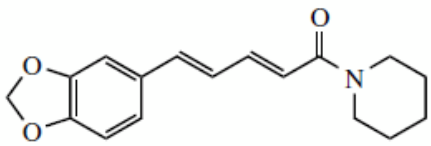
Black Pepper

Medicinal Parts :

The medicinal parts are the berries, which have been freed from the pericarp, and the dried berry-like fruit, which has been collected before ripening.

Phytochemicals

Acid amides) pungent substances *:(*chief components -**piperine**, additionally including among others piperylin, piperolein A and B, cumaperine ***3,4-dihydroxy phenyl ethanol glycosides*** *substratum for the enzymatic black colouring of the fresh fruits*



piperine

Volatile oil *1.2-2.6 :%*chief components -sabinene 15- 25%, limonene 15-20%, caryophyllene 10-15%, betapinene
10-12%, alpha-pinene 8-12%, delta3-carene 5%

Polysaccharides 45%

Fatty oil 10%

Varieties*:*

- Black pepper (ripe green pepper)
- White pepper (skinless)
- Green pepper (unripe drupes)
- Wild pepper (unripe black pepper)
- Orange & red pepper (consists of ripe red pepper drupes preserved in brine and vinegar)
- Pink pepper (Peruvian & Brazilian pepper tree)

EFFECTS

The drug stimulates the thermal receptors and increases secretion of saliva and gastric mucous .It has an antimicrobial effect .It influences liver and metabolic functions, and has an insecticidal effect.

INDICATIONS AND USAGE

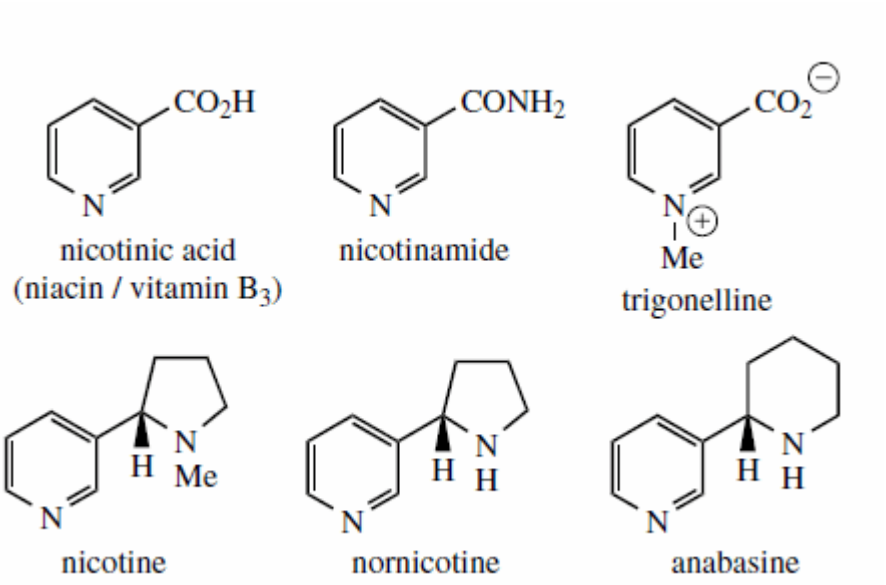
In folk medicine uses include stomach disorders and digestion problems, neuralgia and scabies.

Daily Dosage .Single doses range from 0.3 to 0.6 gm .The daily dosage is 1.5 gm.

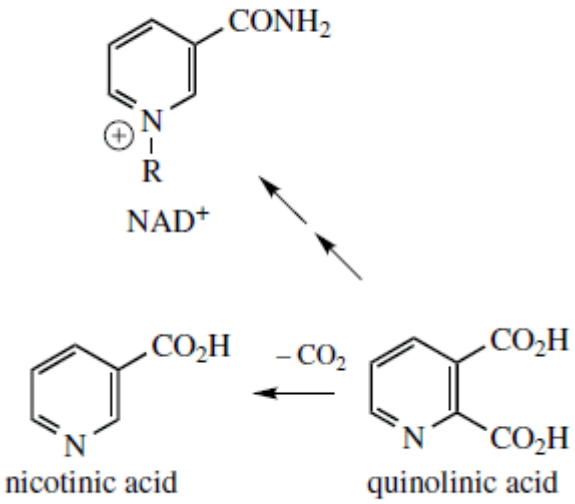
Alkaloids Derived from Nicotinic Acid

PYRIDINE ALKALOIDS

The alkaloids found in tobacco *Nicotiana tabacum*; Solanaceae include **nicotine** and **anabasine** .The structures contain a pyridine ring together with a pyrrolidine ring in nicotine or a piperidine unit in anabasine, the latter rings arising from ornithine and lysine respectively .



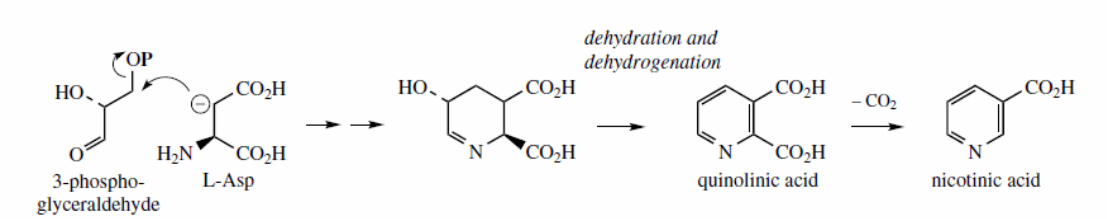
The pyridine unit has its origins in **nicotinic acid**)**vitamin B**3(, the vitamin sometimes called **niacin**, which forms an essential component of coenzymes such as NAD $^{+}$and NADP.$^{+}$



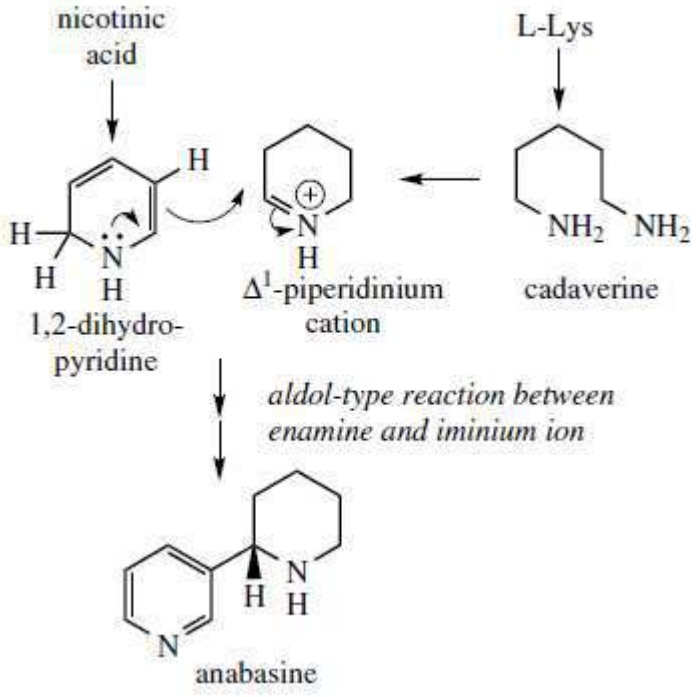
Biosynthesis of Nicotinic acid

The nicotinic acid component of nicotinamide is synthesized in animals by degradation of L-tryptophan . However, plants such as *Nicotiana* use a different pathway employing glyceraldehyde 3-phosphate and L-aspartic acid precursors .

The dibasic acid **quinolinic acid** features in both pathways, decarboxylation yielding nicotinic acid.



Anabasine is produced from nicotinic acid and lysine via the Δ1-piperidinium cation.



Vitamin B3

Vitamin B3 nicotinic acid, niacin is a stable water-soluble vitamin widely distributed in foodstuffs, especially meat, liver, fish, wheat germ, and yeast .However, in some foods, e.g .maize, it may be present in a bound form, and is not readily available. Diets based principally on maize may lead to deficiencies .The amino acid tryptophan can be converted in the body into nicotinic acid, and may provide a large proportion of the requirements .*Nicotinic acid is also produced during the roasting of coffee from the decomposition of the N-methyl derivative trigonelline*. Nicotinic acid is converted into nicotinamide though this compound also occurs naturally in many foods .The term vitamin B3 is often used for the combined nicotinamide–nicotinic acid complement . In the form of the coenzymes NAD +and NADP+, nicotinamide plays a vital role in oxidation–reduction reactions and is the most important electron carrier in primary metabolism .Deficiency in nicotinamide leads to pellagra, which manifests itself in diarrhoea, dermatitis, and dementia .Oral lesions and a red tongue may be more noticeable than the other symptoms .**Nicotinamide** is usually preferred over **nicotinic acid** for dietary supplements since there is less risk of gastric irritation .Both are produced synthetically .It is common practice to enrich many foods, including bread, flour, corn, and rice products.

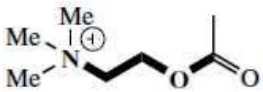
Nicotinic acid in large doses can lower both cholesterol and triglyceride concentrations by inhibiting their synthesis.

Tobacco

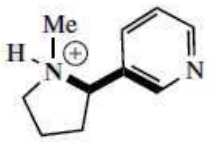
Tobacco is the cured and dried leaves of *Nicotiana tabacum* Solanaceae, an annual herb indigenous to tropical America, but cultivated widely for smoking .

Tobacco leaves may contain from 0.6–9 %of -(−) nicotine an oily, volatile liquid alkaloid, together with smaller amounts of structurally related alkaloids, e.g .anabasine and nornicotine . Nicotine in small doses can act as a respiratory stimulant, though in larger doses it causes respiratory depression .Despite the vast array of evidence linking tobacco smoking and cancer, the smoking habit continues throughout the world, and tobacco remains a major harvest plant.

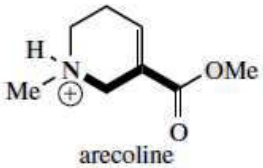
Tobacco smoke contains a number of highly carcinogenic chemicals formed by incomplete combustion, including benzpyrene, 2-naphthylamine, and 4-aminobiphenyl .Tobacco smoking also contributes to atherosclerosis, chronic bronchitis, and emphysema, and is regarded as the single most preventable cause of death in modern society .**Nicotine** is being used by former smokers who wish to stop the habit .It is available in the form of chewing gum or nasal sprays, or can be absorbed transdermally from nicotine-impregnated patches.



acetylcholine



nicotine
(as conjugate acid)



arecoline
(as conjugate acid)

Powdered tobacco leaves have long been used as an insecticide, and nicotine from *Nicotiana tabacum* or *N .rustica* has been formulated for agricultural and horticultural use .Other *Nicotiana* alkaloids, e.g .Anabasine and nornicotine, share this insecticidal activity .

Nicotine is toxic to man due to its effect on the nervous system, interacting with the nicotinic acetylcholine receptors, though the tight binding observed is only partially accounted for by the structural similarity between acetylcholine and nicotine.

Facts about Nicotine

- Tobacco kills up to half of its users.
- 80 %of adult smokers started smoking before the age of 18.
- Causes 87 %of all lung cancers, 90 %of which are fatal.
- 30 %of all cancer deaths.
- 430,000 deaths each year
- High Blood Pressure)Nicotine is a vasoconstrictor(
- Rhinitis and Chronic Sinusitis
- Premature Skin Wrinkling
- 4000 Chemicals with 100 identified poisons and 63 known carcinogens.
    - Arsenic ○ Benzen
    - Cyanide ○ Hydrazine
    - Formaldehyde ○ Benzopyrene
- Sidestream Smoke)Secondhand Smoke (has higher concentration of carcinogens than Mainstream Smoke.
- N-Nitrosodimenthylamine, a potent carcinogen, is found in sidestream smoke at a concentration of 40 to 100 times that found in mainsteam smoke.
- Nicotine is found in low concentration in Sidestream Smoke .Tobacco companies have used this chemical to determine non-smokers exposure to passive smoke.
- Causes the onset of asthma in 26,000 children annually.
- 1962 "Lastly, smoking is a habit of addiction
- 1963 "Moreover, nicotine is addictive.
- Only 3 %of young people have long term success at quitting, it is as hard or harder to quit tobacco as it is to quit heroin or crack cocaine.
- There are three basic steps to quitting smoking :
    - **WANT IT,**
    - **PLAN IT, &**
    - **DO IT.**
- If you smoke **quit** .

If you don't smoke **do not start** .Your life and family depends upon it.

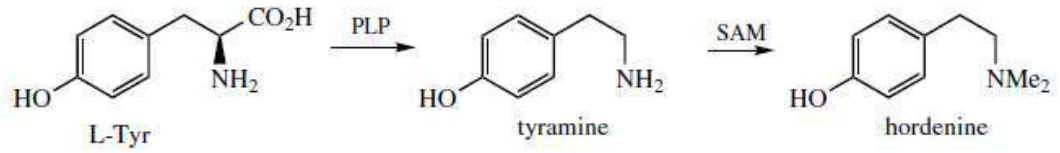
Chapter 4

ALKALOIDS DERIVED FROM PHENYALANINE & TYROSINE

Phenylethylamines and Simple Tetrahydroisoquinoline Alkaloids

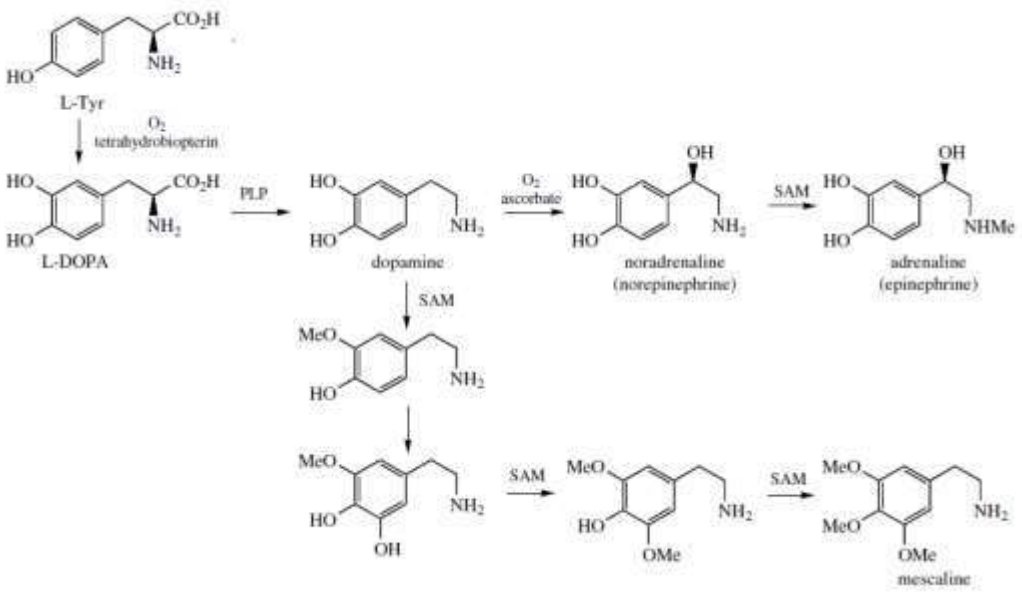
Phenethylamines occur in many plants .Some are species specific)ephedrine, mescaline and cathinone (and have marked pharmacological properties, others are common products of the metabolism of aromatic amino acids such as tyramine or phenylethylamine.

PLP-dependent decarboxylation of L-tyrosine gives the simple phenylethylamine derivative **tyramine**, which on di-*N*-methylation yields **hordenine**, a germination inhibitory alkaloid from barley *Hordeum vulgare*; (Graminae/Poaceae).

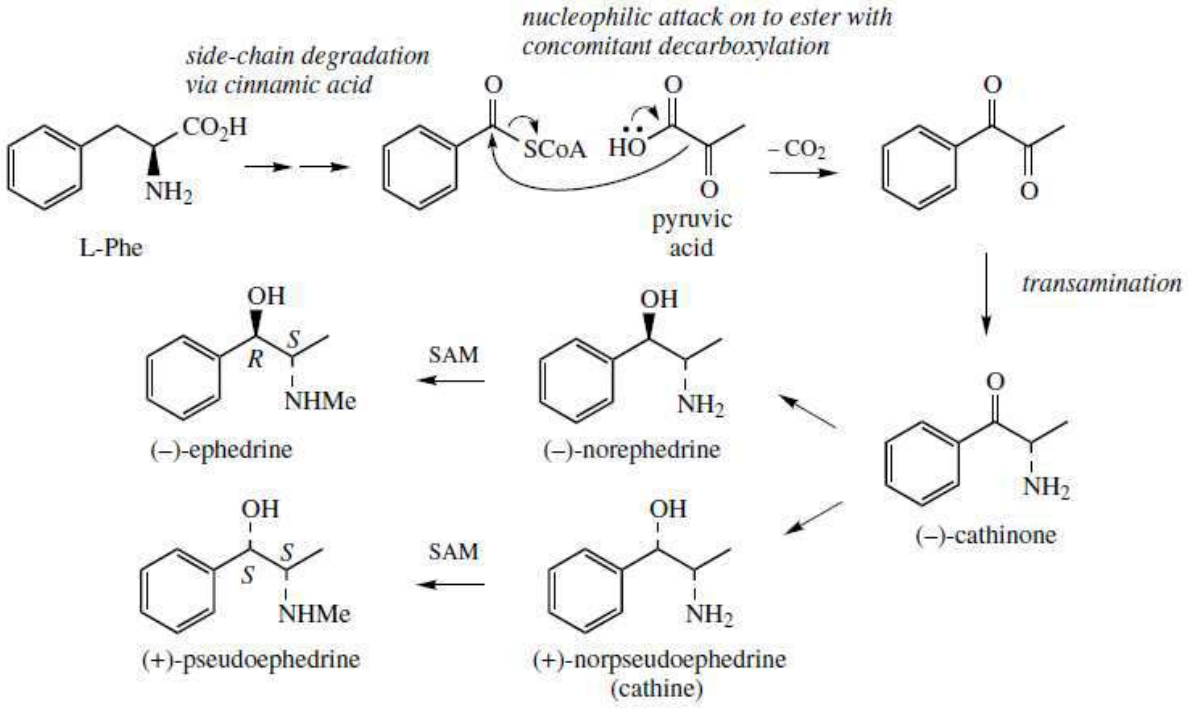


More commonly, phenylethylamine derivatives possess 3,4-di -or 3,4,5-tri-hydroxylation patterns, and are derived via **dopamine,** the decarboxylation product from L-**DOPA** L dihydroxyphenylalanine. Pre-eminent amongst these are the catecholamines **noradrenaline norepinephrine**, a mammalian neurotransmitter, and **adrenaline epinephrine**, the 'fight or flight' hormone released in animals from the adrenal gland as a result of stress.

