Aconitum napellus L.

Alkaloids Derived from Terpene Metabolism

Terpenoid Alkaloids

Many alkaloids, as shown in the preceding chapters, have a mixed biogenetic origin: examples are the monoterpenoid indole alkaloids (tryptophan and secologanin), furoquinolines (anthranilic acid and isopentenyl pyrophosphate). In other cases, the alkaloid does not arise from the metabolism of an amino acid, and is in fact a terpenoid (mono-, sesqui-, di-, triterpenoid, or a steroid) which incorporates a nitrogen atom late in the biosynthesis. Because of their isoprene-type origin, some

authors see in these compounds no more than "pseudoalkaloids" (see generalities), however, they are still widely considered alkaloids.

1. MONO- AND SESQUITERPENOID ALKALOIDS

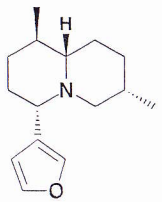
There are a few drugs containing monoterpenoid alkaloids and their pharmacological interest is very limited. Before reporting the finding of such structures in the free state, it is wise to carry out their extraction according to procedures designed to avoid the formation of artefacts: the action of aqueous ammonia on an iridoid readily leads to nitrogen-containing structures.

- **Water Lilies,**
  Nuphar luteum (L.) Sibth. & Sm.
  Nymphaea alba L., Nymphaeaceae

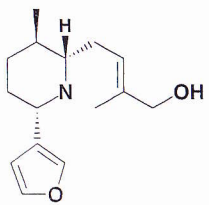
The Nymphaeaceae of western Europe are aquatic herbaceous plants growing from a rhizome, with cordate leaves that generally float on the surface of the water, with large, solitary, showy flowers, above water, regular, yellow (*Nuphar*) or white (*Nymphaea*). The rhizome of these species contains sesquiterpenoid alkaloids: most have a quinolizidine structure (deoxynupharidine, nupharolidine, nuphacristine), some are piperidines (nuphamine), and others are dimers and incorporate a sulfur atom (thiobinupharidine, 1- and 1'-epithiobinupharidine, hydroxylated derivatives of thiobinupharidine).

In vitro, 6,6'-dihydroxythiobinupharidine inhibits the growth of various fungi (*Histoplasma* spp., *Trichophyton* spp., and *Blastomyces* spp.).

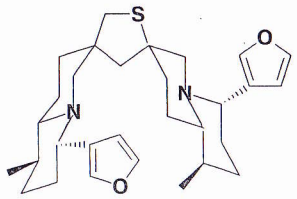
The properties attributed to these species do not appear to have undergone thorough pharmacological investigations or clinical trials. Nevertheless, in France, the rhizome of yellow water lily is an authorized ingredient of phytopharmaceuticals that may claim the following indications: traditionally used locally as adjunctive emollient and itch-relieving treatment of skin disorders, as a trophic protective agent in the treatment of cracks, bruises, chaps, and insect bites; to treat sunburns, superficial and limited burns, and diaper rashes [French Expl. Note, 1998].



Deoxynupharidine



Nuphamine

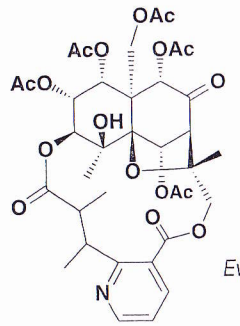


Thiobinupharidine

- **Spindle Tree,**
  Euonymus europæus L., Celastraceae

This small shrub is often found in the woods. It is devoid of medicinal interest, but must be mentioned because of its toxic fruits. These are capsules and are highly characteristic: the four lobes of the capsule, pink when ripe, earned it the popular name "bishop's mitre" in French (= *bonnet d'évêque*). The seeds are bitter and surrounded by a fleshy and colorful aril. They contain a small quantity (0.1%) of alkaloids and cardiac glycosides, which are digitoxigenin glycosides (evonoside, evobioside, evonomoside). The alkaloids are polyesters of sesquiterpenoid polyols: the hydrolysis of evonine yields five molecules of acetic acid, one dicarboxylic pyridine-type acid (evonic acid), and a tetrahydroxylated sesquiterpene, namely evoninol.

Although it is not so rare for the fruits of the spindle tree to tempt young children, intoxications seem exceptional. Stomach pumping, activated charcoal, and symptomatic treatment are the only measures to be taken.



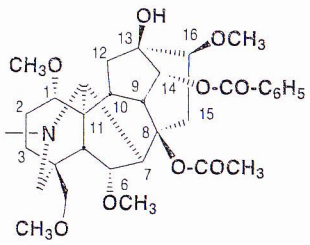
Evonine

This type of alkaloid is not rare in the Celastraceae: they are found in kath (*Catha edulis*, p. 883), as well as in the genera *Maytenus* and *Tripterygium*.

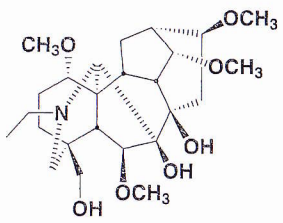
2. DITERPENOID ALKALOIDS

The nitrogen-containing diterpenoid bases known to date have been, for the most part, isolated from various Ranunculaceae (*Aconitum*, *Consolida*, *Delphinium*). They have also been characterized sporadically in some Rosaceae (*Spiraea*), Garryaceae, and Escalloniaceae (*Anopterus*). Most of them are characterized by a substantial toxicity. Their structure is always complex and their skeleta can comprise 19 or 20 carbon atoms: they are referred to as *nor*diterpenoid and diterpenoid alkaloids, respectively.

