

# ALKALOIDS.

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Alack, alack, is it not like that I,  
So early waking, what with loathsome smells,  
And shrieks like mandrakes' torn out of the earth  
That living mortals, hearing them, run mad.

*Romeo and Juliet*; Act IV, Scene 3

The forked root of mandrake was thought to be in the power of dark earth spirits. Mandrake would only be growing after a man was hung on the gallows, being fed by the urine and semen of the dead man. It was believed that it could be uprooted safely only in the moonlight, after appropriate prayer and ritual. With the tip of a willow wand three circles were drawn around the plant, and then a black, hungry dog was attached to the plant by a cord. The dog was put a juicy sausage in front of his nose, and his hunger made him pull the mandrake root out of the ground. It was thought that as the mandrake root was pulled from the ground, it uttered a shriek that killed or made mad those who did not block their ears against it. The dog would die anyway, because of either starvation or instant overfeeding.



Mandrake, also named Mandragora (*Mandragora officinarum*), is probably the most famous magic plant known. Already used in Egypt 3500 years ago, it was in the Grecian times considered as an extremely powerful aphrodisiac and fertility enhancer. Mentioned in the Koran, and strictly forbidden. The sponge that was given to Jesus on the cross is said to contain mandragora juice.

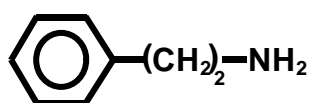
In the dark ages mandragora was loaded with dozens of myths, and it played a major role in witchcraft. Witches prepared mixtures of extracts of henbane (*Hyoscyamus niger*), deadly nightshade (*Atropa belladonna*) and mandrake root, to be applied on the skin or on the genitals. These plants belong to the family of Solanaceae, the nightshade family. The mixture is extremely rich in tropane alkaloids, such as hyoscyamine, scopolamine, atropine, hyoscine, cuscohygrine and mandragorine. Biosynthesis of tropane alkaloids start with ornithine (a dibasic amino acid) or arginine an amino acid with a guanidium group attached to it); the biosynthetic pathway has been completely elucidated. Other alkaloids use lysine, phenylalanine, tyrosine, methionine or tryptophan as the starting amino acid, eventually as their amino aldehydes or amines derived from them.

All of these are characterised as alkaloids, in today's nomenclature identified as organic nitrogen bases from botanical origin (although that is strictly not true as also in the Animal Kingdom alkaloids occur). The name "alkaloid" comes from the Arabic word for ash "*al-qali*". Al-qali was obtained by roasting (European) saltwort (*Salsola kali*), the ashes being rich in sodium and potassium carbonate. In the Golden Century of Damascus craftsman were able to purify the ashes to obtain white crystals composed of a mixture of  $\text{Na}_2\text{CO}_3$  and  $\text{K}_2\text{CO}_3$ , and this enabled them to make transparent glass.

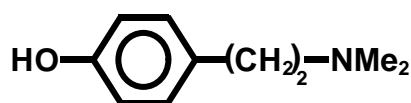
On average alkaloids are poisonous to extremely poisonous, but frequently they are extremely useful applied in pharmacy, usually without a synthetic countertype. Virtually all plants contain alkaloids. Alkaloids are quite frequently responsible for the cosmetic benefits obtained from botanical extracts. Often condemned, frequently glorified. Like the girls on the catwalk who like to apply the juice of a deadly nightshade berry to the eyelids to get nice, large pupils. The name "atropine" comes from Atropos, the Fate who severs the thread of life; you will remember how Atropos works if you have read Stephen King's book "Insomnia". Belladonna is also named Devil's Cherries because of the excellent taste of the glossy, black berries, but eating a few will surely result in a horrible death.

## **β-PHENETYLAMINES**

β-Phenetylamine (a colourless liquid with a boiling point of 197°C) is the parent substance of a group of alkaloids. β-Phenetylamine itself occurs in putrid meat; it is formed by decarboxylation of phenylalanine. It occurs in mistletoe (*Viscum Album*), and in Brassica species (cabbage, kale, cauliflower). d-(-)-Ephedrine is an important derivative which occurs in the genus Ephedra. It is one of the most important drugs in Ma Huang (*Ephedra Sinensis*), a Chinese drug, containing ~2-2,5% ephedrine. Ma Huang, also known as ephedra, is used for weight management and appetite suppression, but is restricted in most countries. Pakistani ephedra contains much smaller amounts of ephedrine (~0,7%).

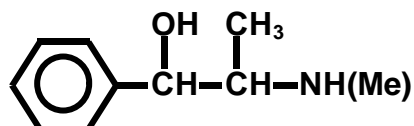


**β-PHENETYLAMINE**

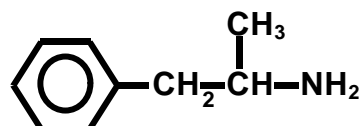


**HORDENINE**

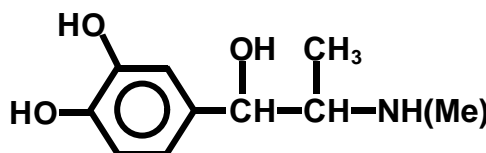
Ephedra-containing supplements produce a state of wakefulness and alertness, a decreased sense of fatigue, and a mood elevation with increased self-confidence and initiative. Unfortunately, the beneficial effects in weight management and mood alteration come at a price: high doses of ephedrine result in depletion of epinephrine (adrenaline) and norepinephrine (noradrenaline), leading to the opposite effects: depression, a sense of loneliness and suspiciousness. Also, ephedrine may elevate blood pressure, increases heart rate and comes with severe palpitations. In very serious cases this can cause ventricular fibrillation and death. The use of Ma Huang, particularly in conjunction with caffeine, should be discouraged because of the side effects.