These compounds are synthesized by successive β-hydroxylation and *N*-methylation reactions on dopamine .Aromatic hydroxylation and *O*-methylation reactions in the cactus *Lophophora williamsii*) Cactaceae (convert dopamine into **mescaline,** an alkaloid with pyschoactive and hallucinogenic properties.



Whilst the aromatic amino acid L-tyrosine is a common and extremely important precursor of alkaloids, L-**phenylalanine** is less frequently utilized, and usually it contributes only carbon atoms, e.g .C_6C_3, C_6C_2, or C_6C_1 units, without providing a nitrogen atom from its amino group colchicine, lobeline, etc .

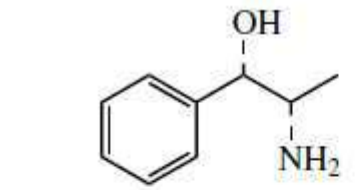


Ephedrine, the main alkaloid in species of *Ephedra* (Ephedraceae) and a valuable nasal decongestant and bronchial dilator, is a prime example .

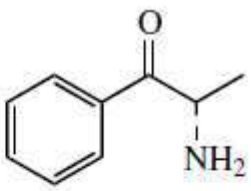
Whilst ephedrine contains the same carbon and nitrogen skeleton as seen in phenylalanine, and L-phenylalanine is a precursor, only seven carbons, a C_6C_1

fragment, are actually incorporated .It is found that phenylalanine is metabolized, probably through cinnamic acid to benzoic acid and this, perhaps as its coenzyme A ester, is acylated with pyruvate, decarboxylation occurring during the addition . Reduction of the carbonyl group from either face provides the diastereomeric **norephedrine** or **norpseudoephedrine cathine** .Finally, *N*methylation would provide **ephedrine** or **pseudoephedrine** .

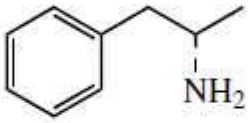
Typically, all four of the latter compounds can be found in *Ephedra* species, the proportions varying according to species .Most of the CNS stimulant action comes from the more active cathinone, the corresponding carbonyl derivative .These natural compounds are structurally similar to the synthetic amfetamine /dexamfetamine; amphetamine/dexamphetamine and have similar properties.



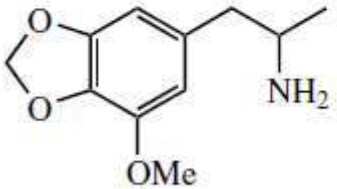
(+)-norpseudoephedrine (cathine)



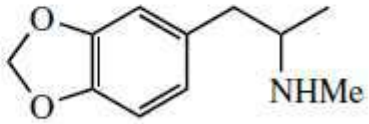
(–)-cathinone



(+)-amfetamine (amphetamine)



MMDA (3-methoxy-4,5-methylenedioxy-amfetamine)



MDMA (3,4-methylenedioxy-methamfetamine; Ecstasy)

Ephedra spp.

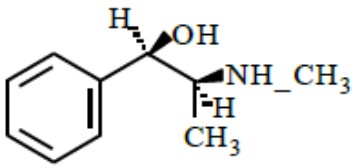
Ephedraceae

Ma Huang

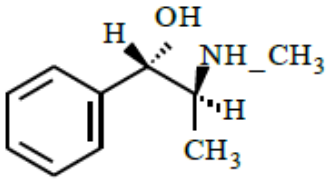
Ephedras

PHYTOCHEMICALS

Alkaloids of the 2-aminophenylpropane type .main alkaloids L-(-)-ephedrine, D-pseudoephedrine L-norephedrine, and D nor-pseudoephedrine.



(-) Ephedrine



(+) Pseudoephedrine

IDENTIFICATION

Color test

Chen's test Copper sulphate test

To a soluble of ephedrine in water add few drops of 5 %CuSO4 .And 0.5ml 20 % NaOH a **violet color is produced** on shaking with 1 ml ether or benzene, the organic layer acquires a purple color and the aqueous layer a blue color.

Crystal test

Ephedrine gives with Dragendorrf's solution long plates.

EFFECTS

Ephedrine is an indirectly acting sympathomimetic amine with effects similar to noradrenaline. Lacking the phenolic groups of the catecholamines, it has only weak action on adrenoreceptors, but it is able to displace noradrenaline from storage vesicles in the nerve terminals, which can then act on receptors .It is orally active and has a longer duration of action than noradrenaline .It also has bronchodilator activity, giving relief in asthma, plus a vasoconstrictor action on mucous membranes, making it an effective nasal decongestant.

The stimulant and thermogenic effects of Ephedra sinica and other ephedra species are due to the presence of the alkaloids ephedrine and pseudoephedrine. These

compounds stimulate the brain, increase heart rate, constrict blood vessels (increasing blood pressure), and expand bronchial tubes (making breathing easier). Their thermogenic properties cause an increase in metabolism, as evidenced by an increase in body heat.

Ephedra is widely used by athletes as a performance-enhancing drug, despite a lack of evidence that it improves athletic performance. Ephedra may also be used as a precursor in the illicit manufacture of methamphetamine.

Ephedra has been used as a weight-loss aid, sometimes in combination with aspirin and caffeine. Some studies in regulated and supervised environments have shown that ephedra is effective for marginal short-term weight loss (0.9 kg/month more than the placebo), although it was unclear whether such weight loss is maintained. However, several reports have documented a number of adverse events attributable to unregulated ephedra supplements.

INDICATIONS AND USAGE

Ma-Huang is used for diseases of the respiratory tract cough and bronchitis, with mild bronchospasms in adults and children over the age of six .Various indications include asthma, cardiovascular stimulation and as a CNS stimulant.

CONTRAINDICATIONS

Contraindications include states of anxiety and restlessness, high blood pressure, angle-closure glaucoma, cerebral perfusions, prostate adenoma with residual urine volume, pheochromocytoma and thyrotoxicosis.

PRECAUTIONS AND ADVERSE REACTIONS

General :Common side effects include headache, irritability, motor restlessness, nausea, sleeplessness, tachycardia, urinary disorders and vomiting .Higher dosages may result in blood pressure and cardiac rhythm disorders.

Dependence can develop with extended intake .Because of the danger of the development of tachyphylaxis and of dependence, the drug should only be administered for short periods.

The herbal drug ephedra/Ma Huang is currently being traded as 'herbal ecstasy' . Consumption gives CNS stimulation, but in high amounts can lead to hallucinations, paranoia, and psychosis.

Pregnancy :Ma-Huang should not to be used during pregnancy

Drug Interactions :Ephedra has an addictive effect on the

CNS when used in conjunction with caffeine, decongestants and other central stimulants.

Cardiac heart glycosides or halothane :disturbance of heart rhythm.

Guanethidine^njfeanGement of the sympathomimetic effect

MAO-inhibitors :potentiate the sympathomimetic action of ephedrine.

Secale alkaloid derivatives or oxytocin :development of high blood pressure.

Daily Dosage :For adults, the average single dose is 15 to 30 mg total alkaloid, calculated as ephedrine, for a total dose of 120 mg per day.

DRUGS IN PHARMACY

Please go personally to nearest pharmacy and search different dosage forms which contain ephedrine & pseudoephedrine and their indications.

Catha edulis Forsk,

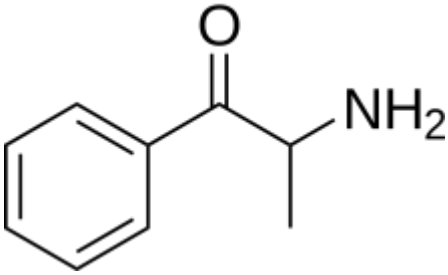
Celastraceae

Khat, cath, jat

*Medicinal Parts :*The medicinal parts of the tree are the leaves.

PHYTOCHEMICALS

Phenyl alkyl amines *0.3 to 0.9 :(%*khatamine, in fresh leaves as chief effective agent)S-(-)-(**cathinone**) 50 %in young leaves, in fully-developed leaves only 2(%, becoming dimers during dehydration, as well as -(+) norpseudoephed rine)cathine(, -(-)norephedrine, merucathinone, pseudome -' rucathinone, -(-) formyl norephedrine.



Cathinone

Sesquiterpene polyester alkaloids:

cathaedulines

Catechin tannins

Volatile oil

Dried leaves contain up to 1 %cathine -(+))norpseudoephedrine, but young fresh leaves contain -(−)cathinone as the principal CNS stimulant .Cathinone has similar pharmacological properties as the synthetic CNS stimulant (+)amphetamine

/dexamfetamine (amphetamine/dexamphetamine) with a similar potency .Both compounds act by inducing release of catecholamines.

EFFECTS

The alkaloid-containing drug chief active ingredient cathinone is centrally stimulating and indirectly sympathomimetic

amphetamine-like effect. In addition, the leaf preparations have ulcer-protective and insecticidal effects, and the drug's high tannin content makes it constipating.

Khat leaves are said to have an aphrodisiac effect and are used for depression, headache, gonorrhea, gastric complaints, coughs, asthma and fever .

Users become cheerful and talkative, and khat has become a social drug . Prolonged usage can lead to hypertension, insomnia, or even mania . Khat consumption may lead to psychological dependence, but not normally physical dependence.

PRECAUTIONS AND ADVERSE REACTIONS

The fresh shoot tips may lead to central excitation, suppression of appetite, widening of the pupils, increased motor activity, hypertonia and hyperthermia through the sympathomimetic effect of cathinone the other constituents account for only approximately 10 %of the effect and its ability to bypass the blood-brain barrier .

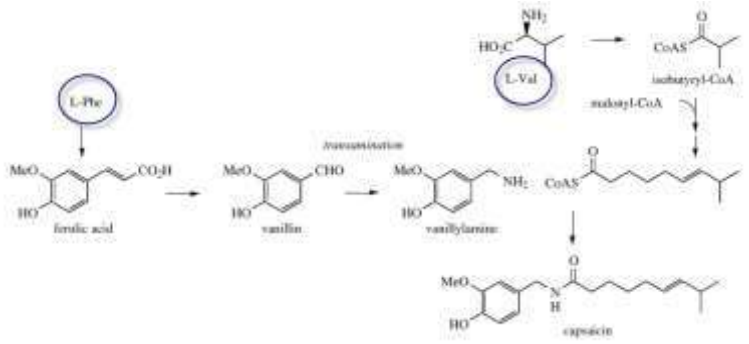
Moderate dosages 100 to 300 g of the fresh leaves (lead to a state of general well being, mental alertness and exaggerated self-regard .Physical ability is temporarily enhanced and the need for sleep is reduced . Depression and anxiety states can follow once the effect wears off . Diabetics could experience hyperglycemia.

The tannin content of the drug leads to constipation and digestive disorders . Acute poisonings have not been recorded. Chronic use can lead to such long-term ill effects as emaciation through appetite suppression, increased susceptibility to infection, nervousness, insomnia and disturbances of the circadian rhythm.

In addition, Khat preparations have been associated with ulcers in the digestive tract and liver and kidney damage .When the drug is used over periods of years, it can lead to personality disorders.

The amide **capsaicin** constitutes the powerfully pungent principle in chilli peppers ; Solanaceae .Apart from its culinary importance, it is also used medicinally in creams to counter neuralgia caused by herpes infections and in other topical pain-relieving preparations .The initial burning effect of capsaicin is found to affect the pain receptors, making them less sensitive .The aromatic portion of capsaicin is derived

from phenylalanine through ferulic acid and vanillin, this aldehyde being the substrate for transamination to give vanillylamine .The acid portion of the amide structure is of polyketide origin, with a branched-chain fatty acyl-CoA being produced by chain extension of isobutyryl-CoA .This starter unit is valine derived.



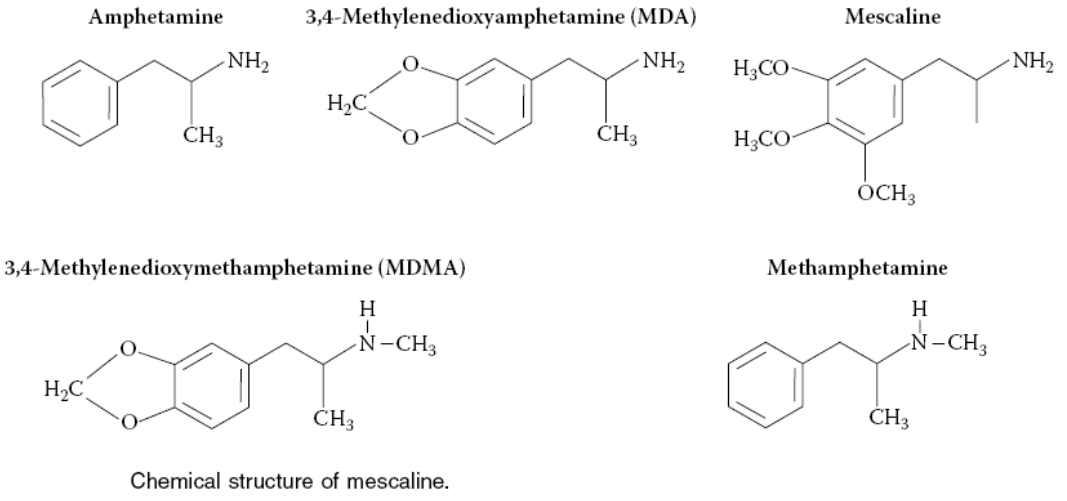
Simple Tetrahydroisoquinolines

Lophophora williamsii

Cactaceae

Peyote

The plant has been used by the Aztecs and since by the Mexican Indians for many years, especially in religious ceremonies to produce hallucinations .The most active of the range of alkaloids found in lophophora)total 8–9 %alkaloids in the dried mescal buttons(is mescaline, a simple phenylethylamine derivative .**Mescaline** has been used as a hallucinogen in experimental psychiatry .The dosage required is quite large 300–500 mg. Mescaline is also found in other species of cactus.



Chemical structure of mescaline.

Extracts of whole peyote plants were prepared in various solvents and screened for antimicrobial activity...and showed positive microbial inhibition...the principle antibiotic substance was given the name Peyocactin.

ECSTASY

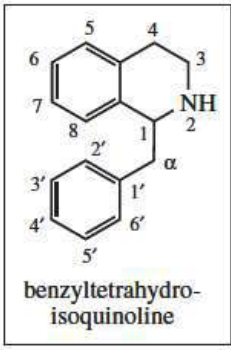
Ecstasy was originally developed by Merck pharmaceutical company in 1912. In its original form, it was known as "MDMA." It was used in 1953 by the US Army in psychological warfare tests, and then resurfaced in the 1960s as a psychotherapy medication to "lower inhibitions."1 It wasn't until the 1970s that MDMA started being used as a party drug.

Ecstasy today can contain a wide mixture of substances—from LSD, cocaine, heroin, amphetamine and methamphetamine, to rat poison, caffeine, dog deworming substances, etc. Despite the cute logos dealers put on the pills, this is what makes Ecstasy particularly dangerous; a user never really knows what he is taking. The dangers are increased when users increase the dose seeking a previous high, not knowing they may be taking an entirely different combination of drugs.