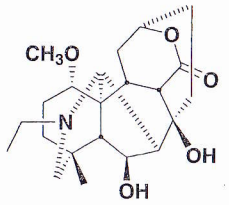
*Nor*diterpenoid alkaloids have a complex structure and are generally classified under the aconitine type (unsubstituted at C-7, like delphinidine), the lycoctonine type (7-substituted), the pyronorditerpenoid type (8,15-dehydro-), and the lactone



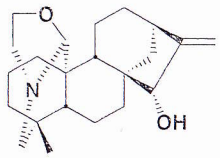
Delphinine



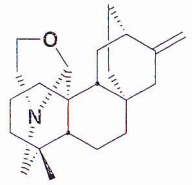
Lycoctonine



Heteratisine



Veatchine



Atisine

Diterpenoid alkaloids: examples of structures

type, in which the C ring is transformed into a lactone by a Baeyer-Villiger-type reaction sequence (e.g., heteratisine).

In the case of the diterpenoid alkaloids in the strict sense of the term (C_{20}), there are three main possible ways in which the rings can be arranged, depending on the position of the carbon atom to which the C-15-C-16 bridge is linked (the atisine, veatchine, and delnudine types), and within these three main types there are several subtypes (denudatine, napelline, anopterine, and more). The biosynthesis of all of these alkaloids is not well known: the mechanism by which the nitrogen atom is introduced (and the corresponding step) and the origin of the *N*-ethyl group remain hypothetical.

• ACONITE, *Aconitum napellus* L., Ranunculaceae

The monograph on the aconite root was a part of the French Pharmacopoeia until 1972 (it was deleted in 1984). The drug is used to obtain the tincture, a galenical which is still an ingredient of many proprietary pharmaceuticals used to treat various respiratory disorders, particularly to relieve unproductive coughs.

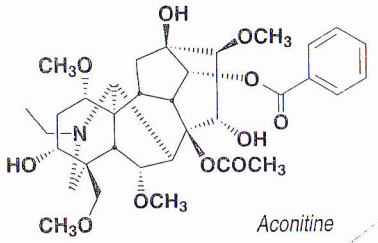
The Plant, the Drug. Aconite is a perennial herb which grows from a tuberized root. The stem is erect and bears alternate, deeply pinnatisect leaves with three to seven segments further divided into narrow lobes. The flowers are grouped into racemes. The calyx is composed of five purplish-blue sepals; the posterior sepal has a very characteristic hood shape and wraps around the lateral sepals. The petals are

reduced to nectariferous elements and ligules. The species is particularly polymorphic: the Flora Europaea describes the *napellus* complex, and includes in it, among others, *A. napellus* L., *A. firmum* Reichenb., *A. compactum* Reichenb., and *A. nevadense* Uechtr. ex Gayer.

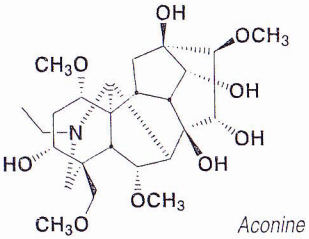
Although the species can be cultivated, the needs for the drug are also fulfilled by collecting the plant in its natural habitat, which essentially corresponds to the mountain areas of western Europe, all the way to the Himalayas. During the harvest, that occurs during floration, there are generally two tuberized roots at the base of the stem: the main tuber, which bears the stalk, and gradually wilts as the vegetative cycle progresses, and a lateral, replacement tuber which gives rise the following year, to a new stalk. It is the lateral tuber that is used (Fr. Ph., 9th Ed.)

The root is napiform, pointed (5-8 x 2-3 cm) and often surmounted by the remnants of the stalk. Its surface is blackish-brown and striated longitudinally; it breaks with a clean whitish fracture. The drug is odorless, tastes mild at first then acrid, and causes tingling and numbness of the tongue.

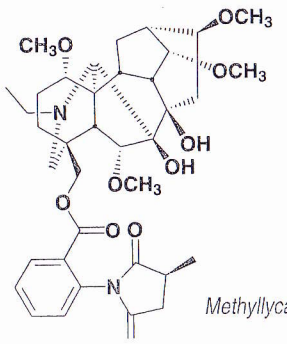
Chemical Composition. The aconite root is rich in sugars (50-60%, mostly starch) and contains 0.5 to 1.5% alkaloids. The principal alkaloid is aconitine. This ester alkaloid of complex structure is a diester: it is the acetylated and benzoylated derivative of a diterpenoid pentahydroxylated alkylamine, namely aconine. Alongside aconitine are found small quantities of compounds of related structure: hypaconitine, jesaconitine, pseudaconitine, lycaconitine, neopelline, napelline, and neoline. The quality of the raw material is very variable: there are probably chemotypes. The time of collection, and drying and storage conditions may also result in qualitative and quantitative variations.



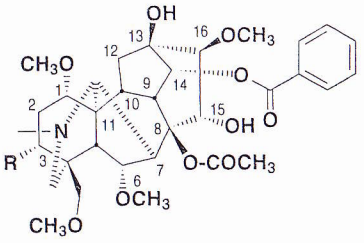
Aconitine



Aconine



Methyllycaconitine



R = H : *Hypaconitine*
R = OH : *Mesaconitine*

Tests. The 9th edition of the French Pharmacopoeia contained a description of the morphological and microscopic characteristics of the drug that allowed the identification and elimination of falsifications by more toxic aconites (*A. balfourii* Stapf., *A. deinorrhizum* Stapf., *A. spicatum* Stapf, *A. laciniatum* Stapf). In that monograph, the assay included a TLC analysis of a tincture, a determination of acute toxicity in mice, and a quantitation of the total alkaloids (back-titration, concentration not less than 0.5%).