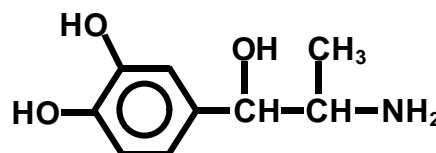
**EPHEDRINE**



**AMPHETAMINE**

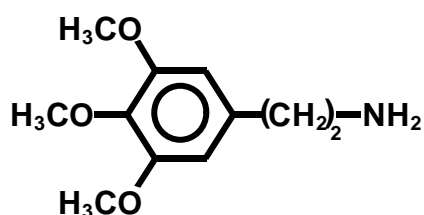


**ADRENALINE**



**NORADRENALINE**

The physiological activity of ephedrine compares to benzedrine (amphetamine) and tyramine. Benzedrine is not found in nature, but tyramine occurs in germinating barley (*Hordeum vulgare*), and is produced by putrefaction of proteins (decarboxylation of tyrosine). It is also found in tangerine (*Citrus reticulata*) and orange (*Citrus Sinensis*), although the amounts are insignificant. Mescaline (3,4,5-trimethoxy- $\beta$ -phenethylamine) is found exclusively in Mexican peyote (*Lophophora Williamsii*), next to related alkaloids such as hordenine. Hordenine (4-hydroxy-N,N-dimethyl- $\beta$ -phenethylamine) is more widespread in plants. It is found in e.g. *Selenicereus grandiflorus* (Queen-of-the-Night) and *Tamarindus indica* (tamarind).



**MESCALINE**

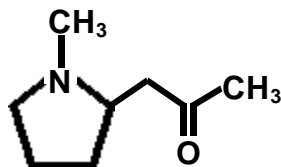
“MESCAL”

Adrenaline is a non-steroid hormone belonging to the  $\beta$ -phenethylamine group; it was the first hormone to be isolated in a crystalline form (Takamine; 1901). It raises blood pressure and is used locally to stop haemorrhage. Adrenaline is responsible for the storage and mobilisation of glycogen and fatty acids and tunes the corresponding metabolic pathways. Adrenaline is also a neurotransmitter of the adrenergic nervous system.

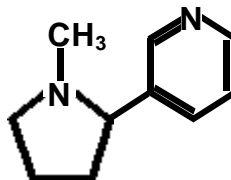
## **PYRROLIDINE ALKALOIDS.**

About 80 pyrrolidine alkaloids are known, hygrine being the simplest representative. It is one of the coca alkaloids (*Erythroxylum coca*), chemically identified as N-

methyl-pyrrolidiny acetone. The coca plant originally comes from the Andes mountain range and is best known for the alkaloid cocaine; it also contains about a dozen other alkaloids as well: benzoylecgonine, benzoyltropine, cinnamylcocaine, cuscohygrine, dihydroxytropine, hygrine, hygroline, methylcocaine, methyl ecgonidine, nicotine, tropacocaine, and  $\alpha$ - &  $\beta$ -truxilline.



**HYGRINE**



**NICOTINE**

With the exception of nicotine all these alkaloids are rather specific for *Erythroxylum coca*; in general little is known about their physiological activity. Nicotine is an alkaloid that can be considered belonging to the group of pyrrolidine alkaloids or to pyridine alkaloids. The most important source for nicotine are the leaves of *Nicotiana tabacum* (Tobacco plant; 2-4%), but it also occurs in very small amounts in Horsetail (*Equisetum arvense*) and Potato (*Solanum tuberosum*). Nicotine has no known cosmetic benefits; it acts both as an ANS stimulant and ANS paralytic (Williamson & Evans, Potter's New Cyclopaedia of Botanical Drugs and Preparations [1989]).

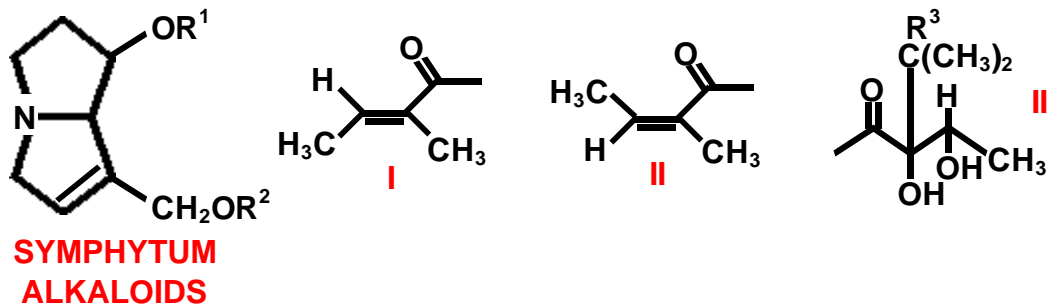
The amino acid proline (pyrrolidine 2-carboxylic acid) can also be considered as an alkaloid. N,N-dimethylpyrrolidine-2-carboxylate (stachydrine), an amphoteric, is found in germinating alfalfa seeds (*Medicago sativa*; ~0,8%), motherwort (*Leonurus cardiaca*) and yarrow (*Achillea millefolium*). In a similar fashion hydroxyproline may be converted to betonicine (4-hydroxy-N,N-dimethylpyrrolidine-2-carboxylate) or turicine, also amphoteric. Betonicine (0,3 %) and turicine are found in *Marrubium vulgare* (Horehound). Horehound is valuable in the treatment of bronchitis where there is a non-productive cough. Topically horehound is used to promote the healing of wounds.