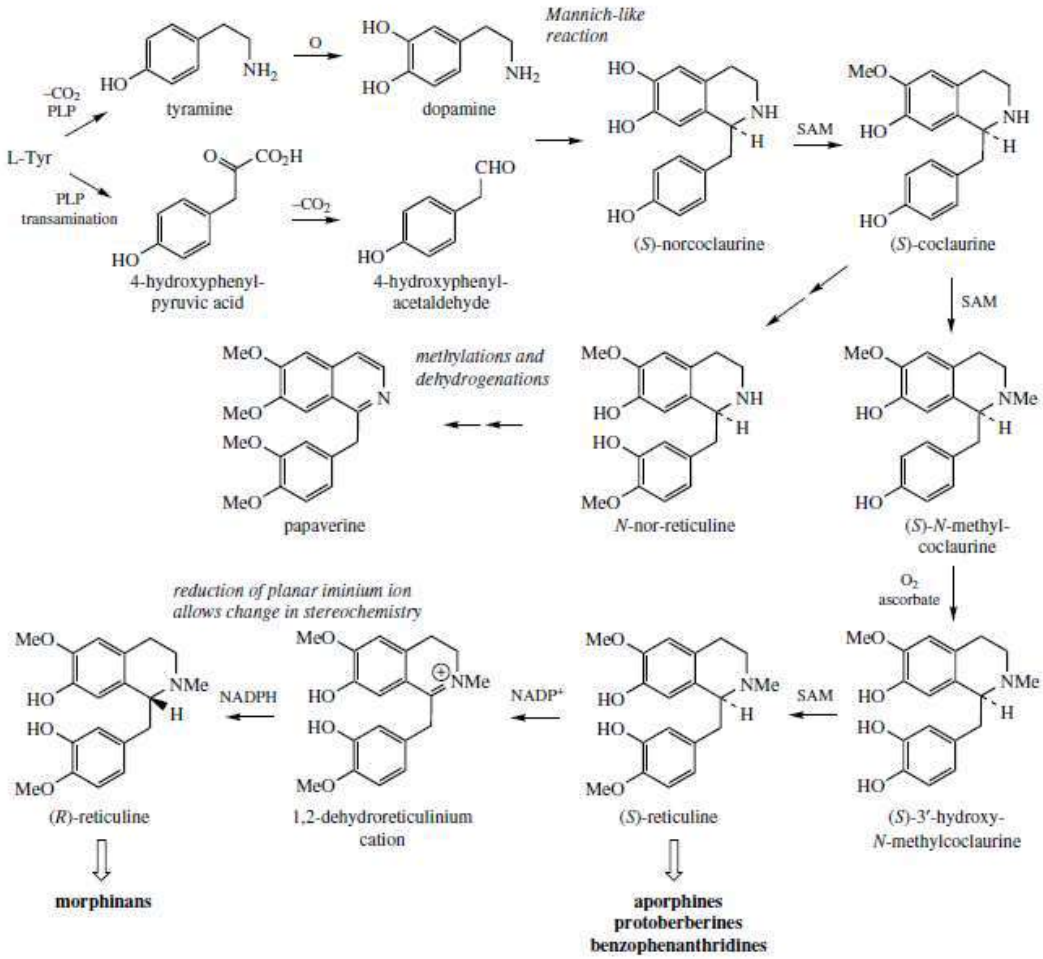
Benzyltetrahydroisoqunolines

Biosynthesis

Most examples of benzyltetrahydroisoquinoline alkaloids and modified structures contain ortho di-oxygenation in each aromatic ring, which pattern is potentially derivable from the utilization of two DOPA molecules.



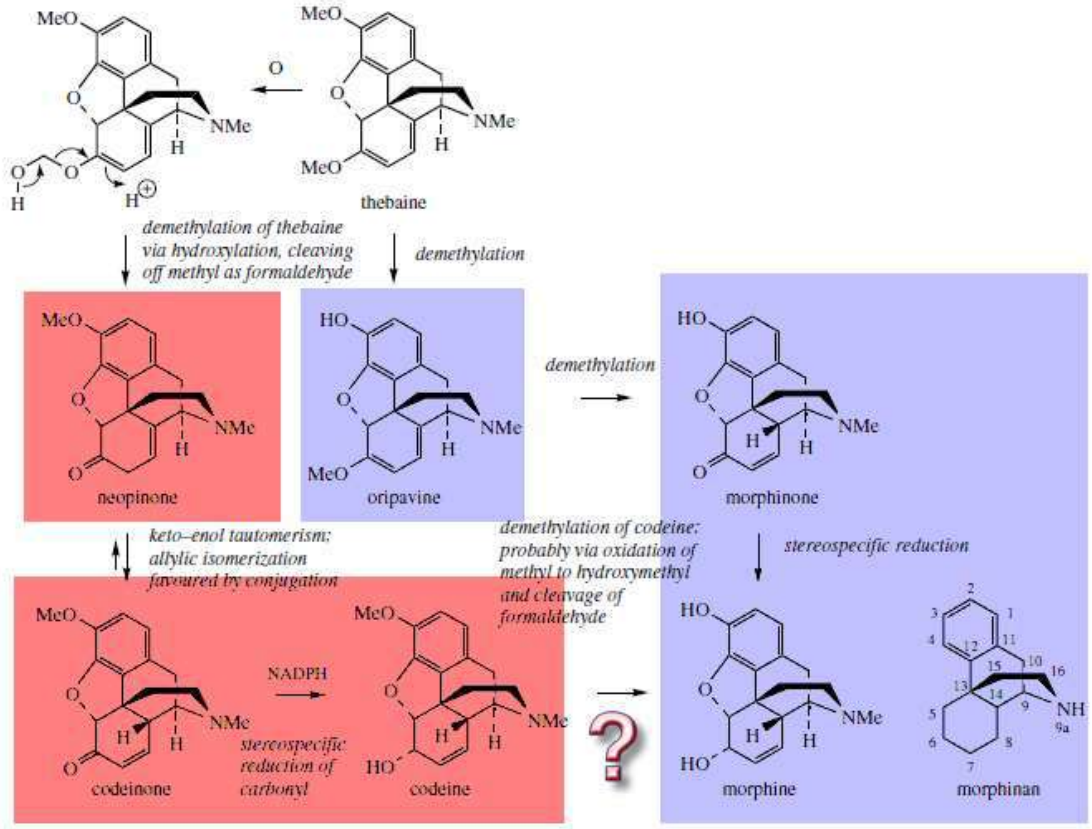
Although two tyrosine molecules are used in the biosynthetic pathway, only the phenylethylamine fragment of the tetrahydroisoquinoline ring system is formed via DOPA, the remaining carbons coming from tyrosine via 4 hydroxyphenylpyruvic acid and 4-hydroxyphenylacetaldehyde.



The product from the Mannich-like reaction is thus the trihydroxy alkaloid norcoclaurine, formed stereospecifically as the (S) enantiomer.
The tetrahydroxy substitution pattern is built up by further hydroxylation in the benzyl ring, though O-methylation giving (S) coclaurine and N-methylation steps precede this . Eventually,(S) reticuline, a pivotal intermediate to other alkaloids, is attained by N-methylation .Surprisingly, some alkaloids, such as the opium alkaloids morphine, codeine, and thebaine are elaborated from (R) reticuline rather than the first-formed (S) isomer .The change in configuration is known to be achieved by an oxidation–reduction process and the intermediate 1,2-dehydroreticulinium ion .Papaverine, a benzylisoquinoline alkaloid found in opium, is formed from N-nor-reticuline by successive Omethylations and oxidation in the heterocyclic ring.

Modified Benzyltetrahydroisoquinoline Alkaloids

The principal opium alkaloids morphine, codeine, and thebaine are derived by this type of coupling, though the subsequent reduction of one aromatic ring to some extent disguises their Benzyltetrahydroisoquinoline origins. (R)-Reticuline is firmly established as the precursor of these morphinan alkaloids.
The alkaloid **thebaine** is obtained by way of **salutaridinol**, formed from salutaridine by stereospecific reduction of the carbonyl group.



Subsequent reactions involve conversion of thebaine into **morphine** by way of **codeine**, a process which modifies the oxidation state of the diene ring, but most significantly removes two *O*-methyl groups .One is present as an enol ether, removal generating **neopinone**, which gives **codeinone** and then codeine by allylic isomerization and reduction respectively.

There is also some evidence that the later stages of the pathway are modified in some strains of opium poppy .In such strains, thebaine is converted by way of **oripavine** and **morphinone**, this pathway removing the phenolic *O*-methyl before that of the enol ether, i.e .carrying out the same steps but in a different order.

Papaver somniferum

Papaveraceae

Opium

Opium Poppy

Opium is the air-dried milky exudate, or latex, obtained by incising the unripe capsules of the opium poppy *Papaver somniferum* Papaveraceae. The plant is an annual herb with large solitary flowers, of white, pink, or dull red-purple color.

Part used: The medicinal part is the latex extracted from the seed capsule (**Immature** fructus). The opium poppy yields seeds, which are used in baking and are also pressed to give poppy seed oil.

Crude opium has been used since antiquity as an analgesic, sleep-inducer (narcotic), and for the treatment of coughs. It has been formulated in a number of simple preparations for general use, though these are now uncommon.

Powdered opium is standardized to contain 10% of anhydrous morphine, usually by dilution with an approved diluent, e.g. lactose powder.

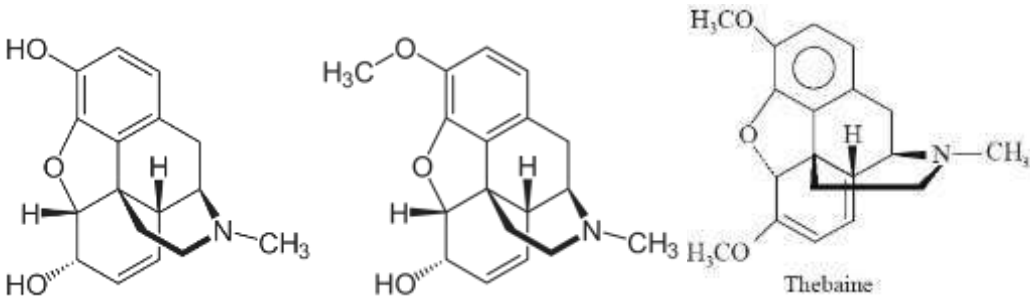
The Opium Poppy Control Act of 1942 declared the possession of this plant illegal.

Phytochemicals:

Isoquinoline alkaloids (20-30%): chief alkaloids morphine (3-23%), narcotine (2-10%), codeine (0.2-3.5%), papaverine (0.5-3%), thebaine (0.2-1%). The alkaloids are present as salts'of meconic acid, lactic acid or fumaric acid.

Benzyl isoquinoline type: papaverine (0.5 to 3%).

Phthalide isochinoline type: narcotine.



Thebaine

EFFECTS

The main alkaloid is morphine, which is a strong analgesic that, even in small doses, causes euphoria, sedation then narcotic sleep. It depresses breathing and slows down evacuation of the stomach, causing constipation and urine retention. Codeine has an antitussive effect and papaverine is spasmolytic and vasodilatory.

Morphine is a powerful analgesic and narcotic, and remains one of the most valuable analgesics for relief of severe pain. It also induces a state of euphoria and mental detachment, together with nausea, vomiting, constipation, tolerance, and addiction. Regular users experience withdrawal symptoms, including agitation, severe abdominal cramps, diarrhoea, nausea, and vomiting, which may last for 10–14 days unless a further dose of morphine is taken. This leads to physical dependence, which is difficult to overcome, so that the major current use of morphine is thus in the relief of terminal pain. Although orally active, it is usually injected to obtain rapid relief of acute pain. The side-effect of constipation is utilized in some anti-diarrhoea preparations, e.g. kaolin and morphine.

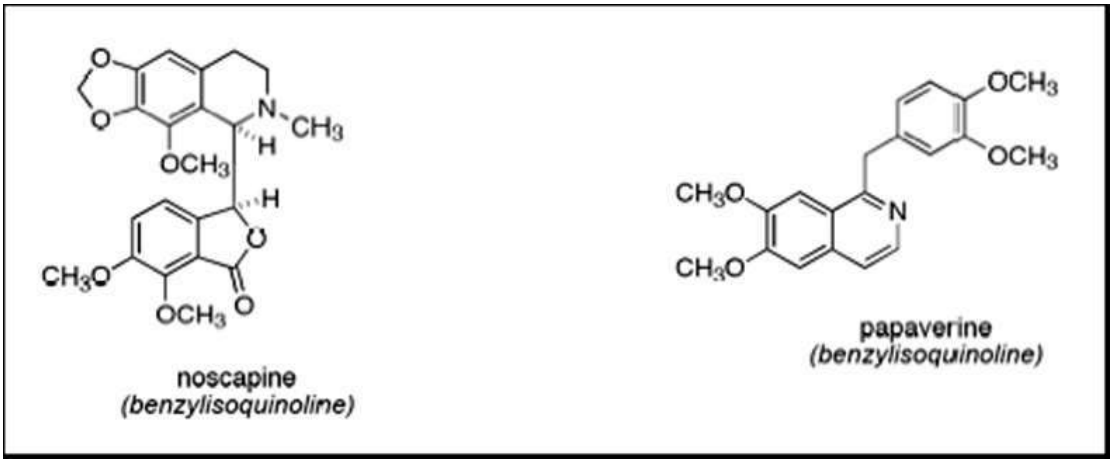
Morphine is metabolized in the body to glucuronides, which are readily excreted. Whilst morphine 3-*O*-glucuronide is antagonistic to the analgesic effects of morphine, morphine

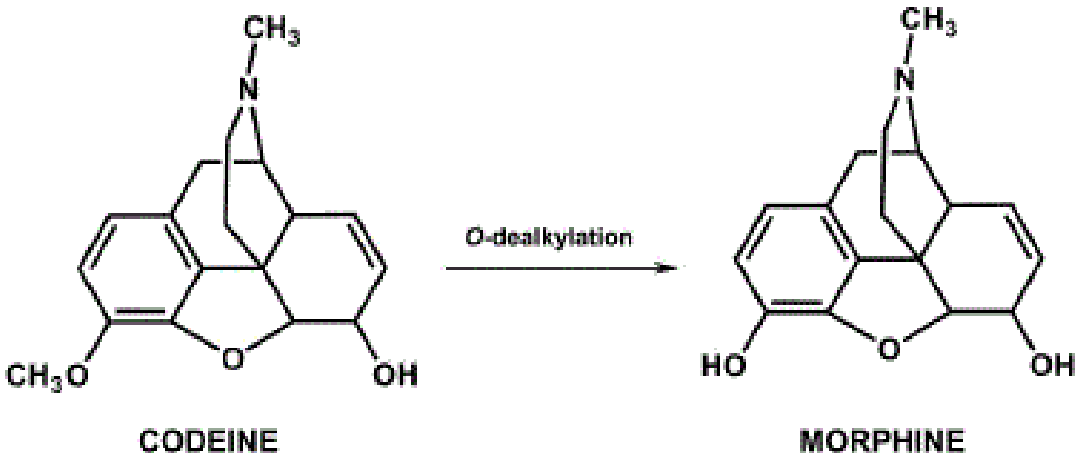
6-*O*-glucuronide is actually a more effective and longer lasting analgesic than morphine, with fewer side-effects.

Codeine is the 3-*O*-methyl ether of morphine, and is the most widely used of the opium alkaloids. Because of the relatively small amounts found in opium, most of the material prescribed is manufactured by semi-synthesis from morphine. Its action is dependent on partial demethylation in the liver to produce morphine, so it produces ***morphinelike*** analgesic effects, but little if any euphoria. As an analgesic, codeine has about one-tenth the potency of morphine. Codeine is almost always taken orally and is a component of many compound analgesic preparations. Codeine is a relatively safe non-addictive medium analgesic, but is still too constipating for long-term use. Codeine also has valuable antitussive action, helping to relieve and prevent coughing. It effectively depresses the cough centre, raising the threshold for sensory cough impulses.

Papaverine is a benzylisoquinoline alkaloid, and is structurally very different from the morphine, codeine, thebaine group of alkaloids (morphinans). It has little or no analgesic or a hypnotic property put possesses spasmolytic and vasodilator activity. It has been used in some expectorant preparations, and in the treatment of gastrointestinal spasms, but its efficacy was not substantiated. It is sometimes used as an effective treatment for male impotence.