Pharmacological Activity and Uses: Aconitine excites, then paralyzes the peripheral nerve endings as well as the brain stem. It induces respiratory slowing and the extinction of atrial impulses within the A-V node. Its activity resembles that of other neurotoxins (grayanotoxin I, batrachotoxin) which act on the sodium channels and hinder repolarization.

Aconites are among the genera most often used as arrow poisons during at least three millennia, in the Orient as well as in the western hemisphere. The names of certain species (e.g., wolfsbane, *A. vulparia, A. lycoctonum*, known in French as *aconit tue-loup* or wolf-killing aconite) are reminiscent of their former use as poisons against wild animals: wolves, foxes, bears, and also rodents. Latin authors report some unspeakable uses of the drug as an efficient means of eliminating undesirable individuals. (This is still a reality: from 1980 to 1984, 25 murders by aconite were recorded in the Sichuan province [People's Republic of China].) The use of aconite as a medicinal plant is as ancient in India or China, and appeared a little later in the western world.

Uses in the Western World. Aconite tincture is the normal form in which the aconite tuber is used. As a decongestant, it is an ingredient of medications, generally syrups, used to relieve unproductive coughs. It is used in many combinations with galenicals (cherry-laurel water, Desessartz syrup or compound ipecac syrup, eucalyptus syrup, Tolu balsam syrup, gum plant tincture, or snakeroot tincture), as well as specific chemicals (bromoform, codeine, sodium camphosulfonate, eucalyptol, or sulfoguaiacol, among others). In contrast with aconitine, which can be extracted from the drug, and is almost no longer used (except for facial neuralgia: 0.1 mg granules), *Aconitum* is widely used in homeopathy.

Uses in the Orient. Chinese medicine finds many uses for aconites, to which it attributes antirheumatic, analgesic, anesthetic, and antinevralgic properties. For example, it uses 1. *chuanwu*, the dried root of *Aconitum carmichaeli* Debx.; 2. *caowu*, the dried root of *Aconitum kusnezofi* Rchb.; 3. *zhichuanwu* and *zhicaowu*, the "prepared" roots of both species; 4. *fuzi*, the lateral roots of *A. carmichaeli*. These species all contain diterpenoid alkaloids, including aconitine, hypaconitine, and mesaconitine, with the major alkaloid varying with the species. All of these drugs are listed in the Pharmacopoeia of the People's Republic of China and are prescribed, *after preparation*, as mixtures for decoction for the following indications: rheumatism, arthritis, post-traumatic pain, fractures, and hemiplegia.

Root "preparation" consists of soaking in water, then cooking for 4-6 hours or treating with steam for 6-8 hours. Only the prepared root must be used. Aconite preparation is a practice common to Oriental and Indian medicines. Thus, in Japan, the procedure is similar: the prepared aconite (*kako-bushi-matsu*) is obtained by autoclaving the roots at 110 °C for 40 minutes. Far less toxic 15-keto-pyro compounds are formed. In India, aconite tubers (*A. ferox* Wall. ex Ser.) are traditionally macerated in cow's urine and in the sun for 3 days; the urine is renewed every day. This treatment decreases the alkaloid content by 60%.

Aconite preparation causes the partial hydrolysis of the naturally-occurring compounds, which diminishes the toxicity substantially: the LD50 for aconitine is 0.12 mg/kg (mouse, IV route) whereas, under the same conditions, it is 23 mg/kg for benzoylaconine and 120 mg/kg for aconine.

Fuzi has a cardiotonic activity (positive inotropic) which does not disappear when aconitine is hydrolyzed; this activity, put to use by Chinese clinicians, is thought to be due to a triphenolic 1-benzylisoquinoline, higenamine. Pure (synthetic) higenamine does display such properties.

Aconite: A Toxic Plant. Aconite is one of the most toxic plants: 25 µg/kg (IV, rat) cause ventricular contractions in 100% of the animals and 90% mortality. *Per os*, 2-4 g of aconite root, 5 mL of tincture, or 3 mg of aconitine are thought to be lethal doses in humans. Although accidents are exceptional in Europe, they are more frequent in Asia, because aconite is used in medicine (doses are exceeded, aconite is not prepared correctly or not prepared at all). Such intoxications also occur in the emigrant communities of large western cities.

At the toxic doses, the victim feels tingling in the lips, the tongue, the throat, then in the face and limbs. Anguish, myasthenia, numbness, and nausea accompany cardiac rhythm alterations, which can evolve toward irreversible ventricular fibrillation. There is no antidote: attempts can be made to remove the toxin from the digestive tract and antiarrhythmics can be administered to try to normalize the situation.

Other Aconites

A large number of species in the genus *Aconitum* contain diterpenoid alkaloids. Some are extremely toxic and ought to be known: wolfsbane, *A. vulparia* Rchb. (= *A. lycoctonum auct.*) has yellow flowers, is frequently found in the mountains, and contains a derivative of lycoctonine, namely lycaconitine. Also toxic are numerous species indigenous to India or eastern Asia. In fact, the French Pharmacopoeia has placed this type of plant on the list of "medicinal plants with an unfavorable benefit-to-risk ratio for traditional use in magistral preparations" (Fr. Ph., 10th Ed., VI.7.B).