The properties of stachydrine, betonicine and turicine compare to ectoine, chemically identified as a pyrimidine derivative. All these amphoteric (but also betaine (trimethylglycine) from sugar beets and trehalose (a diglucoside occurring in yeasts and fungi)) act as osmosuppressants, enabling cells to survive in more harsh, electrolyte-rich environments. Betaine (trimethylglycine) is able to perform its osmoprotecting properties in surfactant compositions, and markedly reduces their irritation potential.

## **PYRROLIZIDINE ALKALOIDS.**

Many pyrrolizidine alkaloids, nearly 100 are known, display toxic, carcinogenic and mutagenic properties. In liver cells pyrrolizidine alkaloids give rise to 10 to 30- fold enlargement of the liver cells (megalocytosis). In serious cases this may result in severe liver damage and death. The frequent occurrence of primary liver tumours in the natives of Central Africa and South Africa is ascribed to the consumption of traditional medicinal plants. The majority of pyrrolizidine alkaloids are hepatotoxic, carcinogenic, teratogenic and mutagenic.

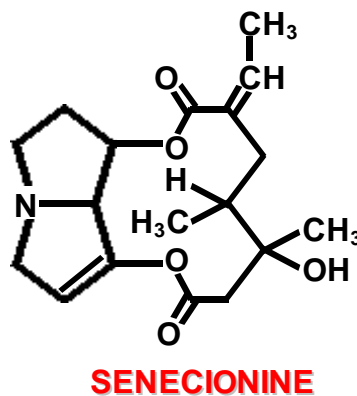
Plants from the Boraginaceae, Compositae and Leguminosae families contain significant amounts of pyrrolizidine alkaloids. Members of the Boraginaceae are for example *Alkanna tinctoria* (alkannet; the root contains 0,25% hepatotoxic triangularine), *Lithospermum officinale* (gromwell; 0,003% lithosenine) and *Symphytum officinale* (comfrey; the roots contain 0,5% intermedine, lycopsamine, symphytine, echimidine and symglandine; the above ground parts contain only small amounts of pyrrolizidine alkaloids and are edible. Comfrey root has been blamed for serious liver damage death in humans. A sincere concern for these plants is also VOD (veno-occlusive disease), which is difficult to diagnose.



ALKALOID	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
RETRONECINE	H	H	H
LYCOPSAMINE	H	(III)	H
SYMPHYTINE	(I)	(III)	H
SYMLANDINE	(II)	(III)	H
ECHIMIDINE	(II)	(III)	OH
UPLANDICINE	Ac	(III)	OH

**TOXIC PYRROLIZIDINE ALKALOIDS FROM  
SYMPHYTUM OFFICINALE**

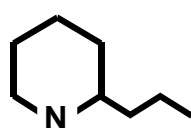
Coltsfoot (*Tussilago farfara*) has been widely used in Europe to treat lung disorders and gastro-intestinal disorders (e.g. diarrhea). It contains, depending on the time of harvesting, significant amounts of senkirkine (~0.015%) and senecionine. Senecionine is also found in groundsel (*Senecio vulgaris*, and its subspecies) next to riddelline, retrorsine, floridanine, monocrotaline, and otosenine, totalling to approximately 0,2%. In subspecies the percentages may be markedly higher, such as in *Senecio bicolor* (up to 0,9%).



Pyrrolizidine alkaloids give rise to major health concerns, and many plants containing them have been marked with a red cross: they shall not be part of food supplements and/or botanical medicines.

## PIPERIDINE AND PYRIDINE ALKALOIDS.

Coniine (2-propylpiperidine) is found in high amounts in hemlock (*Conium maculatum*) and in the leaves of elder (*Sambucus nigra*). It has emetic and paralytic properties, and is considered as highly toxic. It was used by the ancient Grecians for state executions, Socrates († 399 BC) being the best known victim of hemlock. Hemlock contains up to 0,2% coniine. Hemlock also contains other alkaloids such as N-methylconiine, conhydrine, pseudoconhydrine and  $\gamma$ -coniceine. However, these alkaloids are physiologically not very significant for humans.



**CONIINE**



**N-METHYLCONIINE**

At least 700 piperidine alkaloids are known. They arise from lysine in much the same manner as pyrrolizidine alkaloids are derived from ornithine and arginine. Anatabine and anabasine (3-[2-piperidinyl]-pyridine), found in tobacco (*Nicotiana tabacum*), are derived in a manner that parallels the origin of nicotine. Anabasine is severely teratogenic (foetus deforming properties), much stronger than thalidomide [Softenon, caused in the sixties a massive number of birth defects] and diethylstilbestrol. Nicotine, although always accused, has no teratogenic properties. Piperidine alkaloids are also found in the root bark of the pomegranate tree: pelletierine, isopelletierine, methylisopelletierine and pseudopelletierine; the last one is related to atropine.