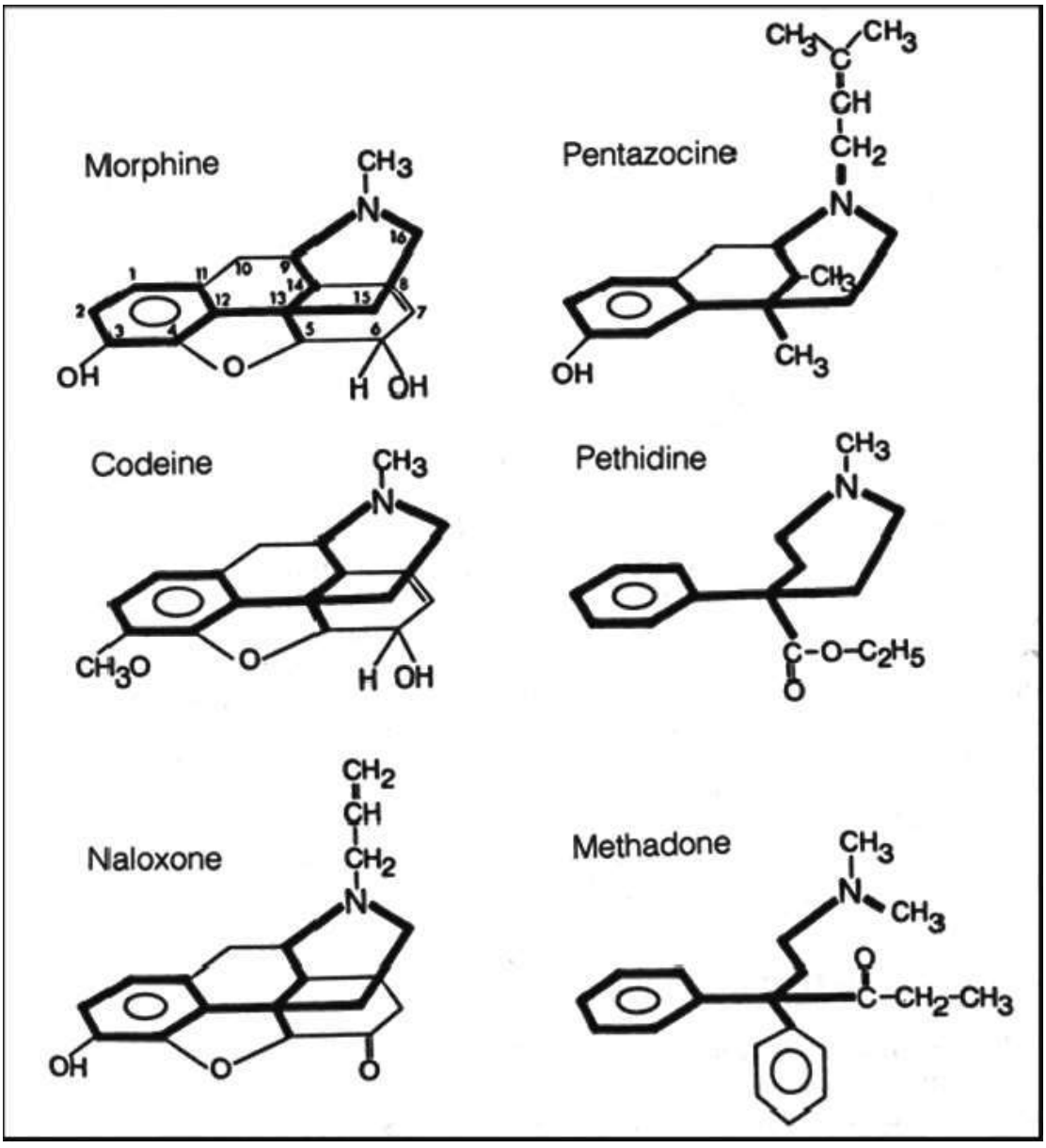
Noscapine is a member of the phthalideisoquinoline alkaloids and provides a further structural variant in the opium alkaloids. Noscapine has good antitussive and cough suppressant activity comparable to that of codeine, but no analgesic or narcotic action. Its original name ‘narcotine’ was changed to reflect this lack of narcotic action. Despite many years of use as a cough suppressant, the finding that noscapine may have teratogenic properties (i.e. may deform a fetus) has resulted in noscapine preparations being deleted. In recent studies, antitumour activity has been noted from noscapine, which binds to tubulin as do podophyllotoxin and colchicine, thus arresting cells at mitosis.

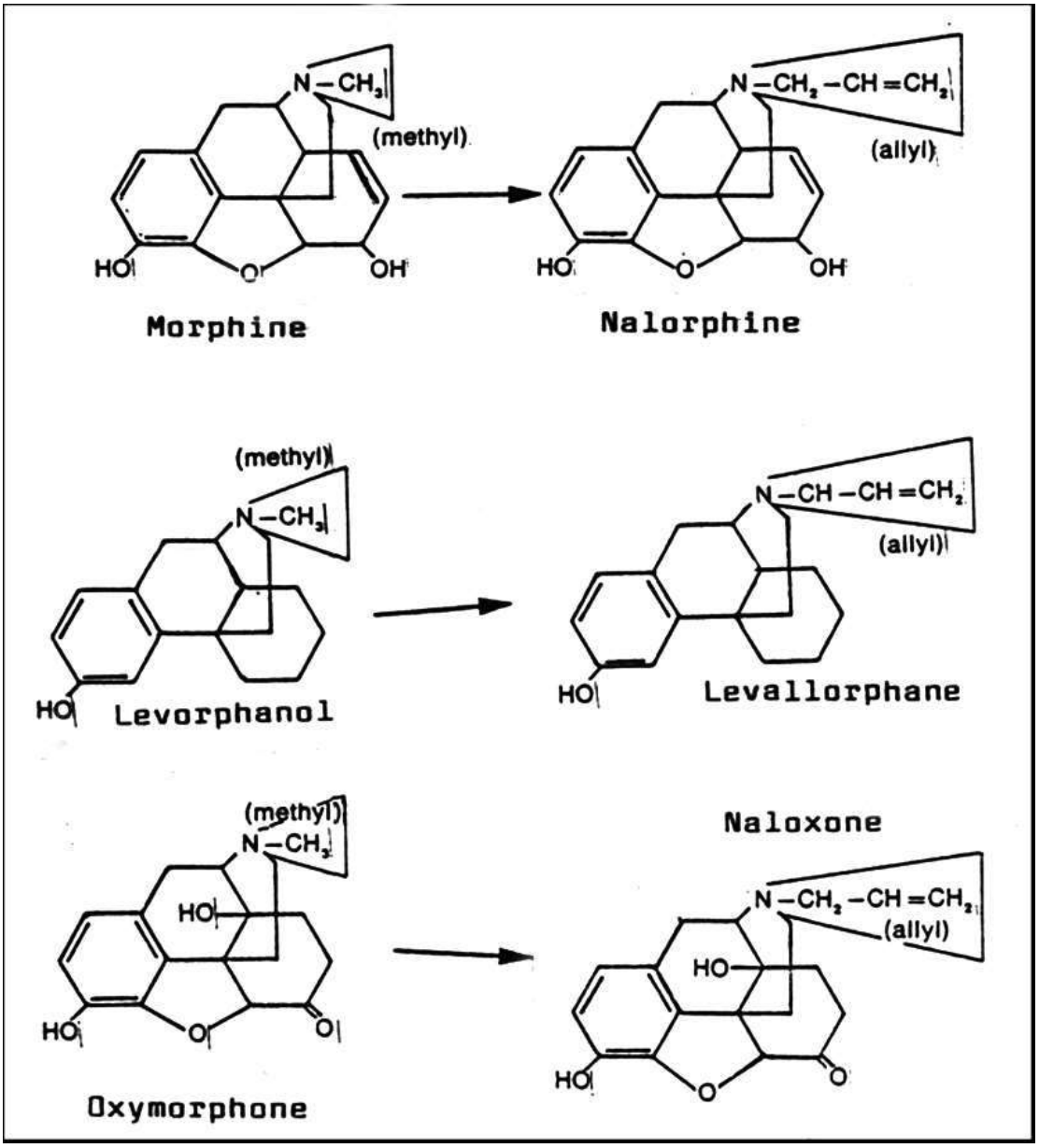

noscapine
(benzylisoquinoline)
papaverine
(benzylisoquinoline)


O-dealkylation
CODEINE
MORPHINE

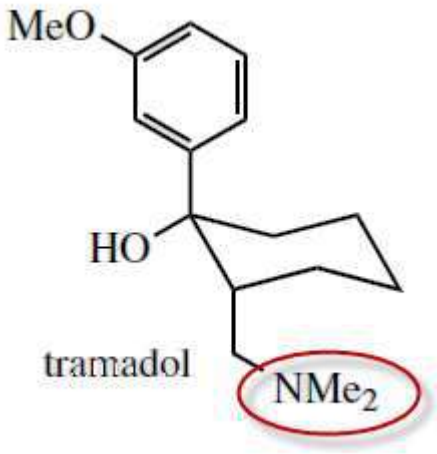
Opiates/Opioids Chemistry & Mechanism of Action

It is interesting to note that all commonly used opioids have a similar structure in regard to their terminal morphine ring and the distance between the ring and the N-substitution.





Even more drastic simplification of the morphine structure is found in **pethidine** (**meperidine**), one of the most widely used synthetic opiates. Only the aromatic ring and the piperidine systems are retained. Pethidine is less potent than morphine, but produces prompt, short-acting analgesia, and is also less constipating than morphine. It can be addictive. **Tramadol** is a recent drug claimed to produce analgesia by an opioid mechanism and by enhancement of serotoninergic and adrenergic pathways, with typical opioid side-effects.



Opioid receptors are distributed widely in brain and found in spinal cord and peripheral sensory and autonomic nerves. There are the three well-characterized members of the opioid receptor family, designated by the Greek symbols δ, κ and μ. An interesting addition to ligands that bind to the κ1 receptor is the hallucinogen salvinorin-A. This is a highly efficacious and potent κ agonist, but is most unusual in that it has no nitrogen atom. Endogenous opioid systems have a functional role in modulating pain perception; opioid agonists are therefore potent analgesics.

Opioid receptors are also present in hypothalamus, where they influence temperature regulation and control of hormonal secretion. In the forebrain, endogenous opioids are involved in behavioral reinforcement and appear to play a role in anxiety and in the expression of emotions. In addition, opioids influence gastrointestinal and autonomic nervous system function.

Opioid receptors are found in several areas of the brain, particularly in the periaqueductal grey matter, and throughout the spinal cord. Supraspinal systems have been described for δ, κ and μ receptors, whereas κ and μ receptors modulate pain at the spinal level.

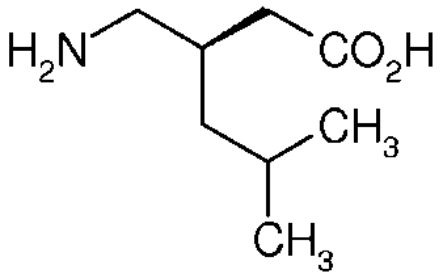
The different distribution of the various opioid subsites suggests different mechanisms of action in the mediation of analgesia. Thus, μ-selective opioids like morphine, fentanyl and sufentanil, due to the high density of binding sites, mediate their main action within the brain stem and the midbrain.

As a consequence and contrary to μ -ligands, κ -ligands induce a marked sedative appearance. In addition, there is a lesser addiction liability with κ-ligands, which is

easily derived from the fact that the relevant areas in the limbic system show a low concentration of κ-binding sites.

Lyrica

GENERIC NAME(S): **PREGABALIN**



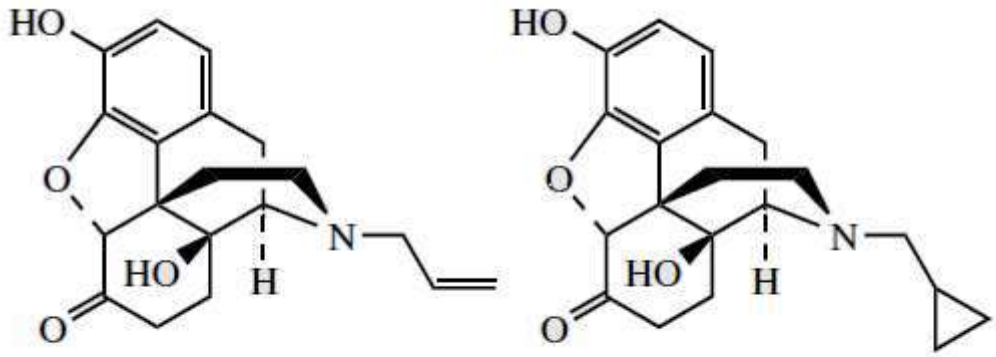
This medication is used to treat pain caused by nerve damage due to diabetes or to shingles (herpes zoster) infection. It may also be used to treat nerve pain caused by spinal cord injury. This medication is also used to treat pain in people with fibromyalgia.

Drugs used to treat seizures **increase the risk of suicidal thoughts or behavior**. LYRICA may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Patients, family members or caregivers should call the doctor right away if they notice suicidal thoughts or actions, thoughts of **self-harm**, or any unusual changes in **mood or behavior**. These changes may include new or worsening depression, anxiety, restlessness, trouble sleeping, panic attacks, anger, irritability, agitation, aggression, dangerous impulses or violence, or extreme increases in activity or talking.

Antidote

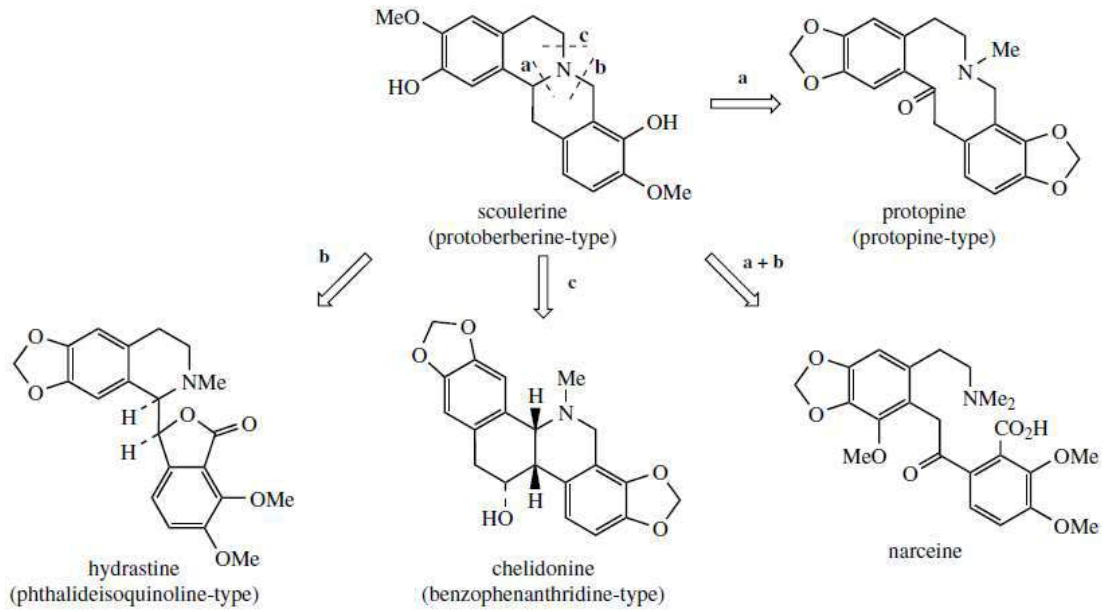
Naloxone shows hardly any agonist activity but is a potent antagonist, and is used to treat opiate poisoning, including that in children born to heroin addicts.

Naltrexone also has antagonist activity similar to naloxone. These agents are *N*-alkyl derivatives related to oxymorphone/oxycodone.



The alkaloid **berberine** is found in many members of the Berberidaceae (e.g.*Berberis*, *Mahonia*), the Ranunculaceae (e.g.
Hydrastis), and other families. Berberine hasantiamoebic, antibacterial, and anti-inflammatory properties and plants containing berberine have long been used in traditional medicine. Its tetracyclic skeleton is derived from a benzyltetrahydroisoquinoline system with the incorporation
of an extra carbon atom, supplied from *S*-adenosylmethionine via an *N*-methyl group.

The protoberberine skeleton of scoulerine may be subjected to further modifications, some of which are given in the following figure.



Cleavage of the heterocyclic ring systems adjacent to the nitrogen atom as shown give rise to new skeletal types: protopine, e.g. **protopine** from *Chelidonium majus* (Papaveraceae), phthalideisoquinoline, e.g. **hydrastine** from *Hydrastis Canadensis* (Ranunculaceae), and benzophenanthridine, e.g. **chelidonine**, also from *Chelidonium majus*.

Chelidonium majus

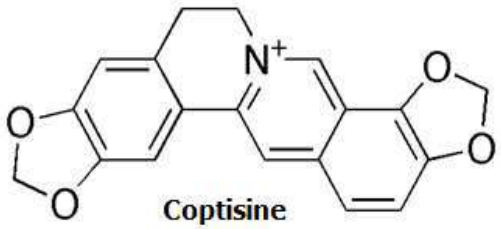
Celandine

Papaveraceae

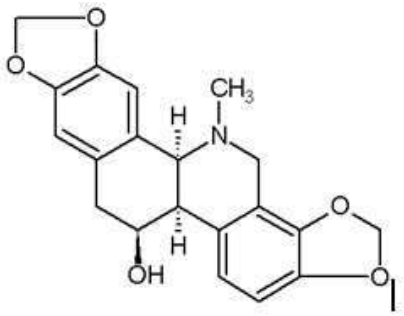
Medicinal Parts: The medicinal parts are the aerial parts that have been collected during the flowering season and dried. The root, which has been collected in late autumn and dried, and the fresh rhizome are also used medicinally.

Phytochemicals:

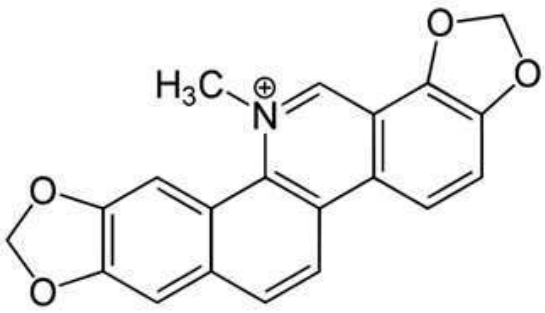
Isoquinoline alkaloids of the protoberberine type: including coptisine (main alkaloid), and berberine.



Isoquinoline alkaloids of the benzophenanthridine type: including chelidonine and sanguinarine.