On the other hand, a few species contain only alkylamines and therefore are less toxic than the official species (e.g., *A. anthora* L., a small species of western Europe with yellow flowers).

Other Ranunculaceae Containing Diterpenoid Alkaloids

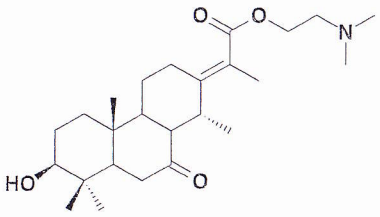
- LARKSPUR,
  Consolida regalis S.F. Gray
  (= *Delphinium consolida* L.) and other species

These ornamental plants are all toxic. So is *D. staphysagria* L., whose seeds were still prized at the beginning of the twentieth century for the external parasiticide properties of their decoctions (they have been used to treat lice infestations for over two millennia).

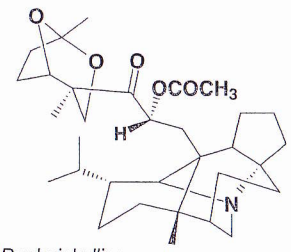
Methyl-lycaconitine, one of the alkaloids frequently found in *Delphinium*, acts as a curare by blocking post-synaptic conduction by acetylcholine. In North America, the *Delphinium* are responsible for the loss of cattle on a regular basis.

Other Plants Containing Diterpenoid Alkaloids

Recall that the toxicity of *Erythrophleum* (Cesalpiniaceae) is due to nitrogen-containing diterpenes. These substances (cassaine and related compounds) are esters of amino ethanols (e.g., *N*-methylethanolamine) and tricyclic diterpenoid acids (cassanes). The plants are known for the toxicity of their leaves in cattle (*E. chlorostachys* [F. Muell.] Baill., Australia) and for the toxicity of the trunk barks, traditionally used as war and ordeal poisons (*E. suaveolens* [Guill. & Perr.] Brenan and other species in the genus, tropical Africa). These nitrogen-containing diterpenoids are cardiac toxins somewhat like digitalis; their toxicity disappears on saponification.



Cassaine



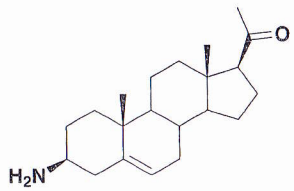
Daphniphylline

3. TRITERPENOID ALKALOIDS

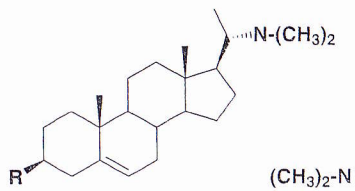
Triterpenoid alkaloids are seldom found in nature: daphniphylline and related alkaloids (yuzurimine) appear to be the only known compounds in this group. They have been isolated from Asian species of the genus *Daphniphyllum*, classified by some workers in the family Euphorbiaceae, and by others in the Daphniphyllaceae, which consists of only one genus.

4. STEROIDAL ALKALOIDS

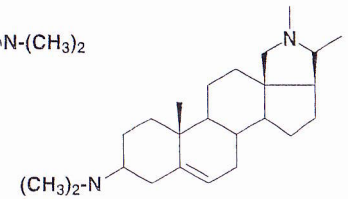
Steroidal alkaloids can be classified simply (although this is arbitrary) in three groups based on whether their skeleton contains 21, 24, or 27 carbon atoms (animal steroidal alkaloids such as those of *Salamandra* and *Phyllobates* will not be covered here).



Holaphyllamine

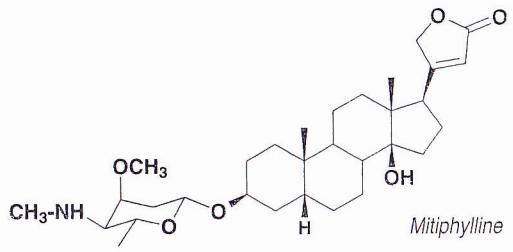


R = OH : *Irehine*
R = $N(CH_3)_2$: *Kurchessine*



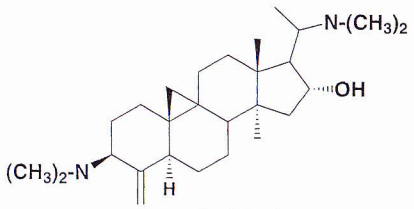
Conessine

• C_{21} alkaloids are derivatives of pregnane with a nitrogen-containing substituent at C-3, or C-20, or in both positions. The nitrogen atom may be part of a side chain as an amine substituent at C-3, C-20, or both, for example in holaphyllamine, irehine, kurchessine, or it may be part of a ring as an amine substituent at C-20, for example in conessine. These alkaloids are characteristic of the Apocynaceae - Apocynoideae (*Funtumia, Holarrhena, Kibatalia, Malouetia*), and are also found in the Buxaceae (*Pachysandra*), and in this case C-4 is substituted (OH, =O). Digitoxigenin-type derivatives are also known, which have an ether function at C-3 and an aminomethylated 2,6-dideoxyhexose at C-5 (mitiphylline).