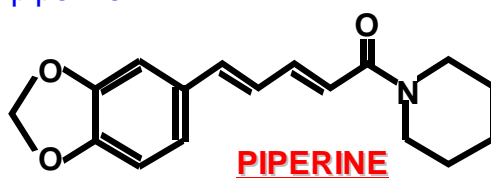
*Sedum acre* (wallpepper, common stonecrop) is topically used for wound treatment, burns, hemorrhoids, warts, eczema and mouth ulcers. It contains the sedative sedamine, which is usually applied in conjunction with barbiturates, and sedine. Sedamine is also a lysine based alkaloid, like pelletierine, pseudopelletierine, halosaline and the more complex tetracyclic lycopodine. Lycopodine has also been isolated from club moss (*Lycopodium clavatum*), and has also sedative properties.

*Lobelia inflata* (Indian tobacco) has anti-asthmatic, antispasmodic, emetic, expectorant and respiratory stimulant effects. The constituent with the highest physiological activity, (-)-lobeline, is known as  $\alpha$ -lobeline, to distinguish it from the mixture of lobelia alkaloids formerly called lobeline. Like nicotine, but weaker,  $\alpha$ -lobeline exhibits effects on the peripheral circulation, neuromuscular system and central nervous system (CNS). Small amounts of lobeline stimulate respiration and have expectorant activity. Larger amounts have emetic, purgative, and diuretic effects. Lobeline is much better known as a partial nicotine agonist; it has been (and still is) used in a variety of commercially available preparations for smoking cessation. More recently it was found that lobeline inhibits the neurochemical and behavioural effects of amphetamine and the results (Miller et.al.) support a role for lobeline as a potential pharmacotherapy for psycho-stimulant abuse.

stimulant abuse. Independently it was found that lobeline reduces self-administration of methamphetamine in rats.

A spectacular issue has been the discovery of epibatidine by Daly et.al. (1976). They took scrapings of the skin of a poisonous Ecuadorian frog, *Epibipedobates tricolor*. They discovered, through tests on mice, that the frog's poison provided pain relief 200 times higher than that of morphine. Unfortunately, as the frogs were endangered, only very small amounts of the chemicals were extracted. At the end of the eighties the structure of this poison was determined using NMR and mass spectroscopy. It was shown that it contained a piperidine moiety, on the 3-position substituted with a 5-[2-chloropyridine] group (the presence of chlorine based heterocyclic unit is unique). Epibatidine binds to nicotinic acetylcholine receptors rather than to opiate receptors, and is therefore not addictive. However, epibatidine shows severe side effects. Based on an extensive screening of 500 similar alkaloids a product coded as ABT-594 was developed that doesn't show the side effects from epibatidine. This is considered a breakthrough in pain control.

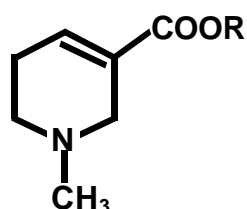
Piperine is an alkaloid found in *Piper nigrum* (black pepper). Piperine significantly increases the rate of absorption of selenium in the body. Selenium is important in the functioning of glutathion (a tripeptide [Glu-CySH-Gly]): glutathion deactivates damaging free radicals, whereby two glutathion molecules dimerise to form glutathion dimer. Glutathion is subsequently regenerated from glutathion dimer by means of the enzyme glutathion reductase, a selenium-containing enzyme of 121 amino acids, using NADPH as the co-factor. Our frequent readers might recognise NADPH as a pyridine-based nucleotide, which finds its origin in vitamin PP (Niacinamide). Piperine also dramatically increases the uptake of the B vitamins, and is therefore highly suitable to treat systemic vitamin B deficiency. In skin care preparations piperine has been demonstrated to greatly enhance the efficacy of topically applied vitamins. Interesting to note is the presence of the vanillin moiety in piperine.



Niacinamide, heavily used as a moisturiser, is chemically identified as pyridine-3-carboxylic acid amide (pyridine-3-carboxamide). Pyridine-2-carboxylic acid (picolinic acid; MP=137°C) and pyridine-4-carboxylic acid (isonicotinic acid; MP=317°C) next to pyridine-3-carboxylic acid (nicotinic acid; MP=234-237°C) also occur in *Nicotiana tabacum*, next to ~140 other alkaloids. Nicotinic acid is not exclusive for the tobacco plant; it also occurs in *Glycyrrhiza glabra* (licorice; ~500 ppm), *Chelidonium majus* (celandine; ~400 ppm) and in the roots of *Taraxacum officinale* (dandelion) and *Gentiana lutea* (gentian).

Methylation of nicotinic acid results in the formation trigonellin, a betaine with significant osmoprotecting properties; it is the most significant constituent of *Mirabilis jalapa* (four o'clock, wonderflower), an old-fashioned but quickly growing plant with nice colourful flowers. Four o'clock was one of the favourites of the famous botanist Mendel.