Chelidonine



Sanguinarine

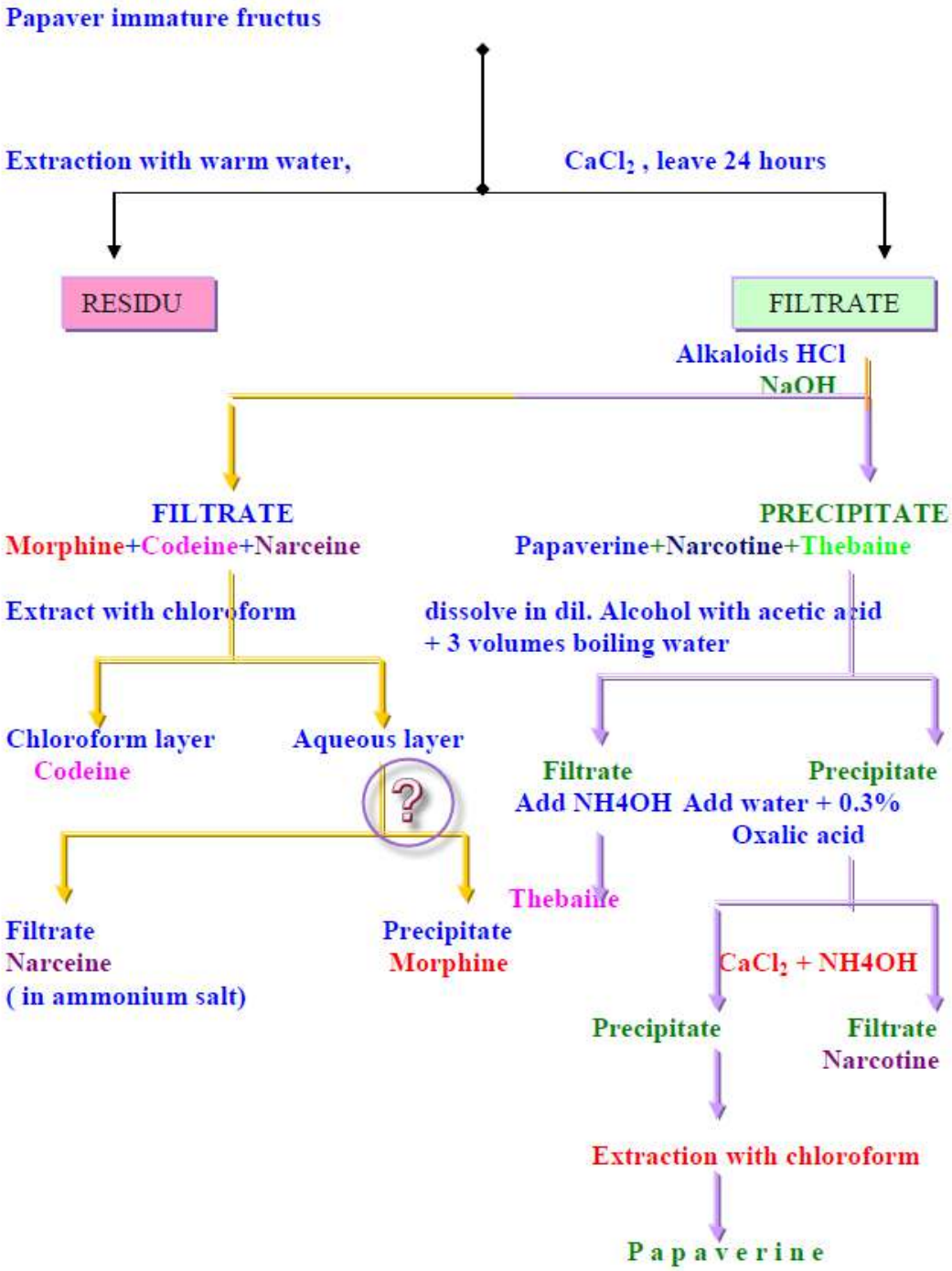
EFFECT

Celandine has mild analgesic, cholagogic, antimicrobial, oncostatic and central-sedative effects. It also acts as a spasmolytic on smooth muscles. In animal tests, Celandine is a cytostatic. It also has a nonspecific immune-stimulating effect.

INDICATIONS AND USAGE

• Liver and gallbladder complaints. Celandine is used also for spasmodic pain of the bile ducts and the gastrointestinal tract.

Isolation of Opium Ingredients



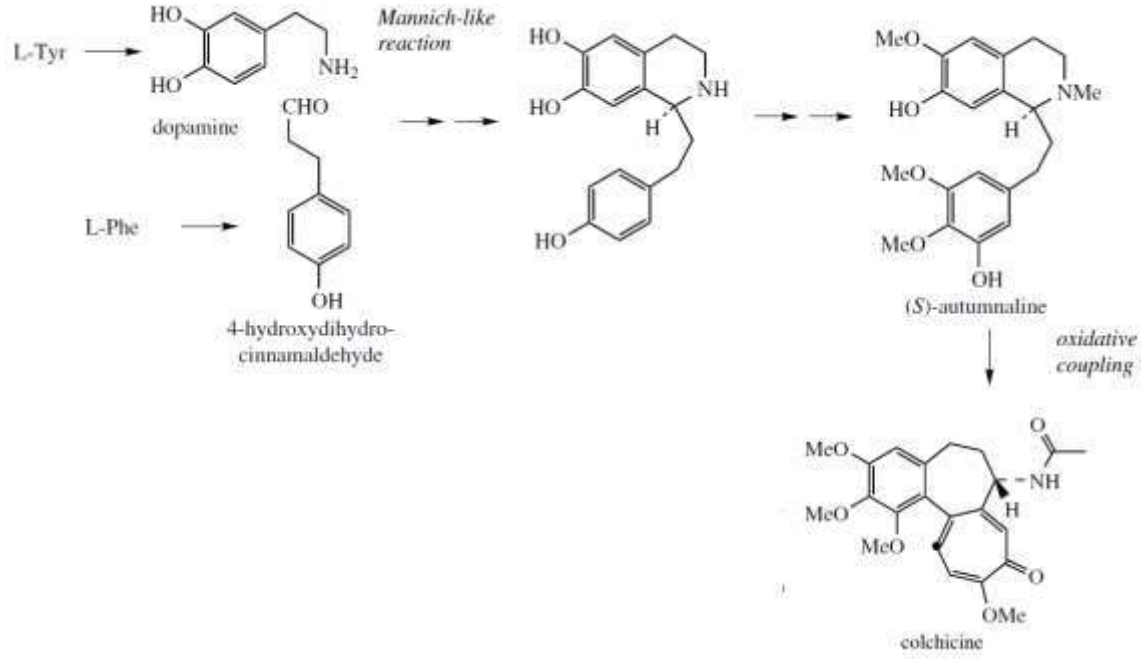
Isoquinoline Alkaloids (Phenethylisoquinolines)

Colchicum autumnale

Tropolonic alkaloids

Medicinal Parts: The fresh flowers and the dried ripe seeds, collected in early summer and then sliced, as well as the tubers (fresh and dried) are the medicinal parts of the plant.

Biosynthesis



Phytochemicals

Tropolone alkaloids: Seeds contains 0.2 to 1.2- % alkaloids, which colchicine represents 65%. Colchicine does not display any significant basicity, and does not form well-defined salts.

Seeds contain 17% fatty acids as palmitic acid and linolic acid. In bulb we found salicylic acid, benzoic acid and tannins.

EFFECTS

Colchicum inhibits mitosis through the inhibition of motility, particularly of the phagocytosing lymphocytes. This is of therapeutic use for blocking the immigration and the autolysis of phagocytes in inflammatory processes and thereby producing an antiphlogistic effect.

INDICATIONS AND USAGE

• Gout

• Mediterranean fever

Dose & Toxicity:

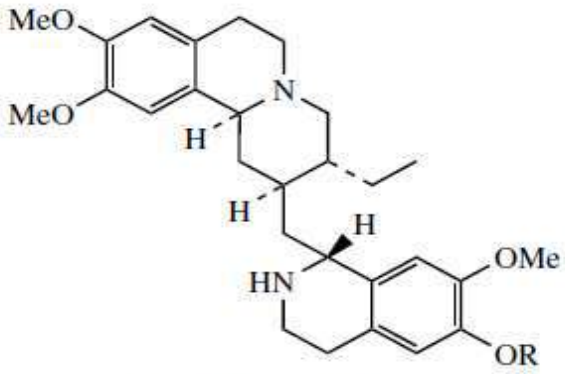
Lethal dose is very appropriate to therapeutically dose. Colchicine is neurotoxic in leukemia.

The dose in the beginning of treatment is 1mg, and the maintenance dose is 0.5mg.

Maximum dose 6mg / 24h.
L.D = 6 - 20mg

Terpenoid Tetrahydroisoquinoline Alkaloids

The alkaloids found in ipecacuanha, the dried rhizome and roots of *Cepahaelis ipecacuanha* (Rubiaceae), have a long history of use in the treatment of amoebic dysentery, and provide unusual examples of tetrahydroisoquinoline structures. The principal alkaloids, e.g. **emetine** and **cephaeline.**



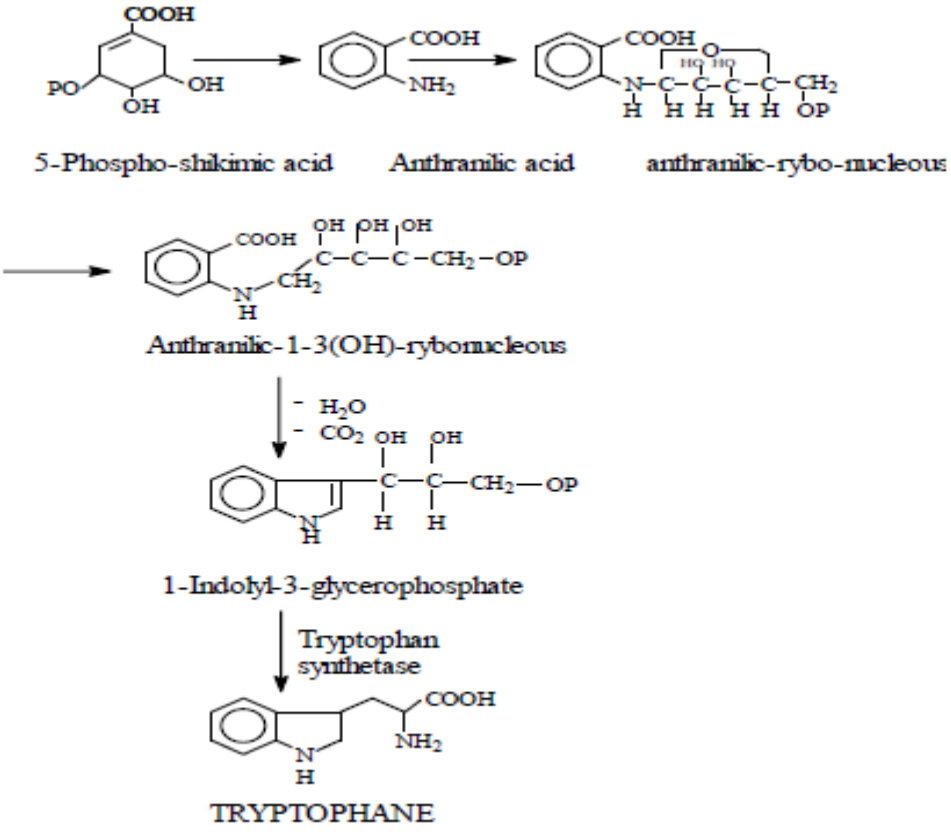
R = Me, emetine
R = H, cephaeline

More recently it was mixed with powdered opium to give Dover's powder, where the ipecac content functioned as a diaphoretic. Emetine and cephaeline are both potent inhibitors of protein synthesis, inhibiting at the translocation stage. They display antitumour and antiviral as well as antiamoebic activity, but are too toxic for therapeutic use.

In common with other treatments for Alzheimer's disease, it does not cure the condition, but merely slows the rate of cognitive decline.

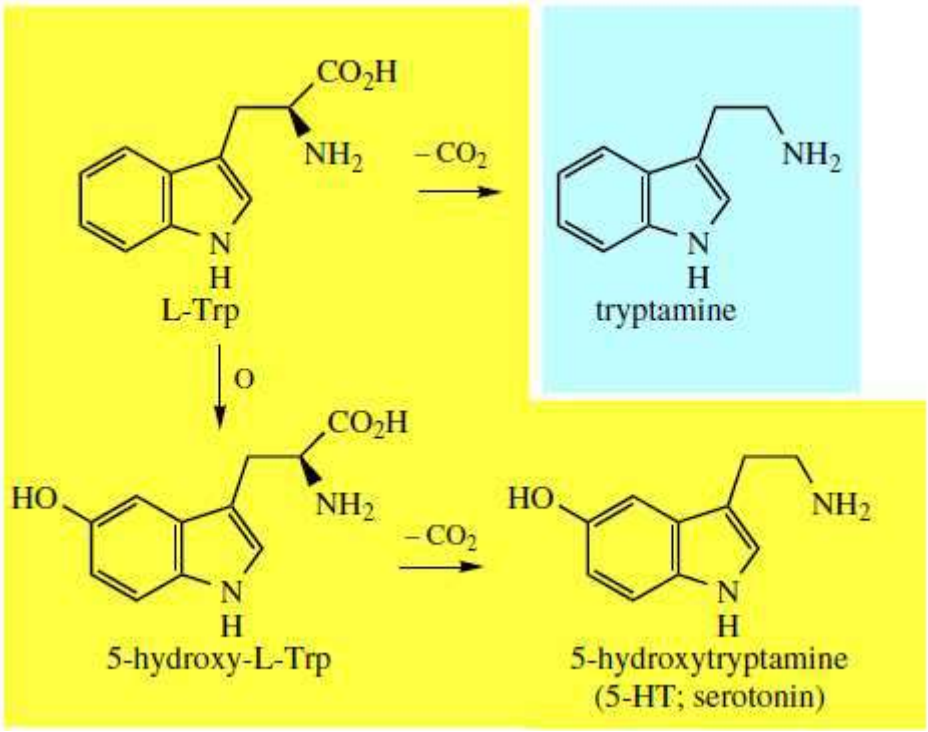
ALKALOIDS DERIVED FROM TRYPTOPHAN

L-**Tryptophan** is an aromatic amino acid containing an indole ring system, having its origins in the shikimate pathway via anthranilic acid. It acts as a precursor of a wide range of indole alkaloids, but there is also definite proof that major rearrangement reactions can convert the indole ring system into a quinoline ring, thus increasing further the ability of this amino acid to act as an alkaloid precursor.



Simple Indole Alkaloids

Tryptamine and its *N*-methyl and *N*,*N*-dimethyl derivativesare widely distributed in plants, as are simple hydroxylated derivatives such as **5-hydroxytryptamine** (**serotonin**).

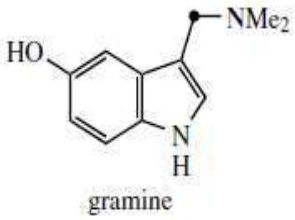


Hordeum vulgare

Barley

Graminae/Poaceae

Gramine is a simple amine found in barley and is derived from tryptophan by a biosynthetic pathway which cleaves off two carbon atoms, yet surprisingly retains the tryptophan nitrogen atom.



According to a recent study, eating whole grain barley can regulate blood sugar (i.e. reduce blood glucose response to a meal) for up to 10 hours after consumption compared to white or even whole-grain wheat, which has a similar glycemic index. The effect was attributed to colonic fermentation of indigestible carbohydrates.

Simple β-Carboline Alkaloids

Alkaloids based on a β-carboline system exemplify the formation of a new six membered heterocyclic ring using the ethylamine side-chain of tryptamine in a process analogous to generation of tetrahydroisoquinoline alkaloids.

β-carboline

Peganum harmala

Harmal

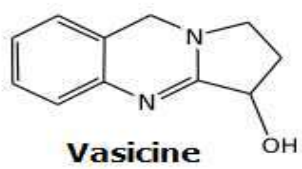
Zygophyllaceae (Nitrariaceae)

Medicinal Parts: Seeds

Phytochemicals

The active alkaloids of Harmal seeds are the MAOI-A (monoamine oxidase inhibitor A) compounds:

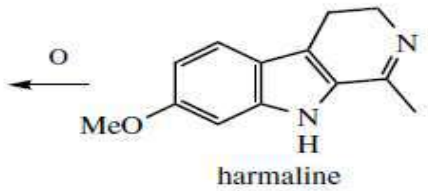
- Harmane
- Harmine: The coatings of the seeds are said to contain large amounts of harmine.
- Harmaline
- Harmalol
- Tetrahydroharmine
- Vasicine (peganine)
- Vasicinone



Vasicine

harman

harmine



harmaline

EFFECT

Peganum harmala is used as an analgesic and anti-inflammatory agent. In Yemen it was used to treat depression, and it has been established in the laboratory that harmaline, an active ingredient in *Peganum harmala*, is a central nervous system stimulant and a "reversible inhibitor of MAO-A (RIMA)," a category of antidepressant.

The reported psychoactive properties of the plants *Peganum harmala* is due to the β-carboline alkaloids such as harmine, harmaline, and tetrahydroharmine.

The beta-carboline alkaloids present in medicinal plants, such as *Peganum harmala*, have recently drawn attention due to their antitumor activities. The studies indicate that beta-carboline derivatives inhibit DNA topoisomerases and interfere with DNA synthesis." *Peganum harmala* has antioxidant and antimutagenic properties.