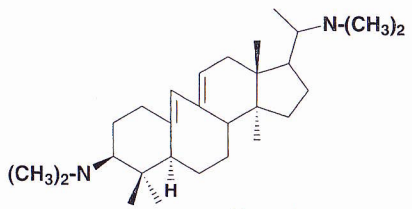


Mitiphylline

• C_{24} alkaloids are derived directly from cycloartenol, and are specific to the family Buxaceae. They have amine functions at C-3 and C-20, and have either retained the original skeleton (cycloartane), or have lost one of the methyl groups at C-4, or else they include a seven-membered ring arising from the 9,10-cleavage of the cyclopropane ring. Thus, two groups of compounds are distinguished, the derivatives of 9β,19-cyclo-4,4,14α-trimethyl-5α-pregnane and those of *abeo*-9(9–>19)-4,4,14α-trimethyl-5α-pregnane. The principal structural variations are the potential oxidation of one of the methyl groups at C-4—which can also be eliminated—or unsaturation, or oxidation at various positions (e.g., at C-15). The C-4 methyl group can be converted to an exomethylene group.



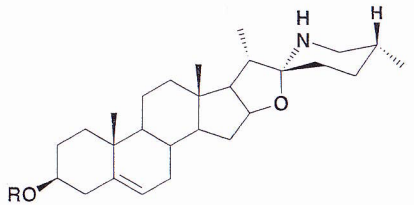
Cyclobuxine



Buxamine

• C_{27} alkaloids are found in the Solanaceae and Liliaceae. In the case of the family Solanaceae, they are true steroids, which are nitrogen-containing derivatives of (22*R*, 25*S*)-solanidane such as solanine or chaconine (these are solanidine glycosides), or of spirosolane, which can be either (22*R*, 25*R*)—as in solasonine and solamargine (solasodine glycosides)—or (22*S*, 25*S*) as in tomatine or sisunine (tomatidine glycosides). In all cases, the C-25 methyl group is equatorial. These alkaloids occur, in the plants, as glycosides, and are closely related, structurally and biogenetically, to steroidal saponins with which they share many physico-chemical and biological properties.

In the case of the family Liliaceae, the C_{27} skeleton undergoes, beyond the addition of an amine function and the cyclization of the side chain (solanidane-type, e.g., rubijervine, epirubijervine), a rearrangement of its rings to form a C-*nor*-D-*homo*-steroid, in other words the C ring loses a carbon atom, which is gained by the