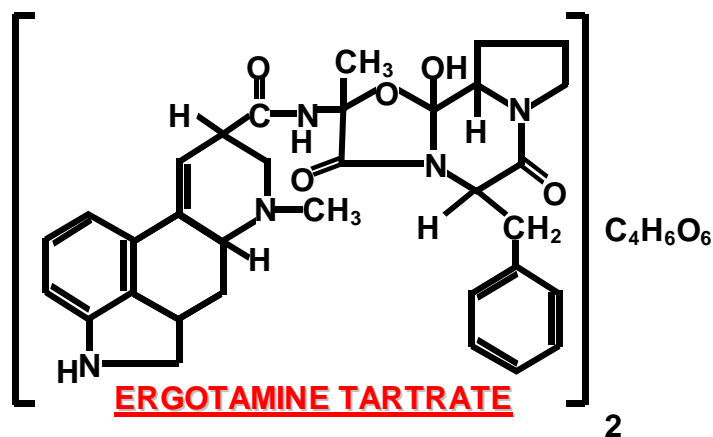
Areca catechu (betel nut, sirih palm) occurs widespread in South-east Asia. The nuts contain a volatile oil, and in the oil a number of alkaloids are present, such as arecoline, arecaidine, guvacine and guvacoline. The pyridine ring has been partially hydrogenated and only the double bond on the  $\Delta(3-4)$  double bond has remained intact. Arecoline is used in medicine. It is a mild central nervous system stimulant. It increases respiration while decreasing the work load on the heart. An overdose of arecoline may cause inebriation, dizziness, diarrhoea, and may damage the teeth and gums. Frequent use results in a red colouring of the teeth. Betel nut is probably the most widely used stimulant worldwide.



R = H: ARECAIDINE  
R = Me: ARECOLINE

***nor*-ARECAIDINE = GUVACINE  
*nor*-ARECOLINE = GUVACOLINE**

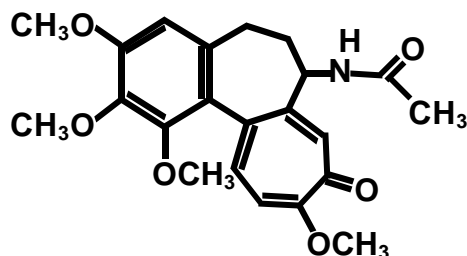
Sometimes it is difficult to categorise particular alkaloids in a group. Ergotamine could be considered as a pyridine alkaloid, but also as a pyrrole alkaloid. It first came in the medical picture during the Middle Ages when mass poisoning by ergotamine occurred throughout Europe due to eating bread carrying *Claviceps purpurea*. This parasite grows on rye, wheat, barley and other grains. Ergotamine (a mycotoxin) is a secretion product of *Claviceps purpurea*. In large quantities it causes ergotism (St. Anthony Fire): complete body parts die off because of permanent damage to the arteries, resulting in loss of toes, legs or arms without losing any blood. Ergotism still asks today for victims. Ergotamine is nonetheless beneficially used in pharmacy to treat migraine and to induce childbirth.



Another important piperidine alkaloid with a highly complex structure is aconitine, found in *Aconitum napellus* (monkshood). Beautiful flowers, but highly toxic. Aconitine is isolated from the monkshood rhizomes and is used as a local analgesic. In the past aconitine was used as a killing poison. Monkshood is therefore one of the most dangerous plants known. From a toxicity point of view monkshood compares to the autumn crocus (*Colchicum autumnale*); it contains the highly toxic alkaloid colchicine. Traditionally autumn crocus is used to alleviate the inflammation associated with gout. Colchicine blocks or suppresses cell division by inhibiting mitosis, the division of a cell's nucleus. Because cancer cells divide much more rapidly than normal cells, they are more susceptible to being poisoned by mitotic inhibitors such as colchicine. Colchicine is a powerful anticancer drug, in a similar fashion as taxol (paclitaxel; *Taxus baccata*, Cephalo-



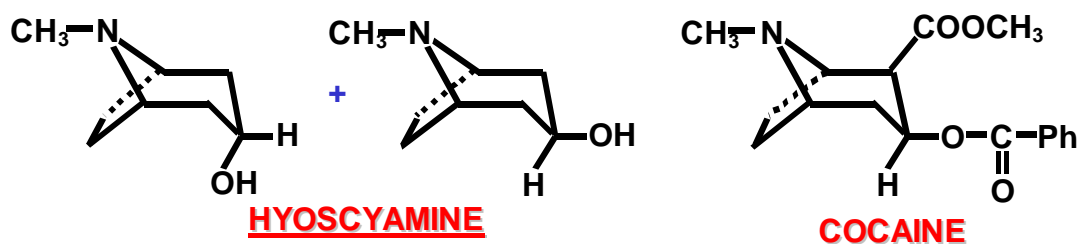
taxus mannii) and vinca alkaloids. For taxol a synthetic pathway has not yet been worked out (and looking at the structure this is not at all surprising). That is also the case for vinca alkaloids from *Cataranthus roseus* (Madagascar periwinkle). The chemical structure of these alkaloids (vincristine, vinblastine, vinepidine, vindesine, etc.) is extremely complex, and they are, like taxol, extremely difficult to make in the laboratory.



**COLCHICINE**

## **SOLANACEOUS AND COCA ALKALOIDS.**

This group includes atropine, hyoscyamine, scopolamine and many other important products. *Mandragora officinarum* (mandragora) contains scopolamine, hyoscyamine, mandragorine, next to many other alkaloids.