INDICATION

Antidepressant

Terpenoid Indole Alkaloids

More than 3000 terpenoid indole alkaloids are recognized, making this one of the major groups of alkaloids in plants. They are found mainly in eight plant families, of which the Apocynaceae, the Loganiaceae, and the Rubiaceae provide the best sources.

Rauwolfia serpentine

Indian snakeroot, *sarpagandha*

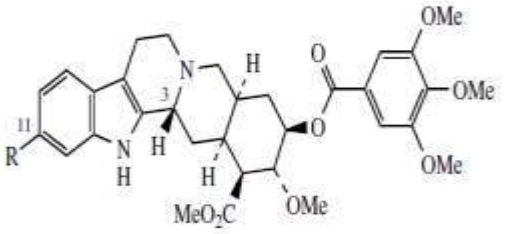
Apocynaceae

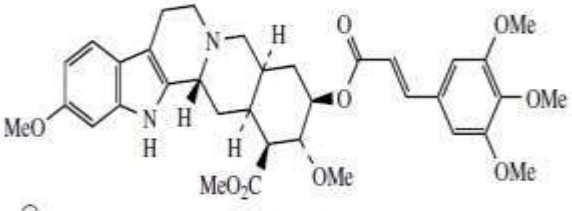
Rauwolfia has been used in Africa for hundreds of years, and in India for at least 3000 years. It was used as an antidote to snake-bite, to remove white spots in the eyes, against stomach pains, fever, vomiting, and headache, and to treat insanity.

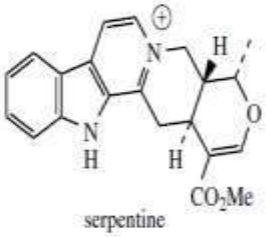
Medicinal Parts: Root

Phytochemicals

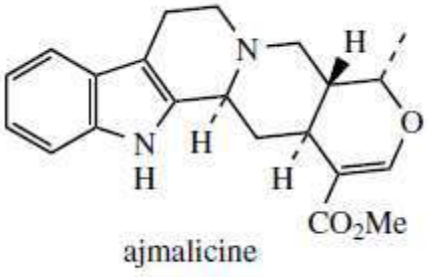
Most of the drug material has been collected from the wild. Rauwolfia serpentine contains a wide range of indole alkaloids, totaling 0.7–2.4%, though only 0.15–0.2% consists of desirable therapeutically active compounds, principally reserpine, rescinnamine, and deserpidine.

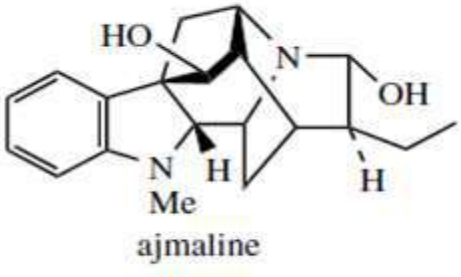






Other alkaloids of note are serpentine, ajmalicine, and ajmaline.





Isolation

Powdered Rauwolfia root is moistened with 10 % NaHCO3 solution and extracted with benzen, solvent is evaporated, residue dissolved in methanol, concentrated and crystallized, aided by addition of few crystals of reserpine. The mother liquid (containing deserpidine, recinnamine and other alkaloids) is evaporated to dryness and individual alkaloids are separated using column chromatography.

EFFECT

Rauwolfia alkaloids belong to the general class of medicines called antihypertensive. They are used to treat high blood pressure (hypertension).

Rauwolfia alkaloids work by controlling nerve impulses along certain nerve pathways. As a result, they act on the heart and blood vessels to lower blood pressure.

Reserpine and **deserpidine** have been widely used as antihypertensive and mild tranquillizers. They act by interfering with catecholamine storage, depleting levels of available neurotransmitters. Prolonged use of the pure alkaloids, reserpine in particular, has been shown to lead to severe depression in some patients, a feature not so prevalent when the powdered root was employed.

Ajmalicine is employed as an antihypertensive, whilst **ajmaline** is of value in the treatment of cardiac arrhythmias.

Uses:

Rauwolfia preparations represented in reserpine are used in the management of essential hypertension and in certain neuropsychiatry disorders.

In small doses used as hypotensive and in big doses used as tranquillizers.

The increase of doses no produce intensification of hypotensive action even if the small doses no gives any amelioration or action.

Side effects

In small doses produce chronic diarrhea, while in big dose neuropsychiatries disorders, drowsiness, nasal congestion, salivary and gastric hypersecretion, anxiety and depression.

Doses

Adult: P.O. 0.5mg / 24h P.O (0.25mg) / daily (minimum dose).

Overdose

The clinical symptoms are dominated by the parasympathomimetic effects of reserpine such as: respiratory depression, bradycardia, hypotension, confusion, tremors, myosis, convulsion and gastrointestinal distress.

Contra indications:

* Pregnancy; * Breast Feeding
* Renal hypertension; * Ulcer;
* Chirurgical intervention; * Epilepsy;
* Depression; * Breast Cancer
* Combination with MAO inhibitors or levodopa.

Interactions with Medicines

Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. The following interactions have been selected on the basis of their potential significance, using medicines in this class with any of the following medicines is not recommended:

- Furazolidone
- Lazabemide
- Phenelzine
- Procarbazine
- Tetrabenazine
- Tranylcypromine
- Colchicine
- Phenytoin

Catharanthus roseus

Vinca rosea;

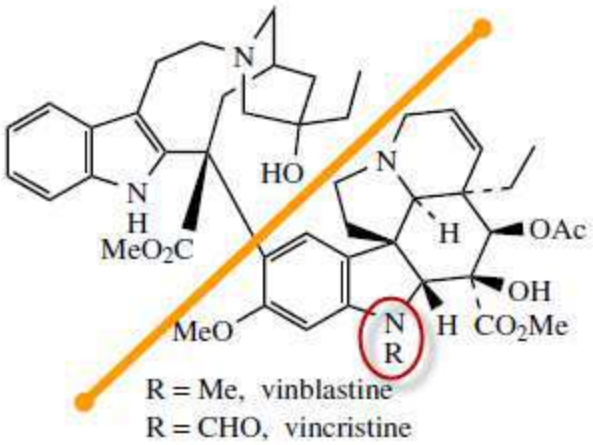
Apocynaceae

Potentially Active Chemical Constituents:

Catharanthus roseus possess carbohydrate, flavonoid, saponins and alkaloids. Alkaloids are the most potentially active chemical constituents of Catharanthus roseus. More than 400 alkaloids are present in the plant, which are used as pharmaceuticals, agrochemicals, flavor and fragrance, ingredients, food additives and pesticides.

The alkaloids like Vinblastin, Vincrestine, Vindesine, Vindeline Tabersonine etc. are mainly present in aerial parts whereas ajmalicine, vinceine, vineamine, raubasin, reserpine, catharanthine etc are present in roots and basal stem.

Alkaloids have been prompted by the anticancer activity. Two of these, **vinblastine** and **vincristine**, have been introduced into cancer chemotherapy and feature as some of the most effective anticancer agents available. These structures are seen to contain the elements of **catharanthine** and **vindoline**, and, indeed, they are derived by coupling of these two alkaloids.



Tests for identification

 Vanillin /HCl reagent gives with;

- Vinblastine a pink color, and

- Vincristine an orange-yellow color.

 para-dimethylaminobenzaldehyde (PDAB) reagent (Van-Urk's reagent): gives vinca alkaloids in presence glacial acetic acid and concentrated H_2SO_4 a reddish - brown color.

EFFECT & USES

Because of its folklore usage as a tea for diabetics, the plant was originally investigated for potential hypoglycaemic activity.

Useful antitumour activity was demonstrated in a number of dimeric indole alkaloid structures (more correctly bis-indole alkaloids), These compounds became known as **vinblastine**, vinleurosine, vinrosidine, and **vincristine** respectively, the vin- prefix being a consequence of the earlier botanical nomenclature *Vinca rosea*, which was commonly used at that time.

The alkaloids vinblastine and vincristine were introduced into cancer chemotherapy and have proved to be extremely valuable drugs.

Despite the minor difference in structure between vinblastine and vincristine, a significant difference exists in the spectrum of human cancers that respond to the drugs. **Vinblastine** is used mainly in the treatment of Hodgkin’s disease, a cancer affecting the lymph glands, spleen, and liver. **Vincristine** has superior antitumour activity compared to vinblastine but is more neurotoxic.

It is clinically more important than vinblastine, and is especially useful in the treatment of childhood leukaemia, giving a high rate of remission.
Some other cancer conditions, including lymphomas, small cell lung cancer, and cervical and breast cancers, also respond favourably. The alkaloids need to be injected, and both generally form part of a combination regimen with other anticancer drugs.

Therapeutic Properties/ Uses:

1. Anti cancer property- The anticancer alkaloids Vinblastine and Vincristine are derived from stem and leaf of Catharanthus roseus . These alkaloids have growth inhibition effect to some human tumors. Vinblastine is used experimentally for treatment of neoplasmas and is recommended for Hodgkins disease, chorio carcinoma. Vincristine another alkaloids is used for leukemia in children. Vinblastine is sold as Velban or Vincristine as oncovin.

2. Anti diabetic property- The ethanolic extracts of the leaves and flower of C. roseus showed a dose dependent lowering of blood sugar in comparable to the standard drug. Lowering of blood sugar in comparable to the standard drug gliben clamide. The Hypo glycemic effect has appeared due to the result of the increase glucose utilization in the liver.

3. Anti bacterial property- Crude extracts from different parts of the plant was tested for anti bacterial activity. Extract from leaves showed significantly higher efficacy. The anti bacterial activity of the leaf extract of the plant was checked against micro organism like Pseudomonas aeruginosa NCIM2036, Salmonella typhimuruim NCIM2501, Staphylococus aureus NCIM5021 and was found that the extracts could be used as the prophylactic agent in the treatment of many of the disease.

4. Anti oxidant property- The anti oxidant potential of the ethanolic extract of the roots of the two varieties of C. roseus namely rosea (pink flower) and alba (white flower) was obtained by using different system of assay. The result obtained proved that the ethanolic extract of the roots of Periwinkle varieties has exhibited the satisfactory scavenging effect in the entire assay in a concentration dependent manner but C. roseus was found to possess more antioxidant activity than that of C. alba.

5. Anti helminthic property- Helminthes infections are the chronic illness, affecting human beings and cattle. Catharanthus roseus was found to be used from the

traditional period as an anti helminthic agent. The anti helminthic property of C. roseus has been evaluated by using

Pherithema postuma as an experimental model and with Piperazine citrate as the standard reference. The ethanolic extract of the concentration of 250 mg/ml was found to show the significant anti helminthic activity.

6. Anti ulcer property- Vincamine and Vindoline alkaloids of the plant showed anti ulcer property.

7. Hyptensive property- Extract of leaves of th plant made significant change in hypotensive.

8. Anti diarrheal property- The anti diarrheal activity of the plant ethanolic leaf extracts was tested in the wistar rats with castor oil as a experimental diarrhea inducing agent in addition to the pretreatment of the extract. The anti diarrheal effect of ethanolic extracts C. roseus showed the dose dependant inhibition of the castor oil induced diarrhea.

9. Phyto remediation- Exposed C. roseus bioaccumulates heavy metal like cd etc., so it is used in phyto remediation.

10. Folkloric uses-

- In India- The juice of leaves is used as application to bee sting/ wasp sting.
- In Philippines- Decoction of leaves is used in diabetes and decoction of young leaves is used in stomach cramps, root decoction is used for intestinal parasitism. Infusion of leaves is used for treating menorrhagia. Crude leaf extracts and root has anti cancer activity. Roots used for dysentery.
- In Madagascar- The bitter and astringent leaves are used as vomitive, roots used as purgative, vermifugl, depurative, hemostatic and toothache remedies.
- In Mauritius- The juice of leaves is used for indigestion and dyspepsia.
- In West Indies and Nigeria- The plant is used in diabetes.
- In Cuba and Jamaica- Flower extract is used for eye wash in infants.
- In Bahamas- Decoction of flower is used in asthma
- In Malaysia- The plant is used in diabetes, hypertension, insomnia
- In Hawai- Extract of boiled plant is used to arrest bleeding.
- In Africa- Leaves are used for menorrhagia and rheumatism.

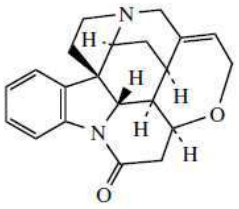
Strychnos nux-vomica

Loganiaceae

The fruit is a large berry with a hard coat and a pulpy interior containing three to five flattish grey seeds.

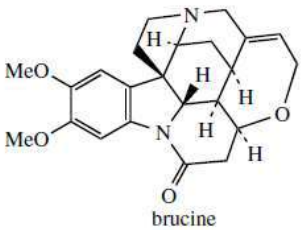
These seeds contain 1.5–5% of alkaloids, chiefly strychnine (about 1.2%) and brucine (about 1.6%).

Strychnine is very toxic, affecting the CNS and causing convulsions. This is a result of binding to receptor sites in the spinal cord that normally accommodate glycine.



strychnine

Fatal poisoning (consumption of about 100 mg by an adult) would lead to asphyxia following contraction of the diaphragm. It has found use as a vermin killer, especially for moles. Its only medicinal use is in very small doses as an appetite stimulant and general tonic, sometimes with iron salts if the patient is anemic.



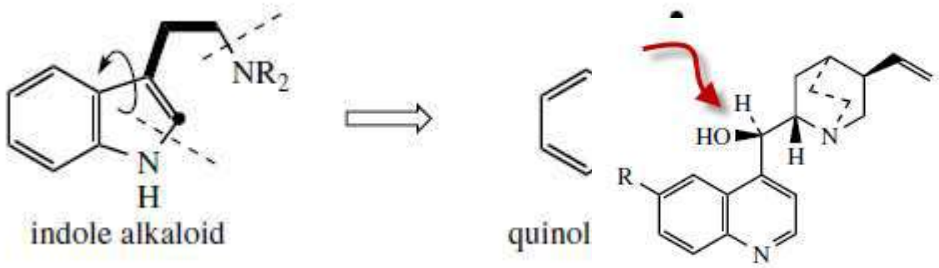
brucine

Brucine is considerably less toxic, used as better standard indicator.

Quinoline Alkaloids

Rubiaceae

Some of the most remarkable examples of terpenoid indole alkaloid modifications are to be found in the genus **Cinchona spp.**



A considerable number of alkaloids have been characterized in cinchona bark, four of which account for some 30–60% of the alkaloid content. These are **quinine**, **quinidine**, **cinchonidine** and **cinchonine,** long prized for their antimalarial properties. Quinine and quinidine have opposite configurations at two centres. Cinchonidine and cinchonine are demethoxy analogues.

Cinchona bark is the dried bark from the stem and root of species of *Cinchona* (Rubiaceae), which are large trees indigenous to South America. Trees are cultivated in many parts of the world.

The alkaloids are often present in the bark in salt combination with quinic acid or a tannin material called cinchotannic acid. **Cinchotannic acid** decomposes due to enzymic oxidation during processing of the bark to yield a **red pigment**, which is particularly prominent in the 'red' bark.

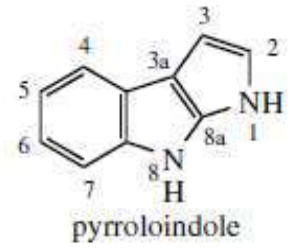
EFFECT & USES

Quinine is a major alkaloid, administered as free base or salts, continues to be used for treatment of multidrug-resistant malaria, though it is not suitable for prophylaxis.

Quinidine is the principal cinchona alkaloid used therapeutically, and is administered to treat cardiac arrhymias. It inhibits fibrillation, the uncoordinated contraction of muscle fibres in the heart. It is rapidly absorbed by the gastrointestinal tract and overdose can be hazardous, leading to diastolic arrest.

Quinidine, cinchonine, and cinchonidine also have antimalarial properties, but these alkaloids are not as effective as quinine.

Pyrroloindole Alkaloids



pyrroloindole

Physostigma venenosum

Calabar beans

Leguminosae/Fabaceae

Medicinal part: seeds

Traditionally:

The seeds are known as Calabar beans have an interesting history in the native culture as an ordeal poison.

The accused was forced to swallow a portion of the ground seeds, and if the mixture was subsequently vomited, he/she was judged innocent and set free. If the poison took effect, the prisoner suffered progressive paralysis and died from cardiac and respiratory failure. It is said that slow consumption allows the poison to take effect, whilst emesis is induced by a rapid ingestion of the dose.

Phytochemicals

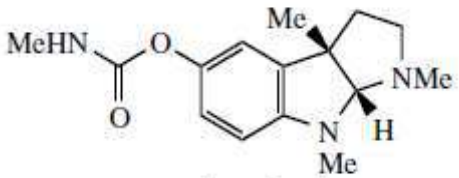
The seeds contain several alkaloids (alkaloid content about 1.5%), the major one (up to 0.3%) being physostigmine (eserine).

Isolation:

Powders seeds are extracted with hot alcohol. Solvent is removed and water is added to residue. The floating fatty layer is removed, the remaining aqueous layer is soluble in alkaline with Na2CO3 followed by extraction with ether to obtain physostigmine. Physostigmine occurs as colorless rhombic crystals, m.p = 106. It is soluble in alcohol, chloroform and benzene, insoluble in petroleum ether.