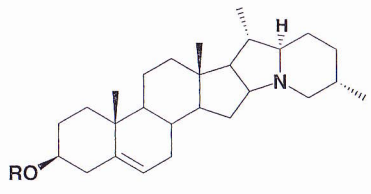


R = H : *Solasodine*

R = β-D-Glc (1—>3)-β-D-Gal (1—>) : *Solasonine*

(1—>2) ↑

α-L-Rha



R = H : *Solanidine*

R = β-D-Glc (1—>3)-β-D-Gal (1—>) : α-*Solanine*

(1—>2) ↑

α-L-Rha

R = α-L-Rha (1—>4)-β-D-Glc (1—>) : *Solamargine*

(1—>2) ↑

α-L-Rha

R = β-D-Glc (1—>3)-β-D-Gal (1—>) : β-*Solanine*

R = β-D-Gal (1—>) : γ-*Solanine*

R = α-L-Rha (1—>4)-β-D-Glc (1—>) : α-*Chaconine*

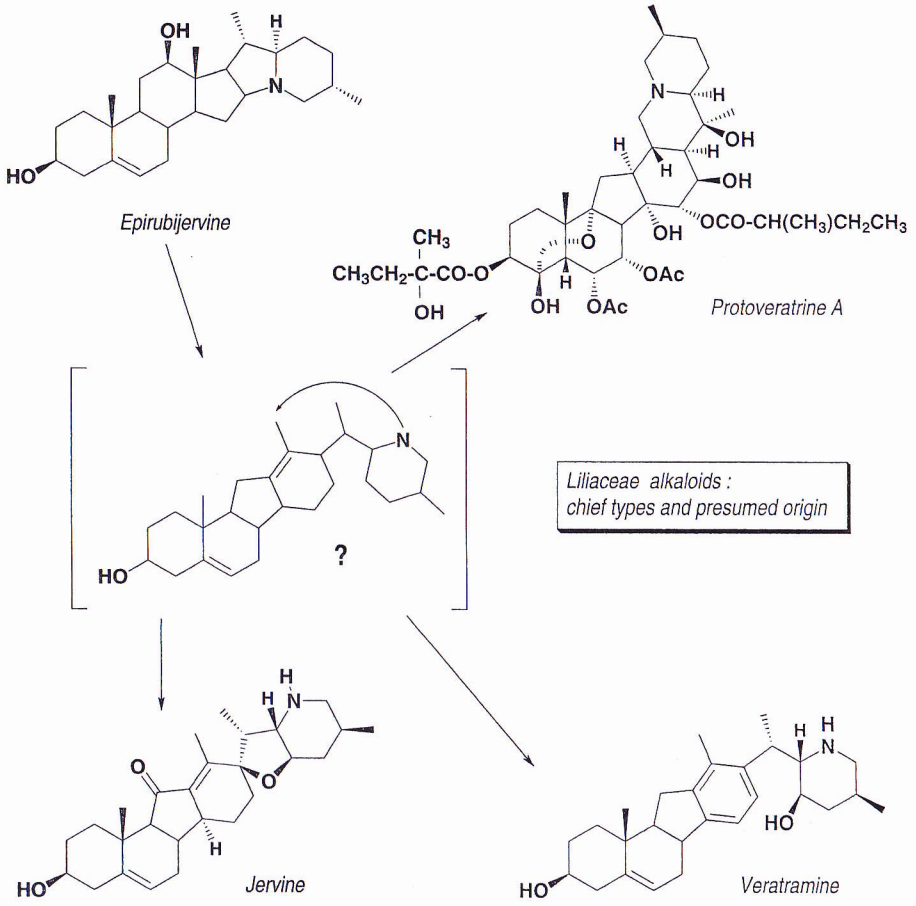
(1—>2) ↑

α-L-Rha

Glc(Rha)-Gal = solatriose
solatriose – rhamose = solabiose

Rha(Rha)-Glc = chacotriose
chacotriose – rhamose = chacobio se

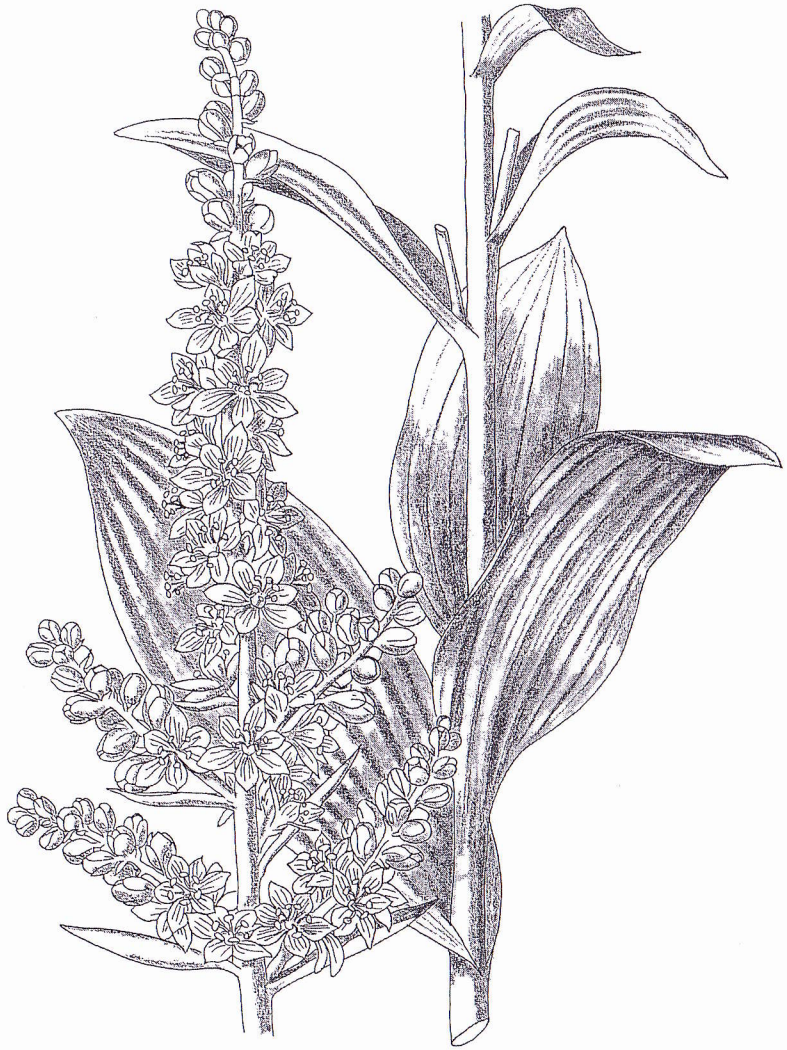
(– Rha-1 = β-*chaconines* ; – Rha-1 et -2 : γ-*Chaconine*)



D ring: this rearrangement is thought to involve the elimination of a leaving group from C-12 and the 1,2 migration of the 13,14 bond (Wagner-Meerwein). Cleavage of the indolizidine nucleus in the α position relative to the nitrogen atom subsequently leads to compounds such as veratramine or jervine (see figure). Recyclization involving the piperidine nitrogen atom and what used to be C-18 (i.e., the angular methyl group)is a possible explanation for the formation of hexacyclic alkaloids such as protoveratrine.

A. Apocynaceae Containing Steroidal Alkaloids

They are devoid of interest, at least in France. For a while, conessine hydrobromide was used for its toxicity in protozoans. Conessine is one of the principal alkaloids of the barks of the trunk of an Asian species, *kurchi* (*Holarrhena pubescens* Wall. ex G. Don) and of an African species, *séoulou* (*H. floribunda* [G. Don] T. Durand & Schinz).



VERATRUM ALBUM L.

B. Liliaceae Containing Steroidal Alkaloids

• White Hellebore, *Veratrum album* L.

The Plant, the Drug. A perennial plant which grows from a rhizome, white hellebore is a hardy herbaceous plant of the mountains of Europe and northern Asia. The leaves are alternate, linear, sheathing, and oval, with parallel veins running along their blade and converging at the apex. The flowers have a perianth which is whitish on the inside and greenish on the outside (or greenish on both sides) and are gathered into panicles. The fruit is a capsule.

The rhizome of white hellebore is short, dark brown—really (*vere* in Latin) black (*ater*)—and completely surrounded by tortuous roots ranging in color from chestnut brown to brownish-black. There is a potential for confusion with the rhizome and root of valerian, but since white hellebore is no longer used, this risk is no longer a concern.

Chemical Composition. The total alkaloids of the rhizome (1.5%) are a complex mixture of steroidal alkaloids, which are almost all C-*nor*-D-*homo* steroids, and which fall into two groups:

- the alkaloids of the jerveratrum group, which contain one to four oxygen atoms, and which also occur as free alkylamines or monoglycosides: jervine, rubijervine, veratramine, and the corresponding glycosides;
- the bases of the cerveratrum group. They contain many more oxygen atoms (seven to nine) and occur in the plant as esters: protoveratrines A and B.