**HYOSCYAMINE**

**COCAINE**

*Datura stramonium* (Jimson Weed) is a major source for scopolamine. It is known under many different names, such as Locoweed, Angels Trumpet, Thorn Apple, Devil's Trumpet, Mad Apple, Stink Weed, Sacred Datura, Green Dragon and Tolguacha. Scopolamine is found in all parts of the plant, with the highest alkaloid content in the seeds (0.4%). Scopolamine (hyoscine) is the ester of scopine with 3-hydroxy-2-phenylpropionic acid (tropic acid). Scopolamine is a constituent of travel sickness tablets, and in combination with morphine it causes "twilight sleep". Jimson weed is smoked or a tea can be made of it. When rubbed onto the skin it is swiftly brought in the bloodstream by transdermal transport. Jimson weed was and is used as a medicine to treat a variety of illnesses and conditions. Extracts are used for the treatment of muscle spasms, controlling salivation in Parkinson's disease, asthma, intestinal cramps, and both diarrhoea and bed-wetting. In older times it was used to reduce or eliminate pain.

Initial symptoms of scopolamine abuse include dry mouth, dilated pupils, reddening of the face and neck, elevated blood pressure & body temperature and significant palpitations. These symptoms may be followed by extreme hallucinations, agitation & aggression, coma and death. Inappropriate use of scopolamine is life-threatening. Scopolamine in the human body acts as a competitor to acetylcholine at peripheral and central muscarine receptors; abuse can easily be recognised by extensive sweating and

slobbering. Like many tertiary amines scopolamine inhibits CNS receptors and abuse results in acute psychosis or delirium.

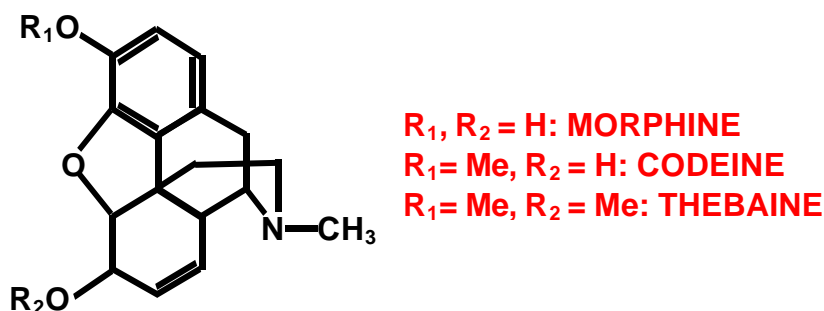
A third major source for tropane alkaloids is henbane (*hyoscyamus niger*). The roots & the leaves contain ~1500 ppm alkaloids, while the seeds only 400 ppm. Henbane contains 15 different alkaloids, and most of these are extremely dangerous in the hands of amateurs. Atropine occurs in *Atropa belladonna* (deadly nightshade) is optically pure. Racemisation results in hyoscyamine, and hyoscyamine is therefore  $\pm$ -atropine (see the picture on page 9).

Erythroxyton coca is responsible for the alkaloid cocaine, probably the most significant export product for Colombia. Cocaine is related to benzoylecgonine, tropacocaine and cuscohygrine (which is also found in mandragora). The health impact of cocaine is so well-known to require further discussion. Cocaine used to be applied in particular soft drinks, until this application was banned in 1929.

### QUINOLINE & ISOQUINOLINE ALKALOIDS.

*Angostura trifoliata* is used orally for preventing recurrence of malaria. In the past it was used in alcoholic beverages (angostura bitter), but nowadays it has been replaced by gentian. The applicable part of angostura is the bark which contains a number of quinoline based alkaloids such as cusparine, galipine and galipoline; these exhibit antispasmodic properties. A far more important quinoline alkaloid is quinine. It is present in the bark of various *Cinchona* species, characterised by the presence of a triethylene diamine tricyclic unit. Quinine has anti-malarial properties.

Camptothecin is found in the bark of the Chinese camptotheca tree and the Asian nothapodytes tree. It is, together with two closely related alkaloids (topotecan, irinotecan), the only known naturally-occurring DNA topoisomerase I inhibitor. Camptotecan is a relatively new chemotherapeutic agent to treat breast and colon cancers, malignant melanoma, small-cell lung cancer and leukemia. While camptotecan inhibits DNA topoisomerase I, the affected cells can't make their proteins and consequently the cell stops growing. Because cancer cells grow and reproduce at a much faster rate than normal cells (whereby the synthesis of proteins plays a vital role) they are far more vulnerable to DNA topoisomerase inhibition compared to normal cells.