Identification:

When treated with strong ammonia solution, it gives a yellowish red color.



physostigmine
(eserine)

EFFECT

It causes an increase in tone in the parasympathetic system and the striated muscles. Eserine is a reversible inhibitor of cholinesterase, preventing normal destruction of acetylcholine and thus enhancing cholinergic activity. Its major use is as a miotic, to contract the pupil of the eye, often to combat the effect of mydriatics such as atropine.

It also reduces intraocular pressure in the eye by increasing outflow of the aqueous humour, and is a valuable treatment for glaucoma, often in combination with pilocarpine.

Because it prolongs the effect of endogenous acetylcholine, physostigmine can be used as an antidote to anticholinergic poisons such as hyoscyamine/atropine, and it also reverses the effects of competitive muscle relaxants such as curare, tubocurarine, atracurium, etc.

Anticholinesterase drugs are also of value in the treatment of Alzheimer's disease, which is characterized by a dramatic decrease in functionality of the central cholinergic system.

Use of acetylcholinesterase inhibitors can result in significant memory enhancement in patients.

INDICATIONS AND USAGE

The drug is frequently used in the treatment of glaucoma. It is also a poison antidote. Its use in the treatment of Alzheimer's disease to reduce memory loss and confusion is being investigated.

PRECAUTIONS AND ADVERSE REACTIONS

The drug is only used in the extraction of physostigmine.

Symptoms of poisoning include: diarrhea, dizziness, nausea, salivation, stupor, sweats and vomiting.

OVERDOSAGE

Lethal doses can cause muscle twitching, spasms, tachycardia and cyanosis through asphyxiation. Following gastric lavage, poisonings are treated with atropine; in the case of spasms, diazepam is also used. Forced diuresis can be useful.

The lethal dose for an adult is 6 to 10 mg of physostigmine (corresponding to approximately 2 to 3 Calabar Beans).

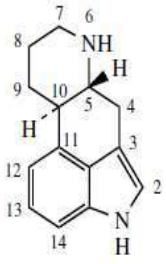
Poisonings are possible through inappropriate administration of physostigmine eye drops, due to drainage into the mouth or nose.

DOSAGE

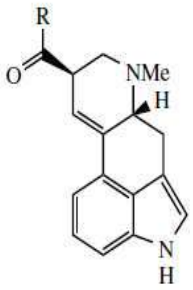
Mode of Administration: As an eye medication, in drops and ointments. It is used as an antidote in the form of an injection solution.

Ergot Alkaloids

Ergot is a fungal disease commonly found on many wild and cultivated grasses, and is caused by species of *Claviceps*.

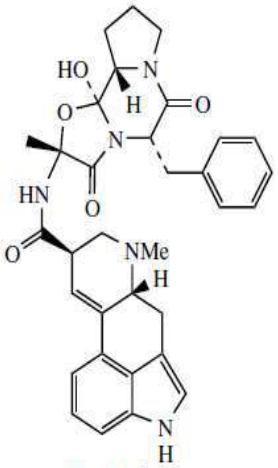


ergoline



R = OH, (+)-lysergic acid
R = NH_2, ergine

ergometrine



ergotamine

Medicinally useful alkaloids are derivatives of (+)-**lysergic acid,** which is typically bound as an amide with an amino alcohol as in **ergometrine**, or with a small polypeptide structure as in **ergotamine**.

Claviceps purpurea

Clavicipitaceae

Medicinal Parts:

The medicinal part of the fungus is the sclerotium, developed on the ovary of rye, ... (**Graminae/Poaceae**), and is later dried.

PHYTOCHEMICALS

The ergot sclerotia contain from 0.15–0.5% alkaloids, and more than 50 have been characterized. The medicinally useful compounds are derivatives of (+)-lysergic acid and can be separated into two groups, the water-soluble amino alcohol derivatives (up to about 20% of the total alkaloids), and water-insoluble peptide derivatives
(up to 80% of the total alkaloids). Ergometrine is an amide of lysergic acid and 2-aminopropanol, and is the only significant member of the first group. The peptide derivatives contain a cyclized tripeptide fragment bonded to lysergic acid via an amide linkage. Based on the nature of the three amino acids, these structures can be subdivided into three groups,

- The ergotamine group,
- The ergoxine group, and
- The ergotoxine group.

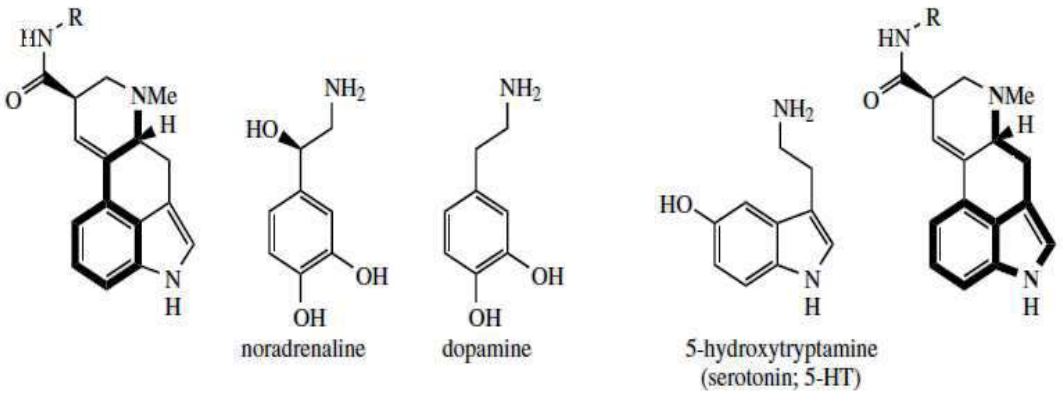
Ergots containing principally ergotamine in concentrations of about 0.35% can be cultivated. In recent times, ergot of wheat (*Triticum aestivum*), and the wheat–rye hybrid triticale (*Triticosecale*) have been produced commercially.

EFFECT

The pharmacologically active ergot alkaloids are based on (+)-lysergic acid, but since one of the chiral centres in this compound (and its amide derivatives) is adjacent to a carbonyl function group.

The ergot alkaloids owe their pharmacological activity to their ability to act at α-adrenergic, dopaminergic and serotonergic receptors.

The relationship of the general alkaloid structure to those of noradrenaline, dopamine, and 5-hydroxytryptamine (5-HT, serotonin) is shown in the following structures:



INDICATIONS AND USAGE

Ergometrine is used as an oxytocic, and is injected during the final stages of labour and immediately following childbirth, especially if haemorrhage occurs.

Bleeding is reduced because of its vasoconstrictor effects, and it is valuable after Caesarian operations. It is sometimes administered in combination with oxytocin itself.

Ergometrine is also orally active. It produces faster stimulation of uterine muscle than do the other ergot alkaloids, and probably exerts its effect by acting on α-adrenergic receptors, though it may also stimulate 5-HT receptors.

Ergotamine is a partial agonist of α-adrenoceptors and 5-HT receptors.

It is not suitable for obstetric use because it also produces a pronounced peripheral vasoconstrictor action. This property is exploited in the treatment of acute attacks of migraine, where it reverses the dilatation of cranial blood vessels. Ergotamine is effective orally, or by inhalation in aerosol form, and may be combined with caffeine, which is believed to enhance its action. The semi-synthetic **dihydroergotamine** is produced by hydrogenation of the lysergic acid Δ9,10 double bond (giving C-10 stereochemistry as in ergoline) and is claimed to produce fewer side-effects, especially digestive upsets.

TOXICITY

There are three broad clinical features of ergot poisoning, which are due to the alkaloids present and the relative proportions of each component:

- Alimentary upsets, e.g. diarrhoea, abdominal pains, and vomiting.

- Circulatory changes, e.g. coldness of hands and feet due to a vasoconstrictor effect, a decrease in the diameter of blood vessels, especially those supplying the extremeties.
- Neurological symptoms, e.g. headache, vertigo, convulsions, psychotic disturbances, and hallucinations.

These effects usually disappear on removal of the source of poisoning, but much more serious problems develop with continued ingestion, or with heavy doses of ergot-contaminated food.

Prolonged treatment with any of the ergot alkaloids is undesirable and it is vital that the clinical features associated with ergot poisoning are recognized. Treatment must be withdrawn immediately if any numbness or tingling develops in the fingers or toes.

SIDE EFFECTS

Will disappear on withdrawal of the drug, but there have been many cases where misdiagnosis has unfortunately led to foot or toe rot, and the necessity for amputation of the dead tissue.

LSD

The lysergic acid derivatives is lysergide (lysergic acid diethylamide or LSD) is a psychedelic drug of the ergoline family, well known for its psychological effects—which can include altered thinking processes, closed- and open-eye visuals, synesthesia, an altered sense of time.

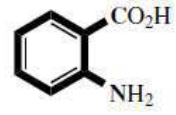
Physically, LSD can cause pupil dilation, reduced appetite, and wakefulness. Other physical reactions to LSD are highly variable and nonspecific, some of which may be secondary to the psychological effects of LSD. Among the reported symptoms are numbness, weakness, nausea, hypothermia or hyperthermia, elevated blood sugar, goose bumps, heart rate increase, mouth clenching, perspiration, saliva production, mucus production, sleeplessness, hyperreflexia, and tremors.

Psychologically, an LSD trip can have long-term psychological or emotional and hallucinogen effects (Hallucinogens are drugs that cause hallucinations. Users see images, hear sounds and feel sensations that seem very real but do not exist. Some hallucinogens also produce sudden and unpredictable changes in the mood of those who use them).

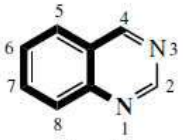
LSD causes an animated sensory experience of senses, emotions, memories, time, and awareness for 6 to 14 hours, depending on dosage and tolerance. Generally beginning within 30 to 90 minutes after ingestion, the user may experience anything from subtle changes in perception to overwhelming cognitive shifts. Changes in auditory and visual perception are typical.

ALKALOIDS DERIVED FROM ANTHRANILIC ACID

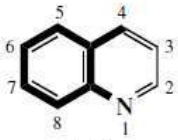
Anthranilic acid is a key intermediate in the biosynthesis of L-tryptophan and so contributes to the elaboration of indole alkaloids. During this conversion, the anthranilic acid residue is decarboxylated, so that only the C_6N skeleton is utilized.



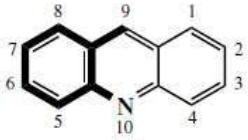
anthranilic acid



quinazoline



quinoline



acridine

Quinazoline Alkaloids

Peganine is a quinazoline alkaloid found in *Peganum harmala* (Zygophyllaceae), where it co-occurs with the β-carboline alkaloid harmine.

Phytochemicals:

- **Vasicine (peganine)**
- Harman
- Harmine
- Harmaline
- Vasicinone

Peganine

Effect:

- In large quantities, it can reduce spermatogenesis and male fertility
- Peganum harmala has been shown to have antibacterial and anti-protozoal activity
- Seed extracts also show effectiveness against various tumor cell lines, both in vitro and in vivo

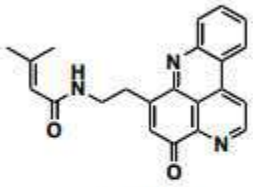
Quinoline and Acridine Alkaloids

Alkaloids derived from anthranilic acid undoubtedly occur in greatest abundance in plants from the family the Rutaceae.

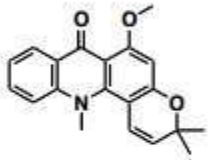
Acridine Isolation:

marine:
a) tunicates & ascidians
b) sponges
c) sea anemones

plant:
a) bark of Australian scrub ash tree

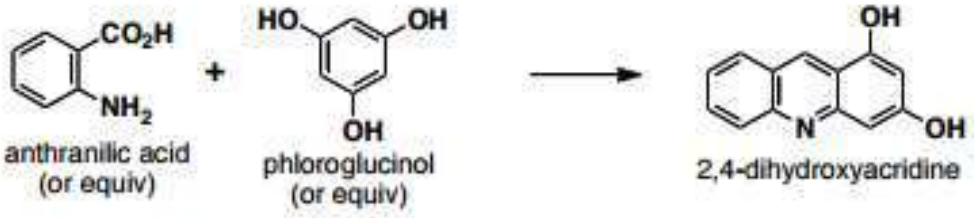


cystodytin A



acronycine

Acridine Biosynthesis:

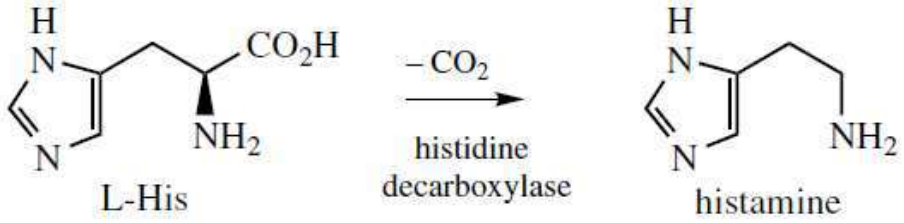


ALKALOIDS DERIVED FROM HISTIDINE

Imidazole Alkaloids

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

There are relatively few examples, however, and definite evidence linking them to histidine is often lacking.



Histamine is the decarboxylation product from histidine and is often involved in human allergic responses, e.g. to insect bites or pollens. Major effects of histamine include dilation of blood vessels, inflammation and swelling of tissues, and narrowing of airways. In serious cases, life-threatening anaphylactic shock may occur, caused by a dramatic fall in blood pressure.

Pilocarpus microphyllus

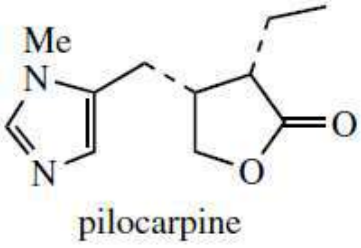
Rutaceae

Medicinal Parts: The medicinal parts are the dried leaves.

PHYTOCHEMICALS

Imidazole alkaloids (0.5-1.0%): chief alkaloid is pilocarpine, through drying and under storage conditions changing over to some extent into isopilocarpine, companion alkaloids including pilocarpidine, pilosine and others.

Volatile oil (0.5%): chief component is limonene.



pilocarpine

Isolation:

Finely powdered Jaborandi leaves are treated with sodium carbonate then extracted with benzene, followed by shaking the benzene extract with dilute HCL or nitric acid. The aqueous solution is then made alkaline and

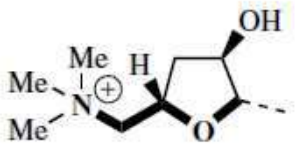
shaken with chloroform. The chloroform solution is then shaken with acid, and the alkaloidal salt allowed crystallizing.

Identity:

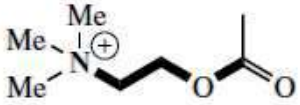
Helche's test: Aqueous solution of pilocarpine salt when treated with H_2O_2, few drops of diluted $K_2Cr_2O_7$ SOLUTION, a violet color is formed; upon shaking with benzene, the benzene layer will give a blue color while the aqueous layer becomes yellow.

EFFECT

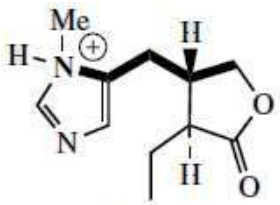
Pilocarpine salts are valuable in ophthalmic practice and are used in eyedrops as miotics and for the treatment of glaucoma. Pilocarpine is a cholinergic agent and stimulates the muscarinic receptors in the eye, causing constriction of the pupil and enhancement of outflow of aqueous humour. The structural resemblance to muscarine and acetylcholine is shown as follow:



Muscarine



Acetylcholine



Pilocarpine

INDICATIONS AND USAGE

Jaborandi has been used in the treatment of glaucoma. In folk medicine, it has been used for epilepsy, convulsions.

PRECAUTIONS AND ADVERSE REACTIONS

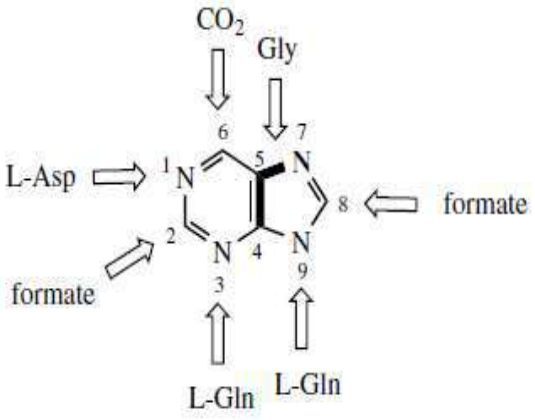
General: No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages. The incorrect administration of pilocarpine eyedrops can lead to poisoning through leakage into the nose or mouth. Symptoms include bradycardia, bronchial spasms, colics, collapse and possible cardiac arrest, convulsions, drop in blood pressure, dyspnea, nausea, severe salivation, strong secretion of sweat and vomiting.

OVERDOSAGE

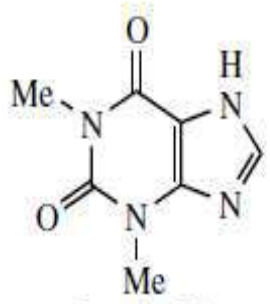
The lethal dose is approximately 60 mg of pilocarpine, corresponding to 5 to 10 gm of the drug.