Pharmacological Activity. The alkaloids of white hellebore are highly toxic for coldblooded animals *, and increase the permeability of fast sodium channels in the membranes of excitable cells, which causes iterative impulses after a unique stimulation. The nerve endings of afferent vagal fibers at the sinus node and left ventricle are the most sensitive to depolarization: their stimulation causes, by a reflex mechanism, an increase in parasympathetic tone which results in bradycardia and severe hypotension. The stimulation of the baroreceptors of the carotid sinus and that of the vasomotor centers increases the hypotensive effect. The white hellebore alkaloids are also emetic and at high doses, they have a direct (toxic) action on the myocardium.

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* Hellebore powder was formerly used as an external parasiticide. Note, in fact, an identical use of another Liliaceae containing steroidal alkaloids of related structure (cevadine, veratridine): sabadilla or cebadilla (*Schoenocaulon officinale* A. Gray), a species of American origin (Mexico, Venezuela) which is particularly toxic and therefore is on the French list of "medicinal plants with an unfavorable benefit-to-risk ratio for traditional use in magistral preparations". These drugs were formerly used as mixtures with *Delphinium staphysagria* and tobacco leaves (and known in France as "Capuchin friars' powder or *poudre des Capucins*).

Toxicity. Formerly used to treat arterial hypertension, the toxaemia of pregnancy, and cardiac insufficiency, the drug has been completely abandoned. Yet health professionals must be aware of its toxicity, even if the drug causes intoxications only in rare cases. The cause of intoxication is almost always the consumption of a home-made yellow gentian wine: these two species, which share the same habitat, are often confused.

The intoxication rapidly manifests itself by numb extremities, malaise, and digestive symptoms (nausea, vomiting, abdominal pain). Next to appear are cardiac symptoms: bradycardia, severe hypotension, and in case of massive intoxication, rhythm alterations shown by the ECG. The administration of atropine makes the symptoms subside.

• Other Veratrum

Note the teratogenic properties of cyclopamine and related alkaloids, found in *Veratrum californicum* Durand, which grows in the western United States, but not in western Europe. When ingested by ewes, they cause cranial and facial malformations (particularly cyclopia). The subterranean parts of the American hellebore (*Veratrum viride* Aiton) are too toxic to be used as a hypotensive (they were formerly used and the rhizome used to be listed in the United States Pharmacopoeia).

The *Veratrum* are not the only Liliaceae to owe their toxicity to steroidal alkaloids: the *Zigadenus* of North America cause accidents with symptoms identical to those of *Veratrum* poisoning.

C. Solanaceae Containing Steroidal Alkaloids (see also p. 687)

The steroidal alkaloids of the Solanaceae fall into two groups, the solanidane type, characterized by an indolizidine moiety, and the spirosolane type in which the nitrogen atom is part of an oxo-azaspirodecane structure: this explains why some workers consider them to be "nitrogen-containing saponins". In addition, they occur as glycosides in which the sugar is generally an oligosaccharide: trisaccharide (solatriose, chacotriose), tetrasaccharide (commertetraose, lycotetraose).

Biosynthetically, these alkaloids arise from the metabolism of cholesterol: the isolation of 27-hydroxycholestan-22-one-type structures and of piperidine derivatives hydroxylated at C-16β (e.g., etioline, teinemine) allows reconstruction of the likely steps in the formation of the two types of compounds (solanidane and spirosolane); the nitrogen atom is probably provided by transamination of a 26-hydroxycholesterol by an amino acid (arginine). The formation of piperidine involves a preliminary oxidation of the 26-aminocholesterol at C-22. In the case of the oxoazaspirodecanes, both configurations are possible for C-22: tomatidenol and solasodine, tomatidine, and soladulcine. It is possible that the spiro structure results from the nucleophilic addition of a hydroxyl group at C-16 onto the imine (or iminium) arising from the oxidation of the secondary piperidine-type amine.

The glycoalkaloids are soluble in water, and like saponins, they are surface active. They are less sensitive than true alkaloids to the precipitating action of the general reagents (Dragendorff, Mayer), and they can be visualized on TLC plates by reagents such as antimony trichloride, vanillin in the presence of hydrochloric acid, and anisaldehyde in the presence of sulfuric acid. They can be extracted by an acidic aqueous solution, precipitated by aqueous ammonia, and crystallized, although this is difficult to achieve from an alcoholic solution.

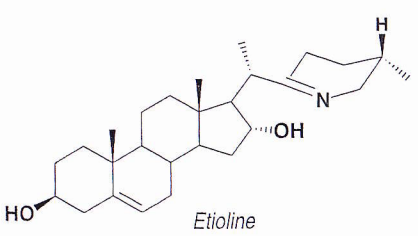
Biologically, the steroidal glycoalkaloids cause cell membrane alterations, probably by interacting with membrane sterols (like saponins). To various degrees, these compounds are cholinesterase inhibitors, but experiments in rats and hamsters do not allow this activity to be formally linked with the symptoms observed during intoxications: the toxic effects observed in animals might be no more than the consequence of pathological alterations in the intestine. Biologically, it is plausible that the steroidal glycoalkaloids participate, among other functions, in the defense mechanisms of the plants that produce them against various predators (helminths, insects) and pathogens (phytopathogenic fungi). Their activity results in part from their activity on the surface tension of cell membranes.

The glycoalkaloids of the Solanaceae are potential molluscicides and insecticides, some are cytotoxic, and they are not used in therapeutics *. It is useful to know about them because of their potential toxicity: the (relative) risk linked to the ingestion of the fruits of western European or American nightshades is known, but the dangers of eating potatoes—under certain conditions—are less known.