The group of isoquinoline alkaloids comprise the both famous and notorious opium alkaloids, as found in *Papaver somniferum* (opium). Representatives of the isoquinoline alkaloids are laudanosine, laudanine, narcotine and hydrastine. In the name one recognises "Laudanum", a very popular drug during the Victorian era. It was an

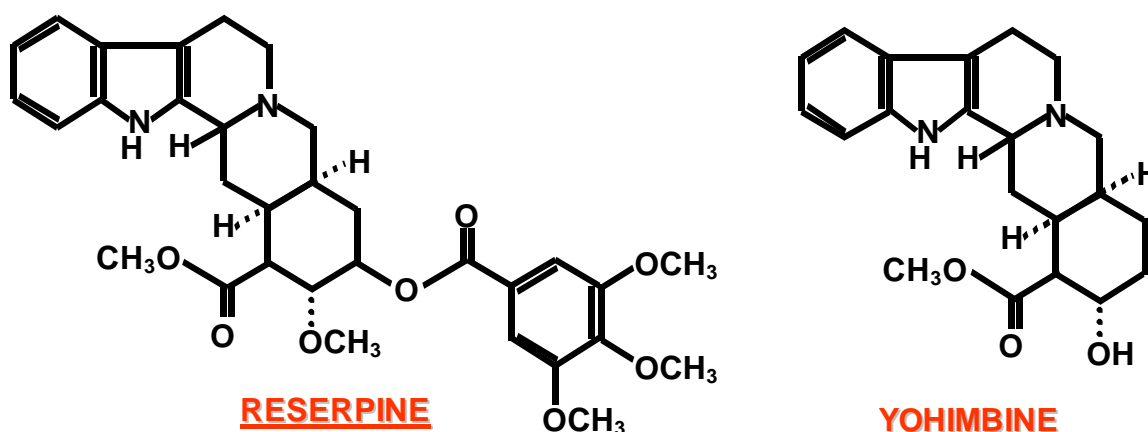
opium-based painkiller prescribed for everything from headaches to tuberculosis. It is in fact an alcoholic extract of opium, frequently with added sugar. Opium also contains alkaloids with condensed systems to which belong codeine, morphine, heroine and thebaine. It is quite striking indeed that the influence on the nervous system is so much different for codeine and morphine: just one methyl group more or less, and we're changing the properties from a modest, non-addictive bronchodilator (codeine) to an addictive pain relief agent (morphine) or a highly addictive euphoricum (heroine).

## INDOLE AND OXINDOLE ALKALOIDS.

The indole alkaloids are usually highly complex structures. The simplest indole alkaloid is gramine which occurs in the leaves of *Hordeum vulgare* (barley). Gramine is clinically used to resist palpitations and to reduce blood pressure. Barley contains a wide variety of other alkaloids such as glaucine, which also occurs in *Glaucium flavum* (yellow poppy). Glaucine is chemically best described as a dibenzo-isoquinoline.

Quebracho is an evergreen tree from South America, which may reach a height of 40 meter. The wood is valued because of its hardness. The name is derived from two Spanish words, *quebrar* and *hacha*, meaning 'the axe breaks'. The bark contains at least six indole alkaloids, quebrachamine deriving its name from the species. Nonetheless, the most important alkaloid is aspidospermine, which could also be identified as a pyrrolizidine alkaloid. Aspidospermine is used to relieve asthma and high blood pressure. Locally it is also used as an aphrodisiac.

The aphrodisiac qualities of aspidospermine are not confirmed, contrary to yohimbine. This is found in the African tree *Pausinystalia yohimbe*. Yohimbine is used to treat high blood pressure and to stimulate blood circulation. It is also used as a veterinarian aphrodisiac. Although yohimbine is strictly forbidden to be used in cosmetics there are many products in circulation containing yohimbine.



Closely related to yohimbine is reserpine, found in *Rauwolfia serpentina* (Indian snakeroot, serpentine wood). It is also known as ajmaline. Orally, Indian snakeroot is used to treat hypertension, symptomatic relief in individuals with agitated psychosis unable to tolerate other agents and insomnia. Indian snakeroot is also used orally for snake and reptile bites, insanity, fever, constipation, feverish intestinal diseases, liver

ailments, rheumatism, mental illness and epilepsy. Reserpine shall always be used under supervision of a medical doctor.

The applicable part of Indian snakeroot is the root. The properties of the whole root of *Rauwolfia serpentina* differ from those of reserpine. The whole root contains over 50 alkaloids. The active constituents of the whole root include the rauwolfia alkaloids reserpine, rescinnamine, and deserpidine (11-desmethoxyreserine). Hypotensive effects are believed to be due to the depletion of both catecholamine and serotonin stores and to the prevention of re-absorption. The greater the proportion of alkaloids present, the greater the hypotensive activity. The sedative effects of Indian snakeroot may result from the depletion of amine stores in the central nervous system (CNS). Reserpine has been in clinical use since the 1950's. At present time it is not so much used anymore as synthetic alternatives have been made available lacking the side effects of reserpine.

Currently there are approximately 5000 indole alkaloids known, with some notorious representatives: ajmacaline (clinically used for the treatment of circulatory disorders; it has hypotensive and vasodilator properties), the extremely toxic strychnine, brucine (even far more toxic than strychnine), vincamine (for the treatment of headaches and vertigo; its principal action is to moderate cerebral vasodilation). Not to forget about the curare alkaloids, which cause an immediate paralysis of the victim. The active ingredients of the so-called calabash curares are bisindole alkaloids. Compounds such as C-toxiferine are many more times more active than tubocurarine. Olivacine and ellipticine have been isolated from Apocynaceae and Loganiaceae. These alkaloids are clinically used as anti-tumour agents, as DNA topoisomerase inhibitors.