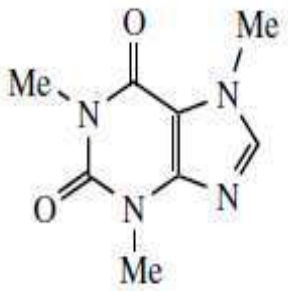
PURINE ALKALOIDS

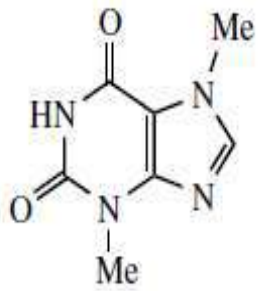
The purine derivatives **caffeine**, **theobromine**, and **theophylline** are usually referred to as purine alkaloids. As alkaloids they have a limited distribution, but their origins are very closely linked with those of the purine bases adenine and guanine, fundamental components of nucleosides, nucleotides, and the nucleic acids. Caffeine, in the form of beverages such as tea, coffee, and cola is one of the most widely consumed and socially accepted natural stimulants.



It is also used medicinally, but theophylline is much more important as a drug compound because of its muscle relaxant properties, utilized in the relief of bronchial asthma. Theobromine is a major constituent of cocoa, and related chocolate products.


theophylline
(1,3-dimethylxanthine)


caffeine
(1,3,7-trimethylxanthine)


theobromine
(3,7-dimethylxanthine)

The purine alkaloids caffeine, theobromine, and theophylline are all methyl derivatives of xanthine and they commonly co-occur in a particular plant. **The major sources of these compounds are the beverage** materials such as tea, coffee, cocoa, and cola, which owe their stimulant properties to these water-soluble alkaloids. They competitively inhibit phosphodiesterase, resulting in an increase in cyclic AMP and subsequent release of adrenaline. This leads to a stimulation of the CNS, a relaxation of bronchial smoothmuscle, and induction of diuresis, as major effects. These effects vary in the three compounds. **Caffeine** is the best CNS stimulant, and has weak diuretic action. **Theobromine** has little stimulant action, but has more diuretic activity

and also muscle relaxant properties. **Theophylline** also has low stimulant action and is an effective diuretic, but it relaxes smooth muscle better than caffeine or theobromine.

Caffeine is used medicinally as a CNS stimulant, usually combined with another therapeutic agent, as in compound analgesic preparations. **Theobromine** is of value as a diuretic and smooth muscle relaxant, but is not now routinely used. **Theophylline** is an important smooth muscle relaxant for relief of bronchospasm, and is frequently dispensed in slow release formulations to reduce side-effects. It is also available as **aminophylline** (a more soluble preparation containing theophylline with ethylenediamine) and **choline theophyllinate** (theophylline and choline). The alkaloids may be isolated from natural sources, or obtained by total or partial synthesis.

Purine alkaloids are weak bases, form salts only with strong acids; they can combine with organic acids, as citric, or with salts of organic acids as sodium acetate or benzoate. They **do not give precipitate with Mayer's reagent**, but give a **brown precipitate with Wagner's reagent** and are precipitated, as well, by tannic acid. They give **positive Murexide test**.

Isolation of Caffeine

Powder Tea leaves is extracted with boiling water, filtered, filtrate is treated with lead acetate solution, to precipitate tannins and other impurities, and again filtred. Filtrate is concentrated and delayed by sodium hydrogen phosphate and filtred again. Caffeine is extracted from the filtrate with chloroform and is purified by recrystallization from water.

Properties

Caffeine occurs as white powder having a bitter taste. Being a very weak base, it does not form salts easily. Caffeine is soluble in water, alcohol, chloroform, acetone and benzene.

Identification

 Murexide test: little of solid alkaloid is mixed with conc. HCL and traces of $KCLO_3$ are added , evaporate on water bath, a reddish colour is produced changing to purple on exposure to ammonia vapour. The colour is destroyed by fixed alkalies.

 Tannic acid: Caffeine is precipitated from its concentrated solution by tannic acid; the precipitate is soluble in excess of the reagent.

 Caffeine gives precipitates with Wagner's (in acid solution) and Dragendorff's reagents.

Coffea arabica

Rubiaceae

Coffee consists of the dried ripe seed of *Coffea arabica*, (Rubiaceae). The plants are small evergreen trees, widely cultivated in various parts of the world, e.g. Brazil and other South American countries, and Kenya.

The fruit is deprived of its seed coat, then dried and roasted to develop its characteristic color, odor, and taste.

Coffee seeds contain 1–2%of caffeine and traces of theophylline and theobromine. The nicotinic acid derivative trigonelline is present in green seeds to the extent of about 0.25–1%; during roasting, this is extensively converted into nicotinic acid (vitamin B3). Volatile oils and tannins provide odor and flavour.

A proportion of the caffeine may sublime off during the roasting process, providing some commercial caffeine. Decaffeinated coffee, containing up to 0.08% caffeine, is obtained by removing caffeine, usually by aqueous percolation prior to roasting. This process provides another source of caffeine.

Caffeine equivalents

In general, each of the following contains approximately **200 mg of caffeine**:

Coffee Composition

The Approximate Composition of Roasted Arabica Coffee[3]

Components		Total (%)	Water soluble (%)
Protein	As amino acids	9	1.5
Carbohydrates	Polysaccharides:		
	Water insoluble	24	—
	Water soluble	6	6
	Sucrose	0.2	0.2
	Glucose, fructose, arabinose	0.1	0.1
Lipids	Triglycerides	9.5	—
	Terpenes: free, esters, glycosides	2	Some
Volatile acids	Formic acid	0.1	0.1
	Acetic acid	0.2	0.2
Nonvolatile acids	Lactic, pyruvic, oxalic, tartaric, citric acids	0.4	0.4
	Chlorogenic acids	3.8	3.8
Alkaloids	Caffeine	1.2	1.2
	Trigonelline	0.4	0.4
Ash	Minerals	4	3.5
Water	—	2.5	2.5
Partially known	Volatile aroma compounds	0.1	0.1
	Browning compounds, phenols, etc.	35	7.5
Total		100	27.5

Camellia sinensis

Theaceae

For black tea, the leaves are allowed to ferment, allowing enzymic oxidation of the polyphenols, whilst green tea is produced by steaming and drying the leaves to prevent oxidation. During oxidation, colorless catechins (up to 40% in dried leaf) are converted into intensely colored theaflavins and thearubigins.

Composition of Fresh Leaf

Tea leaf, in common with all plant leaf matter, contains the full complement of genetic material, enzymes, biochemical intermediates, carbohydrates, protein, lipids, and structural elements normally associated with plant growth and photosynthesis. In addition, tea leaf is distinguished by its remarkable content of methylxathines and polyphenols. These two groups of compounds are predominantly responsible for those unique properties of tea that account for its popularity as a beverage.

Composition of Fresh Green Leaf

Components	% of dry weight
Flavanols	25.0
Flavonols and flavonol glyosides	3.0
Polyphenolic acids and depsides	5.0
Other polyphenols	3.0
Caffeine	3.0
Theobromine	0.2
Amino Acids	4.0
Organic acids	0.5
Monsaccharides	4.0
Polysaccharides	13.0
Cellulose	7.0
Protein	15.0
Lignin	6.0
Lipids	3.0
Chlorophyll and other pigments	0.5
Ash	5.0
Volatiles	0.1

Composition of Green and Black Tea Solids

	Green Tea (%)	Black Tea (%)
Catechins	30	9
Theaflavins		4
Simple polyphenols	2	3
Flavonols	2	1
Other polyphenols	6	23
Theanine	3	3
Amino acids	3	3
Peptides/proteins	6	6
Organic acids	2	2
Sugars	7	7
Other carbohydrates	4	4
Lipids	3	3
Caffeine	3	3
Other methylxanthines	<1	<1
Potassium	5	5
Other minerals/ash	5	5
Aroma	Trace	Trace

Oolong tea is semi-fermented. Tea contains 1–4% caffeine, and small amounts (up to 0.05%) of both theophylline and theobromine. Astringency and flavour come from tannins and volatile oils, the latter containing monoterpene alcohols (geraniol, linalool) and aromatic alcohols (benzyl alcohol, 2-phenylethanol). Theaflavins are believed to act as radical scavengers/antioxidants, and to provide beneficial effects against cardiovascular disease, cancers, and the ageing process generally. Tea leaf dust and waste is a major source of caffeine.

Flavored Teas Earl Grey tea is flavored with the peel oil of bergamot, a citrus fruit, which is added by spraying onto black tea before final packaging. Jasmine flowers are sometimes added to manufactured green tea in the country of origin and they impart characteristic floral notes.

Cola acuminate

Sterculiaceae

Cola seeds contain up to 3% caffeine and about 0.1% theobromine, partly bound to tannin materials. Drying allows some oxidation of polyphenols, formation of a red pigment, and liberation of free caffeine. Fresh cola seeds are chewed in tropical countries as a stimulant, and vast quantities of dried seeds are processed for the preparation of cola drinks, e.g. Coca-Cola and Pepsi-Cola.

Theobroma cacao

Sterculiaceae

Although cocoa as a drink is now rather unfashionable, it provides the raw material for the manufacture of chocolate and is commercially very important.

Cocoa seeds contain 35–50% of oil (cocoa butter or theobroma oil), 1–4% theobromine and 0.2–0.5% caffeine, plus tannins and volatile oils. During fermentation and roasting, most of the theobromine from the kernel passes into the husk, which thus provides a convenient source of the alkaloid. Theobroma oil or cocoa butter is obtained by hot expression from the ground seeds as a whitish solid with a mild chocolate taste. It is a valuable formulation aid in pharmacy where it is used as a suppository base.

INSTANT TEA

Instant tea is the water-soluble extract of tea leaf usually marketed as a powder, either pure or as a part of flavored mixes. Instant tea produced as described above will dissolve completely in hot water but not in cold water, as the caffeine-polyphenol complexes are insoluble under those conditions.

Ilex paraguariensis

Aquifoliaceae

Mate´ Tea

Mate´ or Paraguay tea, the dried leaf contains 0.8–1.7% caffeine and smaller amounts of theobromine (0.3–0.9%) with little or no theophylline.

Components of Maté

Component	Amount (% dry wt. of leaf)
Sucrose	3.33
Raffinose	0.44
Glucose	0.27
Fructose	0.16
Amino acids	?
Trigonelline	0.50
Choline	15 mg/g
Thiamine	1 mg/g
Riboflavin	trace
Ascorbic acid	20 mg/g
Folic acid	16 mg/g
Total extractable ash	5.99

Paullinia cupana

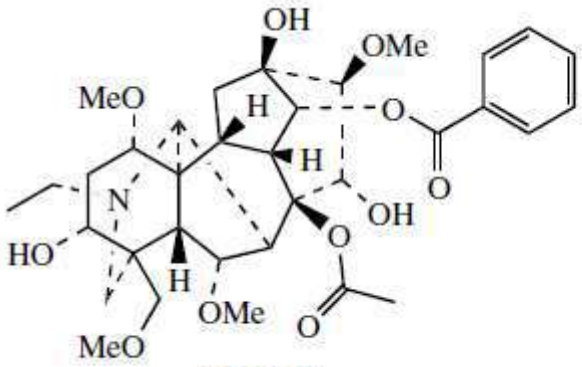
Sapindaceae

Guarana

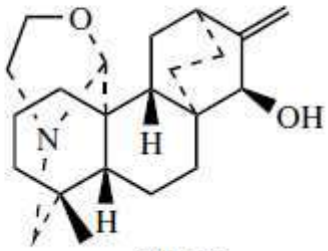
The seeds of the Brazilian plant *Paullinia cupana* are used to make a stimulant drink. The principal constituent, previously called guaranine, has been shown to be identical to caffeine, and the seeds may contain 3–5%. Small amounts of theophylline (0–0.25%) and theobromine (0.02–0.06%) are also present. Guarana is widely available as tablets and capsules, or as extracts, in health food shops where it is promoted to relieve mental and physical fatigue.

Terpenoid Alkaloids

A variety of alkaloids based on mono-, sesqui-, di-, and tri-terpenoid skeletons have been characterized, but information about their formation in nature is still somewhat sparse. Monoterpene alkaloids are in themain structurally related to iridoid materials. Perhaps the most important examples of terpenoid alkaloids from a pharmacological point of view are those found in aconite (*Aconitum* species; Ranunculaceae) and species of *Delphinium* (Ranunculaceae). Whilst *Aconitum napellus* has had some medicinal uses, plants of both genera owe their highly toxic nature to diterpenoid alkaloids. Aconite in particular is regarded as extremely toxic, due to the presence of **aconitine** and related C19 norditerpenoid alkaloids. Species of *Delphinium* accumulate diterpenoid alkaloids such as **atisine**, which tend to be less toxic than aconitine.



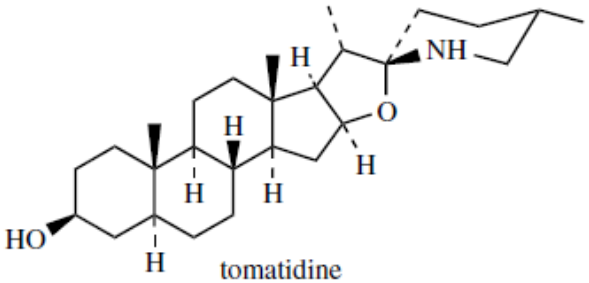
aconitine



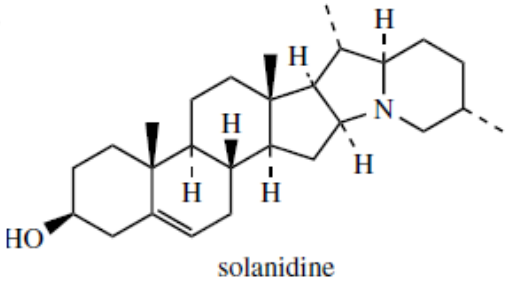
atisine

Steroidal Alkaloids

Many plants in the Solanaceae accumulate steroidal alkaloids based on a C27 cholestane skeleton, e.g. **solasodine** and **tomatidine** from tomato (*Lycopersicon esculente*) are typical examples of such glycosides.

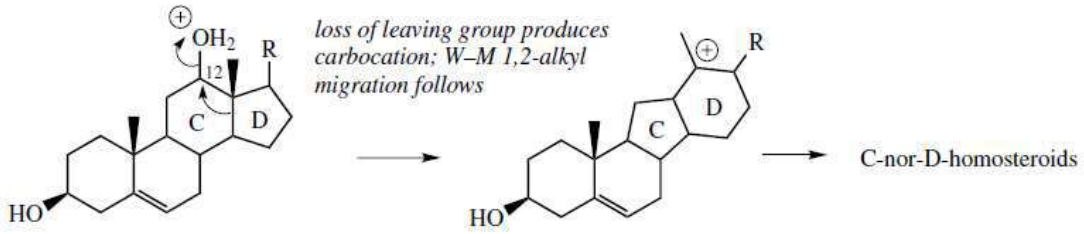


tomatidine

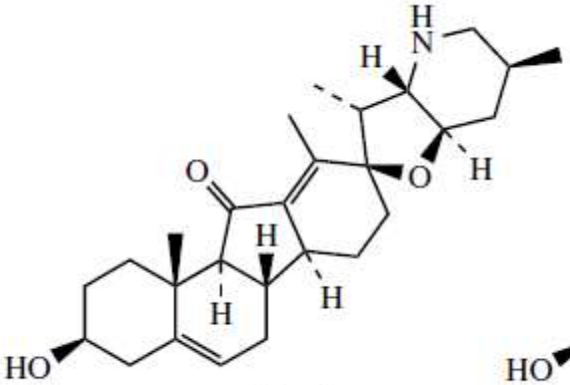


solanidine

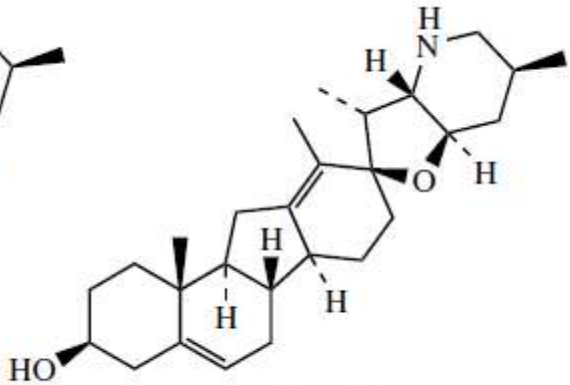
Cholesterol is a precursor of this group of alkaloids, and a mechanism accounting for the ring modifications is shown as follow,



where the changes are initiated by loss of a suitable leaving group from C-12. Typical representatives of Cnor- D-homosteroids are **jervine** and **cyclopamine** from ***Veratrum californicum***, toxic components in this plant that are responsible for severe teratogenic effects. The teratogenic effects of jervine, cyclopamine, and cyclopamine glucoside (cycloposine) on the developing fetus have now been well established. Other *Veratrum* alkaloids, especially those found in *V. album* and *V. viride*, have been employed medicinally as hypotensive agents, and used in the same way as *Rauwolfia* alkaloids.



jervine



cyclopamine

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