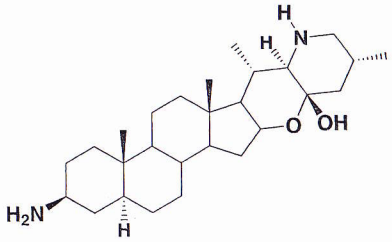
• Woody Nightshade, *Solanum dulcamara* L.

This species, whose stem was long considered a diuretic and "depurative" in folk medicine, is very common in western Europe. It is a herbaceous climbing plant with dimorphic leaves: they are entire or trilobate depending on their position on the stem. Woody nightshade is easy to identify by its flowers with prominent tube-like stamens, five purple petals with a yellow mark at the base, and by its fruits, which are small red berries gathered in bunches. In addition to the fact that there are several chemical breeds within *S. dulcamara* (with soladulcidine glycosides [in eastern Europe], with tomatidenol [in western Europe], or with solasodine [rare]), the concentration of alkaloids varies as a function of the plant part. It is maximal in the unripe fruit (up to 0.65% of the dry weight) and becomes a trace in the ripe fruit, a phenomenon which is common in other species in the family (tomato, eggplant). The concentration of alkaloids is lower in the leaves than in the unripe fruit. Also

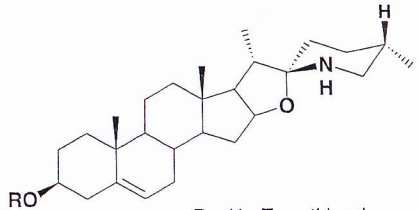
* In France. In Australia, a mixture of solasodine glucosides is available in a preparation for the topical treatment of pre-malignant and malignant skin tumors . *Cf.* Cham, B.E., Daunter, B. et Evans, R.A. (1991). Topical Treatment of Malignant and Pre-malignant Skin Lesions by Very Low Concentrations of a Standard Mixture (BEC) of Solasodine Glycosides, *Cancer Lett.*, **59**, 183-192.



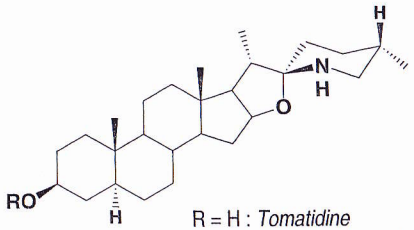
Etioline



Solanocapsine



R = H : *Tomatidenol*
R = solatriose : α-*Solamarine*



R = H : *Tomatidine*
R = lycotetraose : *Tomatine*

* lycotetraose = Gal-Glc -(Glc)-Xyl

found in the drug are saponins, which are bidesmosides of a furostanol, protoyamogenin (solayamocinosides A and B), or monodesmosides of a spirostan-26-one (soladulcosides). The toxicity of this species is far less substantial than older books lead you to think: this is what is shown by the statistics published by poison control centers in Europe and in the United States.

• Black Nightshade, *Solanum nigrum* L.

Formerly official—it passed for an antinevralgic—the black nightshade is a particularly common weed which grows in fields and rubble in Europe and America. It is an annual plant with dark green leaves and a corymb of small white flowers, reminiscent of those of the potato plant. The fruits are greenish-yellow berries which turn black when they ripen. All of the plant parts can contain steroidal alkaloids (solanine and solasodine glycosides, i.e., solasonine and solamargine).

The challenge posed by this species, even more so than by the previous one, is its great variability: the leaves of some specimens are devoid of alkaloids, while others can contain up to 2% of the dry weight. Again the small unripe fruit has the highest concentrations of alkaloids (1% and more), whereas the ripe fruit contains none. The statistics reported by various authors describe, in the worst case of ingestion of black nightshade berries, only minor gastrointestinal symptoms, and possible mydriasis and neurological problems. The rare cases of serious intoxication are characterized by cholinergic-type symptoms that have yet to be explained. There are also a few cases of contamination of vegetables harvested mechanically (green peas) by the unripe fruit of black nightshade.

• Potato, *Solanum tuberosum* L.

The glycoalkaloids occur in the leaves (30-90 mg/100g), fruits (40-100 mg/100 g), flowers (200-500 mg/100 g), and especially the sprouts (500 mg/100 g and more). The principal constituents (α-solanine and α-chaconine) occur alongside their partially hydrolyzed homologs (β- and γ-solanines, β- and γ-chaconines) and sometimes, related compounds (α- and β-solamarine, tomatidenol). Under normal conditions, the tubers only contain small amounts (25-100 mg/kg of fresh weight) and are concentrated in the "skin" and the layers of cells underneath. Peeling eliminates 60 to 95% of the alkaloids. Upon sprouting, turning green, exposure to light, and trauma (shock, cuts*), the alkaloid concentration increases and can become substantial. These alkaloids are not destroyed by cooking and are toxic. They cause necrosis of the gastric and intestinal mucosa (perhaps due to a saponin-like action on membranes), and are cholinesterase inhibitors. Poisoning is particularly rare, and is marked by gastrointestinal distress, fever, confusion in rare cases, rapid breathing, and a drop in blood pressure. The glycoalkaloids are also suspected of teratogenicity: although this has been demonstrated in several animal species, if we assume comparable susceptibilities in hamsters and women, a pregnant woman would have to consume 1 kg of sprouts before endangering her fetus.

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* Hence the higher concentration (290 mg/kg) observed in potato chips and French fries