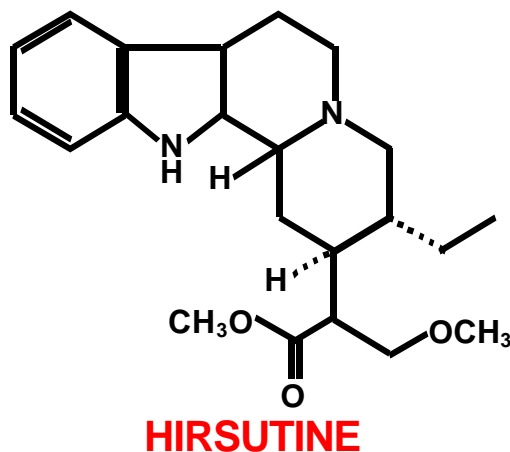
Iboga alkaloids come from *Tabernanthe iboga*, and are used to combat fatigue, sleep and hunger. Highly appreciated by different secret services, and by religious sects. In larger quantities the drug is highly hallucinogenic; the principal alkaloid is the famous ibogaine. Ibogaine is effectively used to reverse drug abuse, predominantly opiates and cocaine.

Indole alkaloids all have a very high biological activity and usually instant bio-availability. They are derived from the amino acid tryptophan. Some indole derivatives (e.g. harmaline) possess anti-protozoal activity, enabling to fight leishmaniasis and various diseases caused by trypanosomes (e.g. sleeping disease). Harmaline is extremely toxic, and for that reason ellipticine and olivacine are preferred. Their anti-protozoal activity was recognised in the 1970's. The use of indole alkaloids is always a balance between desired and undesired properties: to cure or to kill.

Related to indole alkaloids are the oxindole alkaloids. These occur in various vines in swampy territories of South America, Africa and South-east Asia. Previously we reported on alkaloids as the active substances of *Uncaria tomentosa* (cat's claw); approximately 55 have been identified. Present are tetracyclic oxindole alkaloids (TOA's; e.g. rynchophylline, isorynchophylline), pentacyclic oxindole alkaloids (POA's; e.g. pteropodine, isopteropodine, uncarine F, mitraphylline) and indole alkaloids (hirsutine, dihydrocorynantheine). These alkaloids are all physiologically active products.

TOA's mainly affect the nervous system, both peripheral and central, while the POA's affect the immunologic system cells, respecting the cellular immunity. Rynchophylline and isorynchophylline have been described to block tension-depending calcium

channels (Yamahara, 1993), reduce blood pressure and slow down the activity of the heart. A major interest has been raised for POA's because of their anti-proliferative properties to HL60 and U937 leukaemic cell lines, not inhibiting the growth of healthy blood cells. Uncarine F and isopteropodine show the greatest activity; profound testing is ongoing for non-invasive treatment of leukaemia. Important to note is that POA's in low concentration do not show cytotoxic effects.

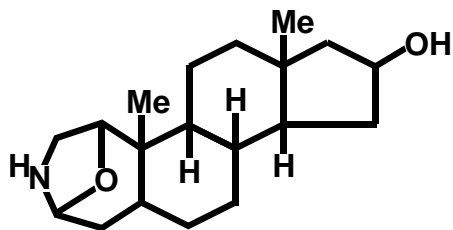


The Shanghai College of Traditional Chinese Medicine studied rynchophylline on its ability to inhibit platelet aggregation and thrombosis, with positive results. This suggests that Cat's Claw, being a source for this alkaloid, may be useful in preventing strokes and reducing the risk of heart attack by lowering blood pressure, increasing circulation, inhibiting formation of plaque on arterial walls and blood clots in the brain, heart and arteries. In other words: cardio-vascular diseases. The drawback of the alkaloids present in Cat's Claw is the potential interaction with anti-hypertensives (ryncophylline reduces blood pressure !). Also, simultaneous use of Cat's Claw and immunosuppressants such as prednisone and other corticosteroids shall be avoided; the result would be rather unpredictable.

Related to the Uncaria species are the Mitragyna species, which occur in Africa and Asia. The genus was given its name because the shape of the stigmas resemble a bishop's mitre. *Mitragyna speciosa* has long been used as a cure for opium addiction; in Thailand the leaves were chewed by the locals, named "kratom". Chewing kratom is now forbidden, but still heavily practised. Different species are used; *Mitragyna javanica* is often used as an alternative, although not so effective. Other alkaloids have been identified as well, such as rynchophylline (also found in cat's claw), mitragynine, mitraversine and mitraspecine. *Mitragyna* has properties comparable to morphine, although the degree of addiction is much lower. At present 22 alkaloids have been isolated from *Mitragyna* species.

### ANIMAL BASED ALKALOIDS.

The vast majority of the alkaloids are plant-derived, although in recent times more and more alkaloids are found in animals. Samandarine (20 mg applied on the skin of an adult human is lethal !), samandarone and cycloneosamandarine were isolated from the skin glands of the European fire salamander (*Salamandra maculosa*); all exhibit the usual properties of alkaloids.



### SAMANDARINE

Batrachotoxinin A, a steroidal alkaloid from the Colombian arrow-poison frog (*Phylllobates aurotaenia*), bufotenine (a tryptamine-type alkaloid from the common European toad), deoxy-nuphradine and castoramine from the Canadian beaver (*Castor fiber*) and muscopyridine from the scent gland of the musk deer (*Moschus moschiferus*) are other animal based alkaloids. Especially toad poisons, and the mystic around it, would require a separate study, as a lot can be learned from them, also taking benefit from what nature has to offer.